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ORIGINAL ARTICLE

Is the Perspective of Radiation Oncologists on Fertility and Contraception in Patients Diagnosed with Breast Cancer in the Reproductive Age Changing? Results of a National Survey

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OBJECTIVE

As survival rates improve among reproductive-age breast cancer patients, fertility preservation, pregnancy, and contraception have become increasingly important quality-of-life issues. Radiation oncologists frequently encounter these patients; however, their awareness and clinical practices regarding oncofertility and contraception in Türkiye remain unclear.

METHODS

A 15-item national survey was conducted among radiation oncologists practicing in Türkiye to evaluate approaches to fertility preservation, pregnancy counseling, ovarian protection, and contraception in premenopausal breast cancer patients. The survey was distributed electronically, and responses were analyzed descriptively.

RESULTS

A total of 131 radiation oncologists viewed the survey, and 29 (22.1%) completed it. None of the respondents routinely contoured ovaries during breast radiotherapy planning. While 71.4% reported that fertility and pregnancy issues had been discussed during prior clinical evaluations, only 42.9% routinely discussed contraception in their own practice. More than one-third of respondents believed that pregnancy could be prevented by concurrent use of GnRH agonists and tamoxifen. Although 92.6% emphasized the importance of a multidisciplinary approach, fertility, pregnancy, and contraception were not consistently integrated into daily radiation oncology practice.

CONCLUSION

Despite growing awareness of the importance of fertility-related issues, radiation oncologists in Türkiye do not routinely address fertility preservation, pregnancy, and contraception in young breast cancer patients. Systematic integration of oncofertility counseling into radiation oncology practice and closer multidisciplinary collaboration are essential to meet the evolving expectations of this patient population.

Keywords: Breast cancer; contraception; fertility; multidisciplinary approach; radiotherapy.
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INTRODUCTION

Breast cancer is the most frequently diagnosed cancer among women in Türkiye, with more than 25,000 new cases reported in 2022, in line with global trends.[1,2] The widespread implementation of screening programs has resulted in an increasing number of patients being diagnosed at earlier stages and at younger ages.[3] Although younger age at diagnosis has historically been considered a poor prognostic factor, survival outcomes have improved substantially over the past decade due to advances in diagnostic methods and treatment strategies.

As survival improves, treatment-related adverse effects increasingly influence patients' quality of life. A study conducted by the Dana–Farber Cancer Institute demonstrated that young breast cancer patients have distinct expectations compared with older patients, particularly regarding treatment-related side effects, fertility, and menopausal symptoms.[4] Consequently, fertility preservation and pregnancy-related concerns have become increasingly important issues for radiation oncologists involved in the management of young breast cancer patients.[5]

Contraception is another critical issue that must be addressed in young patients. It is often assumed that tamoxifen and gonadotropin-releasing hormone (GnRH) agonists used during radiotherapy exert a contraceptive effect due to the induction of amenorrhea. Tamoxifen use represents a notable example of this complexity. Contrary to common misconceptions, tamoxifen does not reduce ovarian reserve and should not be considered a contraceptive method.[6] Failure to adequately counsel young patients receiving tamoxifen about contraception may significantly increase the risk of teratogenic effects in the event of an unintended pregnancy.[7] Although GnRH agonists may have a potential contraceptive effect, they may cause insufficient ovarian suppression and are not licensed as contraceptive agents.[8] For these reasons, in patients who complete anticancer treatments and are referred for radiotherapy, the presence of amenorrhea should not be considered a reliable indicator of contraception, and all patients should be referred for gynecologic consultation for appropriate contraceptive counseling. To ensure proper gynecologic consultation, contraception should be systematically discussed with all premenopausal patients.

In addition, modern radiotherapy techniques such as Intensity-Modulated Radiation Therapy (IMRT) and Volumetric Modulated Arc Therapy (VMAT) may unintentionally deliver low doses of radiation to the ovaries and uterus.[9] Therefore, ovarian protection should be considered during radiotherapy planning in patients of reproductive age who may desire future pregnancy.

To date, no comprehensive study has evaluated communication practices between radiation oncologists and young breast cancer patients in Türkiye or assessed radiation oncologists' awareness regarding fertility, pregnancy, and contraception. In light of these considerations, we conducted a national survey to evaluate radiation oncologists' approaches to the evolving expectations of young breast cancer patients.

MATERIALS AND METHODS

A 15-item survey was designed for radiation oncologists practicing in Türkiye. Survey questions addressed ovarian contouring practices, fertility preservation, pregnancy counseling, hormonal therapy, contraception, and breastfeeding. Each question allowed only one response. The survey was distributed electronically via email and online professional communication platforms. Typeform survey software was used for survey creation and data analysis. Since the study was a survey study, no ethics committee approval was required.

RESULTS

Survey questions, response options, and the statistical distribution of responses are summarized in Table 1. A total of 131 participants viewed the survey, 64 (48.85%) participants start to answer, of whom 29 (45.3%) completed. The highest dropout rate occurred after the third question (17%). Among 131 participants who viewed the survey, only 22.13% of participants completed the survey.

All respondents reported that they did not routinely contour the ovaries during breast cancer radiotherapy planning (100%, n=29). It was found that 71.4% of participants answered "yes" to whether fertility and pregnancy issues had been discussed in the clinics where premenopausal patients had previously been evaluated at their first outpatient visit (Fig. 1).

It was determined that 42.9% (n=12) of radiation oncologists who completed the survey discussed contraception with patients presenting to the Radiation Oncology outpatient clinic. While 21.4% (n=6) reported that they never discussed this issue, 35.7% (n=10) stated that they discussed it occasionally.

Table 1. Survey questions, answer options, and statistical distribution of answers

Questions	Answers' distribution
1. Do you conduct ovarian contouring as part of breast cancer radiotherapy? (PwA: 29)	a. Yes (0% , n=0) b. No (100%, n=29) c. Occasionally (0% , n=0)
2. If you answered "Yes" to the first question, do you discuss pregnancy intentions with young patients after considering the ovarian dose received? (PwA:13)	a. Yes (7.7%, n=1) b. No (76.9%, n=10) c. Occasionally (15.4%, n=2)
3. If a patient wishes to conceive, do you refer them to a gynecology clinic for fertility preservation procedures along with ovarian preservation during planning? (PwA:29)	a. Yes (69%, n=20) b. No (27.6%, n=8) c. Occasionally (3.5%, n=1)
4. If you answered "No" to the third question, do you believe that ovarian preservation alone during the planning phase would be sufficient? (PwA:15)	a. Yes (26.7%, n=4) b. No (60%, n=9) c. Occasionally (13.3%, n=2)
5. Do you have information about the most commonly used method for ovarian protection in our country? (PwA:27)	a. Oocyte/embryo cryopreservation (81.5%, n=22) b. Ovarian tissue preservation (7.4%, n=2) c. Ovarian suppression with GNRH agonist (11.1%, n=3)
6. In your opinion, which medical department should be consulted regarding fertilization-related issues? (PwA:27)	a. Breast Surgeon (0% , n=0) b. Medical Oncologist (7.4%, n=2) c. Radiation Oncologist (0% , n=0) d. All (92.6%, n=25)
7. When young patients are referred to your clinic, do you check if fertility and pregnancy have been discussed with the specialists they previously consulted? (PwA:28)	a. Yes (71.4%, n=20) b. No (14.3%, n=4) c. Occasionally (14.3%, n=4)
8. Do young patients ask you questions about contraception from you when they are referred to your clinic? (PwA:28)	a. Yes (39.3%, n=11) b. No (28.6%, n=8) c. Occasionally (32.1%, n=9)
9. Do you offer information about contraception to your young patients? (PwA:28)	a. Yes (42.9%, n=12) b. No (21.4%, n=6) c. Occasionally (35.7%, n=10)
10. Do you believe that pregnancy can be prevented in patients who are using GnRH agonists and tamoxifen? (PwA:28)	a. Yes (35.7%, n=10) b. No (64.3%, n=18)
11. Do you inform patients using hormonal contraception methods about the need for a gynecological consultation before breast cancer diagnosis and treatment? (PwA:29)	a. Yes (55.2%, n=16) b. No (13.8%, n=4) c. Occasionally (31%, n=9)
12. Do you recommend pregnancy for your patients who express concerns after treatment? (PwA:26)	a. Yes (34.6%, n=9) b. No (15.4%, n=4) c. Dependent on hormone receptor status (50%, n=13)
13. If you do not recommend pregnancy, what is the main reason for that? (PwA:19)	a. Due to complications such as preterm births and low birth weight (5.3%, n=1) b. Because the risk of recurrence may increase in hormone-positive patients (52.6%, n=10) c. Other (42.1%, n=8)
14. Do you assess BRCA1 and BRCA2 carriers for potential risks related to pregnancy? (PwA:25)	a. Yes (64%, n=16) b. No (28%, n=7) c. Occasionally (8%, n=2)
15. Do you recommend breastfeeding after undergoing breast radiotherapy? (PwA:29)	a. Yes (27.6%, n=8) b. No (51.7%, n=15) c. Occasionally (20.7%, n=6)

PwA: Number of participants who answered the question.

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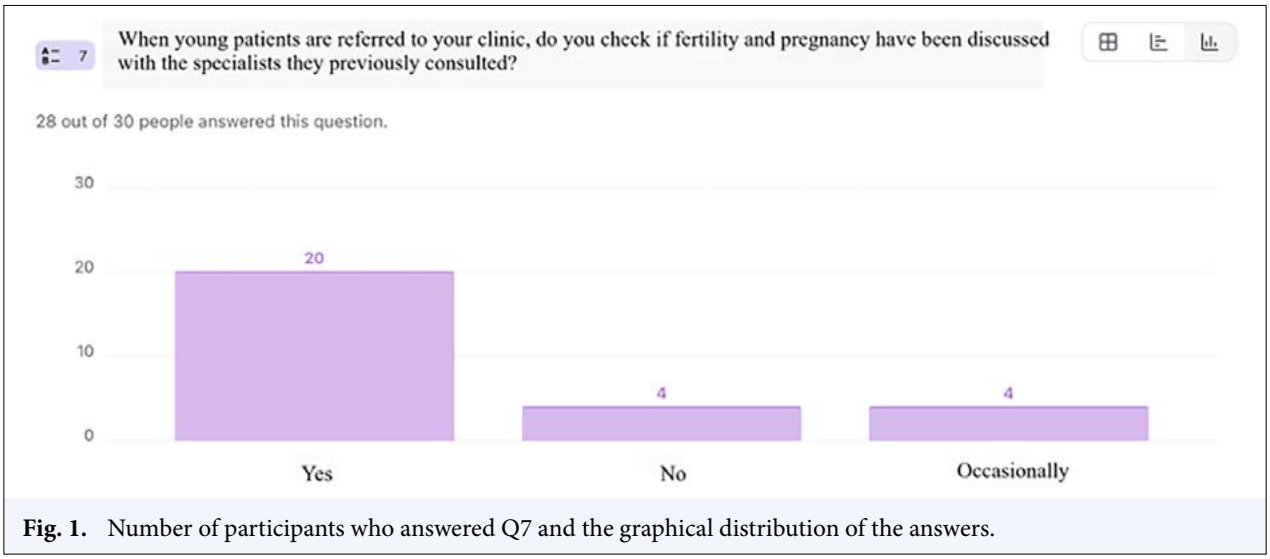


Fig. 1. Number of participants who answered Q7 and the graphical distribution of the answers.

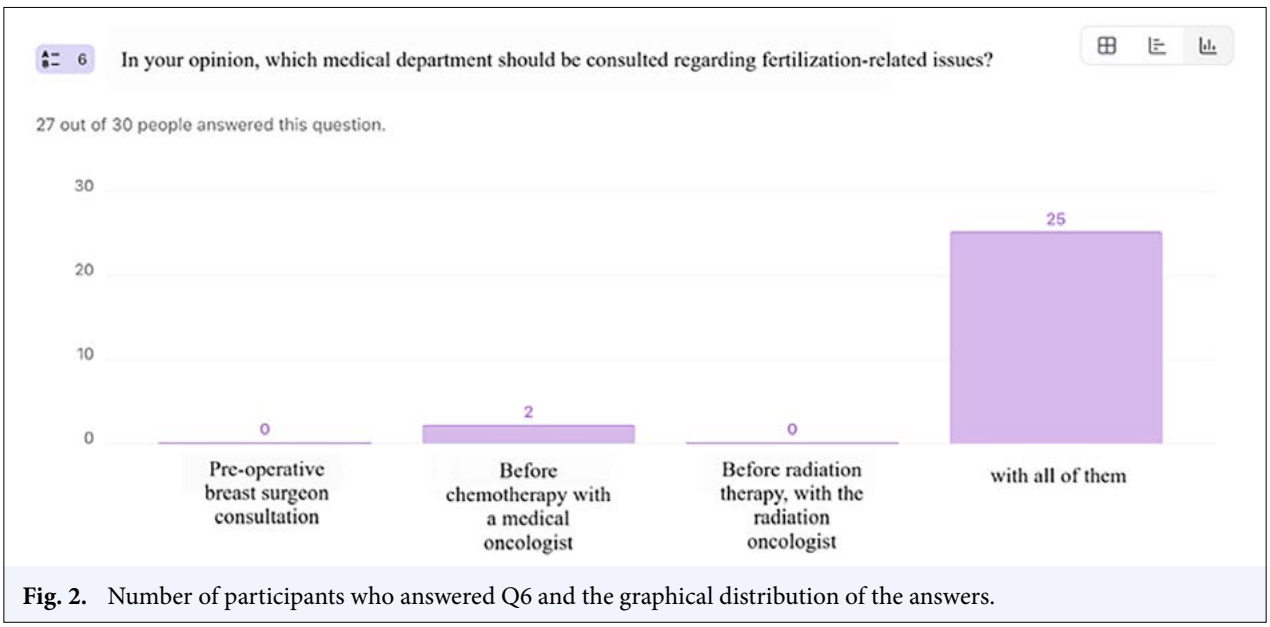


Fig. 2. Number of participants who answered Q6 and the graphical distribution of the answers.

Regarding contraception counseling, 55.2% of participants (n=16) stated that they routinely consult gynecology for young breast cancer patients, whereas 13.8% (n=4) reported that they do not address this issue at all. Notably, 35.7% of respondents (n=10) believed that pregnancy could be prevented in patients receiving both GnRH agonists and tamoxifen.

A large majority of participants (92.6%, n=25) indicated that fertility-related issues should be addressed within a multidisciplinary framework (Fig. 2). However, when the survey results were evaluated collectively, it became evident that fertility, pregnancy, and contraception issues are not routinely integrated into daily radiation oncology practice in Türkiye.

DISCUSSION

Due to widespread mammography screening, the number of patients diagnosed with breast cancer at an early stage has been increasing. In parallel, the proportion of patients diagnosed at a younger age has also risen as a result of changes in dietary habits, lifestyle factors, and genetic predisposition.[10] Consequently, young patients diagnosed at an early stage with curative intent increasingly seek information and solutions regarding fertility preservation, pregnancy desire, and contraception during outpatient visits.

Evaluation of the results of our survey suggests that, in Türkiye, radiation oncologists generally do

not proactively address these issues during treatment initiation or follow-up unless specifically raised by the patient. Although this interpretation may be influenced by the low response rate—of the 131 radiation oncologists who viewed the survey, only 29 completed it, and none answered all questions. 25 respondents (92.6%) expressed the opinion that fertility-related issues should be discussed within a multidisciplinary framework. This finding is consistent with the global literature, where clinicians treating this patient population acknowledge the importance of oncofertility, yet their approaches often remain suboptimal.[11,12] Notably, most studies on this topic have been conducted by medical oncologists rather than radiation oncologists.[5]

Because fertility desire, fertility preservation, and contraception are not routinely integrated into radiation oncology practice, perspectives and reviews from this discipline are limited in the existing literature. However, many young patients diagnosed at an early stage—often treated with breast-conserving surgery and receiving hormonal therapy without chemotherapy—are directly referred to radiation oncology clinics. These patients frequently direct their questions regarding fertility and pregnancy to radiation oncologists. To ensure appropriate counseling, it is essential that radiation oncologists are familiar with the hormonal therapies initiated and provide patient-specific information accordingly. Tamoxifen, one of the most commonly used agents during and after radiotherapy, is known not to negatively affect ovarian reserve, and studies have demonstrated no significant change in anti-Müllerian hormone levels.[13]

When ovarian suppression with a GnRH agonist is administered during chemotherapy, the rate of premature ovarian insufficiency decreases from 30.9% to 14.1%. However, the risk of premature ovarian insufficiency when aromatase inhibitors are used in combination with GnRH agonists remains unclear.[13]

Ovarian risk assessments in radiotherapy are primarily performed in patients receiving pelvic irradiation, and ovaries are not routinely contoured as organs at risk in breast cancer radiotherapy. In a dosimetric study by Oonsiri et al.,[9] left breast radiotherapy planning using standard two-dimensional tangential fields, IMRT, and VMAT resulted in ipsilateral ovarian doses of 42 centigray (cGy), contralateral ovarian doses of 31 cGy, and uterine doses of 38 cGy. Similarly, Aral et al.[14] evaluated eight breast cancer patients treated with modern radiotherapy techniques and observed zero ovarian dose with three-dimensional conformal planning. In helical IMRT plans, ipsilateral ovarian doses were calculated as 12 cGy (range 10–30 cGy) and contralateral ovarian doses as 8 cGy (range 5–13 cGy). In patients who underwent breast-conserving surgery and IMRT planning, the ipsilateral ovarian dose was 15 cGy (range 12–30 cGy).

Ovarian reserve decreases markedly with radiotherapy. Radiation-induced ovarian follicle loss occurs at doses below 2 Gray (Gy), while LD5 and LD50 values for infertility are reported as 2–3 Gy and 6–12 Gy, respectively.[15] Kerr et al.[16] demonstrated a significant reduction in primordial follicles following exposure to 45 cGy of gamma radiation. Although ovarian doses during breast radiotherapy generally remain within acceptable limits, patient- and treatment-related factors—particularly age at diagnosis and treatment protocol—may alter ovarian sensitivity.

In the present survey, responses to the twelfth question indicated that four respondents (15.4%) did not recommend pregnancy, while 13 (50%) based their recommendation on hormone receptor status. Considering that many radiation oncologists reviewed the survey but did not respond, it appears that a substantial proportion may feel hesitant to address pregnancy-related issues. Medical oncologists, similar to radiation oncologists, may prioritize oncologic outcomes over fertility concerns or may express concerns regarding increased recurrence risk in hormone-positive patients.

As the number of young patients diagnosed at an early stage with long-term survival continues to increase, fertility, pregnancy, and contraception issues should be systematically incorporated into routine clinical practice. Until these topics are fully embedded within multidisciplinary care, oncofertility boards should be implemented, and patients should undergo comprehensive multidisciplinary evaluation. In the interim, radiation oncologists managing patients who have not received counseling on these issues should request gynecological consultations, assess anti-Müllerian hormone levels, and reconsider radiotherapy planning techniques for patients desiring pregnancy.[17]

Although hypofractionated regimens are increasingly used, patients typically attend radiation oncology clinics daily for at least 20 treatment days. This frequent interaction allows for closer communication between patients and physicians and may prompt more questions regarding contraception. Nevertheless, a considerable proportion of respondents reported that patients did not raise contraception-related

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questions. One possible explanation is treatment-related amenorrhea, leading patients to assume that pregnancy is not possible.

Patients may concurrently receive tamoxifen or GnRH analogues during radiotherapy. While tamoxifen does not alter ovarian reserve, pregnancy occurring under tamoxifen exposure may result in teratogenic effects, and GnRH analogues are not licensed as contraceptive agents.[13] Therefore, updating clinicians' knowledge on this issue is critically important.

Hormonal contraceptive methods are contraindicated in breast cancer patients. Even intrauterine levonorgestrel, although protective for the endometrium, may increase the risk of breast cancer recurrence. Lambertini et al.[18] reported that 54.2% of breast cancer patients were using hormonal contraceptive methods at diagnosis. Consequently, discussing contraception with patients and requesting gynecological consultations are essential components of clinical follow-up.

Although the majority of respondents indicated that fertility-related discussions should be conducted within a multidisciplinary framework, the overall responses suggest that oncofertility and contraception are not routinely addressed in clinical practice. These findings are consistent with previous studies involving other oncology disciplines, where awareness of the importance of oncofertility exists but clinical implementation remains suboptimal.[5] As diagnosis and survival rates increase among reproductive-age breast cancer patients, fertility and contraception issues must be systematically incorporated into routine clinical care to improve quality of life.

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REFERENCES

1. Filho AM, Laversanne M, Ferlay J, Colombet M, Piñeros M, Znaor A, et al. The GLOBOCAN 2022 cancer estimates: Data sources, methods, and a snapshot of the cancer burden worldwide. Int J Cancer 2025;156:1336–46.
2. Ferlay J, Ervik M, Lam F, Laversanne M, Colombet M, Mery L, et al. Global Cancer Observatory: Cancer Today. Lyon: International Agency for Research on Cancer; 2024.
3. Bleyer A, Welch HG. Effect of three decades of screening mammography on breast-cancer incidence. N Engl J Med 2012;367:1998–2005.
4. Ruddy KJ, Greaney ML, Sprunck-Harrild K, Meyer ME, Emmons KM, Patridge AH. Young women with breast cancer: A focus group study of unmet needs. J Adolesc Young Adult Oncol 2013;2:153–60.
5. Nardin S, Arecco L, Delucchi V, Blondeaux E, Stana M, Leite LM, et al: Physicians' knowledge, practice, and attitudes on fertility and pregnancy-related issues in young women with advanced breast cancer: Results of the ABC6 and ABC7 survey. Breast 2025;82:104479.
6. Paluch-Shimon S, Cardoso F, Partridge AH, Abulkhair O, Azim Jr. HA, Bianchi-Micheli G, et al. ESO–ESMO 4th International Consensus Guidelines for Breast Cancer in Young Women (BCY4). Ann Oncol 2020;31:674–96.
7. Jyoti B, Bharat C, Ankita N, Munita B, Sudeep G. Pregnancy on tamoxifen: Case report and review of literature. South Asian J Cancer 2016;5:209–10.
8. Lambertini M, Moore HCF, Leonard RCF, Loibl S, Munster P, Bruzzone M, et al. Gonadotropin-releasing hormone agonists during chemotherapy for preservation of ovarian function and fertility in premenopausal patients with early breast cancer: A systematic review and meta-analysis of individual patient-level data. J Clin Oncol 2018;36:1981–92.
9. Oonsiri P, Vannavijit C, Wimolnoch M, Suriyapee S, Saksornchai K. Estimated radiation doses to ovarian and uterine organs in breast cancer irradiation using radio-photoluminescent glass dosimeters (RPLDs). J Med Radiat Sci 2021;68:167–74.
10. Cathcart-Rake EJ, Ruddy KJ, Bleyer A, Johnson RH. Breast cancer in adolescent and young adult women under the age of 40 years. JCO Oncol Pract 2021;17:305–13.
11. Masciello MC, Bartholomew AJ, Haslinger M, Bozzuto LM, Tung SS, Thibodeau R, et al. Physician perspectives on fertility preservation discussions with premenopausal breast cancer patients: Results from a multihospital health care system. Ann Surg Oncol 2019;26:3210–15.

12. Lambertini M, Di Maio M, Poggio F, Pagani O, Curigliano G, Del Mastro L, et al. Knowledge, attitudes and practice of physicians towards fertility and pregnancy-related issues in young BRCA-mutated breast cancer patients. Reprod Biomed Online 2019;38:835–44.
13. Razeti MG, Spinaci S, Spagnolo F, Lambertini M. How I perform fertility preservation in breast cancer patients. ESMO Open 2021;6:100112.
14. Aral IP, Inan GA, Beyaz H, Karadeniz HG, Arpacı E, Eser MK, et al. Evaluation of ovary radiation dose in breast cancer radiotherapy with modern techniques: A prospective pilot study. Clin Exp Obstet Gynecol 2024;51:138.
15. Duncan FE, Kimler BF, Briley SM. Combating radiation therapy-induced damage to the ovarian environment. Future Oncol 2016;12:1687–90.
16. Kerr JB, Hutt KJ, Michalak EM, Cook M, Vandenberg CJ, Liew SH, et al. DNA damage-induced primordial follicle oocyte apoptosis and loss of fertility require TAp63-mediated induction of Puma and Noxa. Mol Cell 2012;48:343–52.
17. Lambertini M, Peccatori FA, Demeestere I, Amant F, Wyns C, Stukenborg JB, et al. Fertility preservation and post-treatment pregnancies in post-pubertal cancer patients: ESMO clinical practice guidelines. Ann Oncol 2020;31:1664–78.
18. Lambertini M, Massarotti C, Havas J, Pistilli B, Martin AL, Jacquet A, et al. Contraceptive use in premenopausal women with early breast cancer. JAMA Netw Open 2022;5:e2233932.

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ORIGINAL ARTICLE

Survey on Turkish Radiation Oncologists' Approach for Brain Metastases of Small Cell Lung Cancer: A Study from Turkish Radiation Oncology SRS Group (TROD 10-014)

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OBJECTIVE

Prophylactic cranial irradiation (PCI) reduces the risk of intracranial progression and improves overall survival (OS) in small cell lung cancer (SCLC). However, with advances in systemic therapies and improvements in neuroimaging, the OS benefit has been increasingly questioned. Herein, we report the results of a survey study which evaluates the approach of radiation oncologists in patients with SCLC and brain metastases with or without a prior PCI.

METHODS

The online survey was conducted by the Steering Committee of The Turkish Society of Radiation Oncology Stereotactic Surgery (TROD-SRS) subgroup and distributed to the members of TROD-SRS in Türkiye. The survey consisted of two sections including 16 questions.

RESULTS

One hundred and sixty-four respondents completed the questionnaire. While 88% of the respondents preferred SRS in patients with a prior PCI, WBRT came forward in patients without a prior PCI. More than half of the respondents opted for SRS after metastasectomy. The decision to perform SRS in patients with brain metastases of SCLC depend on the presence of a prior PCI, number and volume of metastases, and the availability of SRS. More experienced respondents had a decreased concern for deciding for SRS treatment but these respondents also looked over more factors when deciding for SRS.

CONCLUSION

The results of this survey study indicate that SRS is widely accepted for the management of brain metastasis in patients with SCLC in our country. We anticipate that the utilization of SRS will continue to increase as access to SRS-capable centers.

Keywords: Brain metastasis; small cell lung cancer; stereotactic surgery.
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INTRODUCTION

Small cell lung cancer (SCLC) is an aggressive variant of lung cancer. Despite a high response rate to treatment, it is characterized by early treatment resistance, rapid progression and distant metastasis (DM).[1] Approximately two-thirds of patients with SCLC have DM at the time of diagnosis and the rate of brain metastasis is around 10%.[2,3] The timely and accurate diagnosis of brain metastasis is the most important factor contributing to the prognosis of SCLC.[4] In patients without a brain metastasis, prophylactic cranial irradiation (PCI) has been shown to reduce the rate of intracranial progression and prolong overall survival (OS).[5] Following two pivotal trials, PCI has become the standard of care for patients with at least a stable disease after treatment.[6,7] A meta-analysis also reported that the addition of PCI reduced the frequency of brain metastasis and improved 1-year OS, yet had no effect on long term survival in extensive stage SCLC.[8] On the other hand, this meta-analysis also reported an increased neurotoxicity following PCI.

Recent studies have informed us that neurocognitive functions can be preserved with hippocampal-sparing cranial radiotherapy (RT).[9,10] However, although administered safely, protecting cognitive functions after hippocampal-sparing cranial RT is controversial.[11] In the phase II/III NRG-CC003 study which compares conventional and hippocampus-sparing PCI, although the primary endpoint of less deterioration on the Hopkins Verbal Learning Test-Revised delayed recall test was not achieved, hippocampus-sparing PCI was found to be beneficial for reducing the risk of overall neurocognitive toxicity with similar rates of intracranial recurrence and survival.[12] As systemic therapies for SCLC have evolved, the survival advantage of PCI has been questioned by new strategies that include a close follow-up with brain magnetic resonance imaging (MRI) and early salvage therapy for brain metastasis.[13] A comprehensive multicenter analysis, the FIRE-SCLC study, also provided strong evidence for the use of stereotactic radiosurgery (SRS) for brain metastasis in SCLC, particularly efficient for patients with a single metastasis.[14] The authors emphasized the disadvantages such as a shorter time to central nervous system progression and decreased OS which are similar to SRS-based strategies in other malignancies. The researchers believe these data provide a benchmark for SRS outcomes and support the use of first-line SRS as a treatment option in carefully selected patients with SCLC.

As whole-brain radiotherapy (WBRT) has been associated with increased neurocognitive toxicity, SRS has become an up-front option for patients with limited brain metastasis with other histologies of lung cancer.[15] On the other hand, the traditional approach for brain metastasis of SCLC is still WBRT.[16] The aim of this study was to design and carry out a survey to evaluate the approach of radiation oncologists in Türkiye in patients with brain metastasis diagnosed with SCLC.

MATERIALS AND METHODS

The survey was developed under the approval and supervision of the executive council of the SRS subgroup of Turkish Society of Radiation Oncology and distributed to the radiation oncologists. The survey was not sent to the members on residency at that time. Participation was voluntary and all responses were collected anonymously. No personal identifying information was obtained. The survey consisted of two sections with a total of 16 questions and took approximately five minutes to complete. The first section included the demographic information and clinical experience of the institution of the respondent. The second part focused on the clinical opportunities, clinical scenarios and treatment options. The survey questionnaire translated to English is provided as Supplementary Appendix 1.

This study was approved by the Ethical Committee of Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital, Ankara, Türkiye (approval number 2025-02/31) on Feb 20, 2025 and conducted according to declaration of Helsinki.

Statistical Analysis

The median, mean (±standard deviation [SD]), minimum, and maximum values were used as descriptive variables. In assessing normality, the Shapiro Wilk test and the Kolmogorov Smirnow test was used in case the number of data was >30 and ≤30, respectively. The Chi-square test was used for evaluating binary data. If no cell contained a value <5, the Fisher-Exact Probability Test was used, but if the cells contained a value >5, the Pearson Chi-square Test was used. For independent groups, Student's t-test or Mann-Whitney U test, as appropriate, was used.

The univariate and multivariate logistic regression analyses were used to measure the relationship between respondent characteristics and treatment preferences for brain metastases in SCLC using odds ratios (OR) and 95% confidence intervals (CI). Independent variables evaluated in the univariate model included

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Table 1 Replies of the respondents to questions 2–7 and 11 (n=164)

Questions	n (%)	Questions	n (%)
2) What is the type of institution you currently work in?*		6) What is your preferred approach for patients who develop brain metastases after PCI?	
University Hospital	56 (34)	Surgery	5 (3)
Private Hospital	30 (18)	WBRT	15 (9)
Public Hospital	9 (6)	SRS	144 (88)
Training and Research Hospital	68 (42)	7) What is your preferred treatment approach for patients with SCLC who present with brain metastases and have not received PCI?	
3) How many years have you been practicing as a radiation oncologist? *		WBRT	53 (32)
0–5 years	18 (11)	SRS	42 (26)
6–10 years	23 (14)	WBRT followed by SRS	61 (37)
11–20 years	62 (38)	Surgery followed by cavity-directed SRS	8 (5)
21 years or more	60 (37)	Surgery	0
4) How many SCLC cases do you see per year?		11) What is your preferred approach for a patient who has undergone intracranial metastasectomy?	
1–10	31 (19)	WBRT	37 (23)
11–30	77 (47)	SRS	96 (56)
31–50	37 (23)	WBRT followed by SRS	24 (15)
≥51	19 (11)	Observation / Follow-up	2 (1)
5) Does your institution have the facility and equipment to perform SRS?		Other	5(3)
Yes	151 (92)		
No	13 (8)		

*: One respondent was not included in the analysis as the responses had data entry errors. Not every respondent answered every question. n: Number; PCI: Prophylactic cranial irradiation; SCLC: Small cell lung cancer; SRS: Stereotactic radiosurgery; WBRT: Whole brain radiotherapy.

age, study year, study region, access to treatment-related technologies, treatment center, and the number of patients treated per year. While performing statistical analysis of numerical values, the ROC curve or median/mean values were taken as the absolute points and analyzed separately by grouping. Nonparametric tests were used to analyze Likert-type scale responses. A cross-tabulation was performed to examine the association between prior PCI and years of experience of the respondents, between years of experience and number of cases seen per year, instution type, facility SRS. Statistical analyses were conducted by using Statistical Package for the Social Sciences (SPSS™) version 22.0 (IBM, Armonk, NY, USA). A two-sided statistical test was used in all analyses and a p value of ≤0.05 was considered as statistically significant.

RESULTS

One hundred and sixty-four respondents completed the survey. The median age of the respondents was 46 years (range: 25–66 years). The other characteristics of the respondents are given in questions 2–5 Table 1. Two responses regarding the demographic information from a single respondent were identified as data entry errors attributable to typographical mistakes and were excluded from the final analysis. The majority of the respondents have been working in a university or a research and training hospital and more than half have been working as a radiation oncologist for more than 10 years. Almost half of the respondents treat 11–30 patients with SCLC per year and 92% can apply SRS in their institution. The number of cases seen per year was similar regarding the years of experience and type of institution of the respondents (p>0.05).

When the questions about the clinical practice were evaluated (Table 1), the majority of the respondents were shown to prefer SRS in patients that had undergone a prior PCI. On the other hand, WBRT comes forward, either alone or followed by SRS, in patients without a prior PCI.

In response to the 8th question 'To what extent do the following factors influence your treatment decision in patients with brain metastases in SCLC?', the performance status, number of brain metastases, total intracranial tumor volume, a prior PCI and extracranial disease status significantly affected the treatment decision of the respondents (Table 2).

Table 2 Responses to question 8 (To what extent do the following factors influence your treatment decision in patients with brain metastases in SCLC?)

	Never n (%)	Rarely n (%)	Sometimes n (%)	Often n (%)	Always n (%)
Performance status	0	7 (4)	22 (13)	66 (40)	68 (42)
N of brain metastases	3 (2)	7 (4)	19 (12)	67 (41)	66 (40)
Total intracranial tumor volume	3 (2)	10 (6)	23 (14)	68 (42)	59 (36)
Prior PCI irradiation	2 (1)	11 (7)	34 (21)	54 (33)	61 (37)
Extracranial disease status	1 (1)	12 (7)	34 (21)	57 (35)	59 (36)

n: Number, PCI: Prophylactic cranial irradiation; SCLC: Small cell lung cancer.

For the respondents affected by the total number and volume of brain metastases when deciding to perform SRS (questions 9 and 10), the respective median values were 5 (range: 1–20) and 20 cc (range: 2–250 cc).

For the 11th question (Table 1), the majority of the respondents preferred SRS after intracranial metastasectomy, either alone or after WBRT. Thirty-seven (23%) respondents preferred WBRT alone, and only two (1%) respondents opted for observation. For the 12th question, 60% of the respondents had no corcerns when deciding to use SRS (Table 3). On the other hand, rapid intracranial progression, lack of scientific evidence and short survival were the main concerns when deciding for SRS treatment in patients with brain metastases of SCLC.

The impact of the type of institution, years of experience, number of cases seen per year and SRS availability in the institution on the respondent's approach for SRS were seperately analyzed. The treatment of choice in patients both with and without a prior PCI was not affected by most of the characteristics and experience of the respondents. Nevertheless, 69% of the respondents without SRS in their institution chose WBRT for patients with a prior PCI while 71% with SRS chose to apply SRS either alone or together with WBRT or surgery.

Similarly, while the type of institution, years of experience, and number of SCLC cases seen per year did not have a significant impact, the availability of SRS in their institution significantly affected the respondents while deciding for treatment after intracranial metastasectomy. Despite 62% of the respondents without SRS in their institution preferred

WBRT, 62% of those with SRS stated that they would perform SRS (p=0.013).

The number of SCLC cases seen per year significantly affected the responses to many questions. While 53% of the respondents that see >30 patients per year reported that performance status was important, 35%

Table 3 Responses to question 12 (What are your concerns regarding the use of SRS in patients with SCLC with brain metastases? You may select more than one option)

	n (%)
Rapid intracranial progression	83 (51)
Lack of sufficient evidence	46 (28)
Short survival	38 (23)
High cost	5 (3)
Limited access to SRS technology	13 (8)
I have no concerns	65 (40)

n: Number; SCLC: Small cell lung cancer.

of the respondents that see ≤30 patients considered it less important (p=0.006). Likewise, 51% of the respondents that see >30 patients per year thought that previous PCI was important for their treatment decision compared to 31% of the respondents that see ≤30 patients per year (p=0.024). The presence of extracranial disease also significantly affected the the respondents while deciding for treatment. Forty-two percent of more experienced respondents thought that it was important whereas 33% of the less experienced respondents thought so (p=0.008).

None of the characteristics significantly affected the treatment decision regarding the number or volume of brain metastases.

Nevertheless, as the number of SCLC patients seen per year increased, the concerns about performing SRS decreased and even disappeared in some respondents. While 34% of the respondents that see fewer cases had no concerns, the respective rate for the respondents that see more patients was 50% (p=0.074). The fear of rapid progression and short survival were significantly affected by the number of cases seen per year (p=0.018 and p=0.028, respectively). The respondents that see fewer patients per year were more concerned about short survival while the concerns decreased as the

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number of patients see per year increased. The concern for rapid progression was significantly increased in the respondents that see ≤30 patients per year (p=0.048). Similarly, the concern for a short survival was also increased when patients seen per year was ≤30 (p=0.033). There was a statistically significant difference between the respondents with and without SRS in their institution in terms of concerns for the lack of evidence. While no respondents without SRS had concerns about the lack of evidence, the respective rate for those with SRS was 31% (p=0.02). The distribution of concerns for the lack of evidence was similar across different institution types and years of experience.

DISCUSSION

This survey among Turkish radiation oncologists shows that the decision to perform SRS in patients with brain metastases of SCLC depend on the presence of a prior PCI, number and volume of metastases, and the availability of SRS. The majority of the respondents were experienced for treating SCLC patients with brain metastases which came with a decreased concern for deciding for SRS treatment. On the other hand, this survey is evidence that the more experienced the radiation oncologist is, the more complex the decision for SRS is. The performance status of the patient, prior PCI and extracranial disease were the most important factors while deciding for SRS.

Brain metastasis is frequently encountered in patients with SCLC and the management is often complicated. Cranial prophylaxis is recommended in patients without a brain metastasis. However, as cranial prophylaxis is known to negatively affect the neurocognitive functions, omitting prophylaxis and treating the metastasis with SRS once it develops is a frequently discussed option. Current approach is to perform WBRT for brain metastases of SCLC in patients without a prior PCI. Contemporary guidelines acknowledge SRS as an option in selected patients while adding WBRT to SRS is generally not recommended due to the absence of a demonstrated survival benefit and the risk of increased neurocognitive toxicity.[17] Similarly, there were also significant variations among the respondents in our survey. Whole brain RT, WBRT+SRS and SRS was preferred in patients with brain metastases without a prior PCI was 32%, 37%, and 26%, respectively.

In patients with a prior PCI, the optimal management strategy remains less clear due to limited prospective data.[14] Retrospective series have reported acceptable local control and survival outcomes with SRS for intracranial relapse after PCI, supporting its role as a reasonable salvage treatment option in selected patients.[18] Current guidelines also emphasize an individualized decision-making and often favor SRS when feasible rather than re-irradiation with WBRT.[17] Consistent with these observations, in our survey the majority of the respondents (88%) preferred SRS for the management of brain metastases in patients with a prior PCI.

Prognostic factors play an important role in treatment decisions in patients with brain metastases of SCLC. A study have consistently shown that several clinical variables including performance status, the number of brain metastases, total intracranial tumor volume, prior PCI and the presence or last status of extracranial disease play an important role in determining both survival outcomes and optimal treatment strategies.[19] However, increasing evidence from retrospective series has suggested that upfront SRS may be a reasonable alternative in carefully selected patients with a limited number of metastases, demonstrating comparable overall survival but higher rates of distant intracranial failure requiring close follow up via imaging and potential salvage therapy.[16] In our survey, the performance status, number of brain metastases, total intracranial tumor volume, a prior PCI and extracranial disease status significantly affected the treatment decision of the respondents.

Current evidence suggests that SRS may be considered in carefully selected patients with a limited number of lesions and low cumulative intracranial tumor volume.[20] Clinicians are increasingly considering both the number of lesions and the cumulative intracranial tumor volume when determining the eligibility for focal therapy.[21] In a study by Aizer et al.,[22] the neurological mortality rates were lower when SRS was used compared to WBRT in patients with 1–10 brain metastasis of SCLC. Furthermore, the authors reported a salvage brain RT rate of 22% during the follow-up period after SRS which is very low. On the other hand, the rate of a new brain metastasis was high after SRS. However, in this study, brain metastases were detected early with regular MRI follow-ups after SRS. Salvage SRS yielded disease control in most patients, reducing the need for an additional WBRT. These findings support the benefit of SRS in this patient population. In our survey, respondents influenced by both the number and total volume of brain metastases indicated a median threshold of 5 metastases and a median total intracranial tumor volume of 20 cc.

In a multi-institutional evaluation of SRS for brain metastases, the availability of SRS was found to be the strongest prognostic factor and more effective than the other clinical eligibility factors.[23] In our study, the most important factor determining the approach to treat a brain metastasis in the non-PCI group was having the availability of SRS.

In cases where surgical resection of brain metastases is performed, postoperative irradiation is generally recommended to reduce the risk of local recurrence.[24] Stereotactic radiosurgery directed to the surgical cavity has emerged as a potential alternative to WBRT, particularly because it may achieve comparable local control while minimizing neurocognitive toxicity associated with WBRT. The results of our survey demonstrated that Turkish radiation oncologists predominantly preferred postoperative SRS following brain metastasectomy in patients with SCLC. Furthermore, the availability of SRS was highly influential in the treatment selection for patients after metastasectomy.

In a survey conducted among the United States-based radiation oncologists, the number of brain metastasis was the most important factor followed by the performance status, cognitive function, and response to prior treatment when deciding for the RT technique.[25] Also, in an analysis conducted among European radiation oncologists and medical oncologists, WBRT followed by chemotherapy was the most frequently recommended treatment method for symptomatic patients with brain metastases of SCLC. On the other hand, some experts preferred SRS in patients with a limited number of metastases. Significant differences were observed in the clinical decision-making process among the European experts regarding the first-line treatment for patients with SCLC and brain metastases in that analysis.[26] In our survey, 23% of the respondents hesitated to perform SRS due to concerns of short survival in patients with SCLC. Also, the respondents that treat a higher number of patients per year were mostly affected by the performance status. We also observed that the respondents with a more extensive clinical experience assigned a greater significance to prior PCI.

This study has several limitations. The survey does not reflect the evolving treatment paradigms in the era of immunotherapy, nor does it address modern neurocognitive protection strategies such as memantine use or hippocampal avoidance techniques. Furthermore, current approaches integrating SRS with contemporary systemic treatments have not been evaluated. However, the results provide valuable insights into common approaches to managing brain metastasis in patients with SCLC. Future research that reflect modern clinical practices, particularly the integration of immunotherapy, neurocognitive protective RT strategies, and the increasing role of SRS in the management of brain metastasis from SCLC is warranted.

CONCLUSION

Due to the concerns about the rapid recurrence rate in other brain regions, 37% of the respondents participating in our study preferred adding SRS to WBRT in patients without a prior PCI. However, in patients with a prior PCI, the most preferred technique was SRS/SRT presumably to avoid toxicity. Our findings are consistent with the literature. The concern of a rapid progression increases as the number of metastatic lesions increases. As the experience of the respondents increases, they are more likely to choose SRS/SRT alone. While the respondents are justified in their concerns about the rapid appearance of a new brain metastasis, the less toxic and less time-consuming technique of SRS/SRT can become increasingly available in patients with a good performance and an opportunity to undergo regular MRI checkups.

Ethics Committee Approval: The study was approved by the Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital Ethics Committee (no: 2025-02/31, date: 20/02/2025).

Informed Consent: Informed consent was not needed for this study.

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REFERENCES

1. Krpina K, Vranic S, Tomic K, Samaržija M, Batičić L. Small cell lung carcinoma: Current diagnosis, biomarkers, and treatment options with future perspectives. Biomedicines 2023;11:1982.
2. Tian Y, Zhai X, Han A, Zhu H, Yu J. Potential immune escape mechanisms underlying the distinct clinical outcome of immune checkpoint blockades in small cell lung cancer. J Hematol Oncol 2019;12:67.
3. Quan AL, Videtic GM, Suh JH. Brain metastases in small cell lung cancer. Oncology (Williston Park) 2004;18:961–72.
4. Zhu Y, Cui Y, Zheng X, Zhao Y, Sun G. Small-cell lung cancer brain metastasis: From molecular mechanisms to diagnosis and treatment. Biochim Biophys Acta Mol Basis Dis 2022;1868:166557.
5. Zhang W, Jiang W, Luan L, Wang L, Zheng X, Wang G. Prophylactic cranial irradiation for patients with small-cell lung cancer: A systematic review of the literature with meta-analysis. BMC Cancer 2014;14:793.
6. Aupérin A, Arriagada R, Pignon JP, Péchoux CL, Gregor A, Stephens RJ, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. N Engl J Med 1999;341:476–84.
7. Slotman B, Faivre-Finn C, Kramer G, Rankin E, Snee M, Hatton M, et al. Prophylactic cranial irradiation in extensive small-cell lung cancer. N Engl J Med 2007;357:664–72.
8. Wang Z, Chen L, Sun L, Cai F, Yang Q, Hu X, et al. Prophylactic cranial irradiation for extensive stage small cell lung cancer: A meta-analysis of randomized controlled trials. Front Oncol 2023;13:1086290.
9. Gondi V, Pugh SL, Tome WA, Caine C, Corn B, Kanner A, et al. Preservation of memory with conformal avoidance of the hippocampal neural stem-cell compartment during whole-brain radiotherapy for brain metastases (RTOG 0933): A phase II multi-institutional trial. J Clin Oncol 2014;32:3810–6.
10. Rodríguez de Dios N, Couñago F, Murcia-Mejía M, Rico-Oses M, Calvo-Crespo P, Samper P, et al. Randomized phase III trial of prophylactic cranial irradiation with or without hippocampal avoidance for small-cell lung cancer (PREMER): A GICOR-GOECP-SEOR study. J Clin Oncol 2021;39:3118–27.
11. Maragkoudakis E, Kouloulias V, Grenzelia M, Kougioumtzopoulou A, Zygogianni A, Ramfidis V, et al. Impact of hippocampal avoidance-prophylactic cranial irradiation in small cell lung cancer patients. Cancer Diagn Progn 2022;2:279–84.
12. Gondi V, Pugh SL, Mehta MP, Wefel JS, Tomé WA, Sun AY, et al. Hippocampal avoidance during prophylactic cranial irradiation for patients with small cell lung cancer: Randomized phase II/III trial NRG-CC003. J Clin Oncol 2025;43:3516–25.
13. Rusthoven CG, Kavanagh BD. Prophylactic cranial irradiation (PCI) versus active MRI surveillance for small cell lung cancer: The case for equipoise. J Thorac Oncol 2017;12:1746–54.
14. Rusthoven CG, Yamamoto M, Bernhardt D, Smith DE, Gao D, Serizawa T, et al. Evaluation of first-line radiosurgery vs whole-brain radiotherapy for small cell lung cancer brain metastases: The FIRE-SCLC cohort study. JAMA Oncol 2020;6:1028–37.
15. Hartgerink D, van der Heijden B, De Ruysscher D, Postma A, Ackermans L, Hoeben A, et al. Stereotactic radiosurgery in the management of patients with brain metastases of non-small cell lung cancer: Indications, decision tools and future directions. Front Oncol 2018;8:154.
16. Robin TP, Rusthoven CG. Radiosurgery for small-cell lung cancer brain metastases: A review. J Thorac Dis 2020;12:6234–9.
17. National Comprehensive Cancer Network. NCCN guidelines version 2.2026: Small cell lung cancer. J Natl Compr Canc Netw 2026;24(1):e260002.
18. Bernhardt D, Bozorgmehr F, Adeberg S, Opfermann N, Eiff DV, Rieber J, et al. Outcome in patients with small cell lung cancer re-irradiated for brain metastases after prior prophylactic cranial irradiation. Lung Cancer 2016;101:76–81.
19. Rades D, Dziggel L, Segedin B, Oblak I, Nagy V, Marita A, et al. The first survival score for patients with brain metastases from small cell lung cancer (SCLC). Clin Neurol Neurosurg 2013;115:2029–32.
20. Wang VH, Juneja B, Goldman HW, Turtz A, Bilbao C, Xu Q, et al. Stereotactic radiosurgery for brain metastases in patients with small cell lung cancer. Adv Radiat Oncol 2023;8:101237.
21. Viani GA, Gouveia AG, Louie AV, Moraes FY. Stereotactic radiosurgery for brain metastases from small cell lung cancer without prior whole-brain radiotherapy: A meta-analysis. Radiother Oncol 2021;162:45–51.
22. Aizer AA, Tanguturi SK, Shi DD, Catalano PJ, Shin K, Ricca I, et al. Stereotactic radiosurgery in patients with small cell lung cancer and 1–10 brain metastases: A multi-institutional, phase II, prospective clinical trial. J Clin Oncol 2025;43:2986–97.
23. Hodgson DC, Charpentier AM, Cigsar C, Atenafu EG, Ng A, Bajl G, et al. A multi-institutional study of factors influencing the use of stereotactic radiosurgery for brain metastases. Int J Radiat Oncol Biol Phys 2013;85:335–40.
24. Gondi V, Bauman G, Bradfield L, Burri SH, Cabrera AR, Cunningham DA, et al. Radiation therapy for brain metastases: An ASTRO clinical practice guide-

line. Pract Radiat Oncol 2022;12:265–82.
25. Gjyshi O, Lin SH, Pezzi TA, Ning MS, Ma J, Liu S, et al. Care patterns for stereotactic radiosurgery in small cell lung cancer brain metastases. Clin Lung Cancer 2022;23:185–90.
26. Putora PM, Fischer GF, Früh M, Califano R, Faivre-Finn C, Houtte PV, et al. Treatment of brain metastases in small cell lung cancer: Decision-making amongst a multidisciplinary panel of European experts. Radiother Oncol 2020;149:84–8.

Dear Colleague,

First of all, we would like to thank you for participating in this survey.
By taking part in this study, you will share your institution's approach to the management of patients with brain metastases from small cell lung cancer.
Through this nationwide survey conducted across Turkey, we aim to obtain an overall perspective on current clinical practices for the treatment of these patients.
All information collected will be used solely for research purposes. No personal data will be shared, and the results of the survey will be presented anonymously.

Thank you for your valuable contribution.

1. How old are you?

____ years

2. What is the type of institution you currently work in?
(Please select one)

☐ University Hospital

☐ Training and Research Hospital

☐ Private Hospital

☐ Public (State) Hospital

3. How many years have you been practicing as a radiation oncologist?

☐ 0–5 years

☐ 6–10 years

☐ 11–20 years

☐ 21 years or more

4. How many small cell lung cancer (SCLC) cases do you see per year?

☐ 1–10

☐ 11–30

☐ 31–50

☐ ≥51

5. Does your institution have the facility and equipment to perform stereotactic radiosurgery (SRS)?
(Please select one)

☐ Yes

☐ No

6. What is your preferred approach for patients who develop brain metastases after prophylactic cranial irradiation (PCI)?
(Please select one)

☐ Surgery

☐ Whole-brain radiotherapy (WBRT)

☐ Stereotactic radiosurgery (SRS)

7. What is your preferred treatment approach for patients with SCLC who present with brain metastases and have not received PCI?
(Please select one)

☐ Whole-brain radiotherapy (WBRT)

☐ Stereotactic radiosurgery (SRS)

☐ WBRT followed by SRS

☐ Surgery

☐ Surgery followed by cavity-directed SRS

8. To what extent do the following factors influence your treatment decision in patients with brain metastases in SCLC?

	Never	Rarely	Sometimes	Often	Definitely
Performance status	☐	☐	☐	☐	☐
Number of brain metastases	☐	☐	☐	☐	☐
Total intracranial tumor volume	☐	☐	☐	☐	☐
Prior prophylactic cranial irradiation (PCI)	☐	☐	☐	☐	☐
Extracranial disease status	☐	☐	☐	☐	☐

9. If the number of brain metastases influences your decision to perform SRS, what is the maximum number of metastases for which you would consider SRS?

____ metastases

10. If the total intracranial tumor volume influences your decision to perform SRS, what is the maximum total tumor volume (in cc) for which you would consider SRS?

____ cc

11. What is your preferred approach for a patient who has undergone intracranial metastasectomy? *(Please select one)*

☐ Whole-brain radiotherapy (WBRT)

☐ Stereotactic radiosurgery (SRS)

☐ WBRT followed by SRS

☐ Observation / Follow-up

☐ Other: _____

12. What are your concerns regarding the use of SRS in patients with SCLC with brain metastases?*(You may select more than one option)*

☐ Rapid intracranial progression

☐ Lack of sufficient evidence

☐ Short overall survival

☐ High cost

☐ Limited access to SRS technology

☐ I have no concerns

☐ Other: _____

TURKISH JOURNAL of ONCOLOGY

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ORIGINAL ARTICLE

Extramedullary Plasmacytoma of the Head and Neck: A Retrospective Study

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OBJECTIVE

Solitary extramedullary plasmacytomas (SEP) are rare plasma cell tumors that primarily occur in the head and neck regions. Due to their rarity, retrospective series can provide valuable insights into their clinical behavior and management, contributing to the refinement of treatment strategies. This study aimed to report cases of SEPs in the head and neck region treated with radiotherapy (RT) over the last 20 years.

METHODS

Ten patients were enrolled in this study between January 2004 and January 2024. Their clinicopathological features and treatment protocols were recorded, and disease outcomes were analyzed.

RESULTS

The most common tumor site was the nasopharynx (n=5), followed by the nasal cavity (n=2). Nine of ten patients were initially treated with RT at the primary site. The median RT dose was 45.5 Gy (40–58). Complete response (CR) was achieved in nine of 10 patients. The median survival duration was 74 months. The 5-year progression-free survival (PFS) rate was 85%. Only one patient developed a new bone plasmacytoma during the follow-up. No patient experienced transformation to multiple myeloma.

CONCLUSION

The prognosis of SEP is favorable, with rare recurrence, metastasis, and transformation to multiple myeloma. Further multicenter prospective studies are necessary to optimize management strategies for this rare entity.

Keywords: Extramedullary plasmacytoma; head and neck; nasal cavity; nasopharynx; solitary plasmacytoma.
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INTRODUCTION

Solitary plasmacytomas are a subset of plasma cell neoplasms, ranging from monoclonal gammopathy of undetermined significance to multiple myeloma (MM).[1] Histologically, they are characterized by increased proliferation of plasma cells. Unlike MM, solitary plasmacytomas do not exhibit end-organ damage or widespread bone involvement. These tumors account for 5% of all plasma cell neoplasms and can be categorized as solitary extramedullary plasmacytomas (SEPs) or solitary bone plasmacytomas.[2] SEPs constitute one-third of all plasmacytoma cases.[3]

Extramedullary solitary plasmacytomas can develop throughout the body, with a predilection for the head and neck region.[3] These tumors typically reside sub-

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mucosally in the upper respiratory tract and often lead to symptoms such as obstruction, swelling, and bleeding.[4] The median age at SEP diagnosis is the 5th or 6th decade, approximately 10 years younger than that for MM diagnosis.[5,6] A notable sex disparity has been reported in SEP cases, with two-thirds of the patients being male.[7] Diagnostic evaluation involves a comprehensive approach including medical history taking, physical examination, blood tests, imaging studies, bone marrow biopsy, serum protein electrophoresis, urine evaluation for myeloma proteins, and skeletal survey.[1]

The rarity of SEPs has resulted in a paucity of high-level evidence regarding their treatment. Given the radiosensitivity of these tumors, radical RT is typically administered after biopsy.[8] RT doses reported in case reports from the 1950s to the present vary widely, ranging from 35 to 65 Gy.[8–10] Local control rates following RT have been reported to range from 80% to 100%.[8–15] The benefits of elective lymphatic irradiation remain unclear, and it is generally not recommended.[7]

Surgical intervention is not initially advised because of the challenges associated with achieving complete tumor removal and the potential for morbidity in the head and neck region.[8,16] Adjuvant RT is often necessary even when surgical excision is performed. Some case studies have suggested that combined treatment modalities may result in improved local control.[7] The role of systemic therapy at the plasmacytoma stage remains unclear, and it is not routinely recommended.[2]

RT achieves high local control rates during the treatment of plasmacytomas. However, posttreatment disease progression can manifest as local recurrence, new plasmacytoma sites (most commonly in the bone), or transformation to MM. Transformation to MM is less frequent in patients with extramedullary plasmacytomas than in those with bone plasmacytomas.[7] Progression to MM is a significant prognostic factor for survival. Various factors, such as tumor size, bone involvement, and radiation dose, have been investigated for their predictive value.[3,5,7,13] Nonetheless, the very low incidence of this tumor type precludes the optimal determination of predictive factors without prospective studies.

Given the rarity of SEPs, insights from retrospective studies are essential for bridging existing knowledge gaps, refining treatment protocols, and providing a foundation for future research to improve patient care and prognosis. Understanding the clinical behavior of these tumors, particularly in the head and neck region, is crucial for tailoring effective and individualized treatment strategies. This study aims to evaluate the clinical features and treatment management of SEPs in the head and neck region reported over the last 20 years at Istanbul University Oncology Institute and Koç University.

MATERIALS AND METHODS

The medical records of all patients treated for SEPs of the head and neck at the two institutions between January 2004 and January 2024 were retrospectively reviewed. The Istanbul University Oncology Institute Review Board approved this study (Date: 29/04/2025, No: 2025/1174) and the study is conducted according to Declaration of Helsinki. Patient demographic data, initial tumor presentation, treatment details and survival outcomes were retrieved from institutional databases. Written informed consent was obtained from the all patients.

The inclusion criteria were as follows:[17]

1. Histologically confirmed plasmacytoma of the soft tissue of the head and neck region,
2. Normal skeletal survey,
3. Normal bone marrow biopsy,
4. No evidence of end-organ damage (anemia, hypercalcemia, renal insufficiency).

Patients with solitary bone lesions were excluded. Ten patients from two institutions were analyzed.

Systemic staging for all patients included physical examination, complete blood counts, biochemical analysis, serum and urine protein electrophoresis, and bone marrow aspiration/biopsy. Regarding imaging modalities, while positron emission tomography (PET-CT) has been performed systematically for initial staging and follow-up since its clinical introduction in our center in 2009, staging for patients treated prior to this period relied on conventional methods, including skeletal surveys (plain radiography) and/or magnetic resonance imaging (MRI) or computed tomography (CT).

Response assessment was typically performed 3 to 6 months after the completion of therapy, preferably utilizing MRI and/or PET-CT scans. Treatment response was assessed using the RECIST (Response Evaluation Criteria in Solid Tumors) criteria v1.1, where CR was defined as the disappearance of all target lesions on follow-up imaging.

Following the completion of RT, patients were followed concurrently by radiation oncology and hematology clinics every 3 months for the first 2 years, every 6 months for the subsequent 3 years, and annually thereafter. Follow-up evaluations consisted of physical and endoscopic examinations, laboratory tests (including complete blood count, biochemistry, and serum

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Table 1 Clinical characteristics of patients with solitary extramedullary plasmacytomas

Patient	Age	Sex	Tumor location	Tumor diameter (cm)	Bone erosion	Immunohistochemical analysis	First surgery	PET-CT	Bone marrow biopsy
1	37	M	Maxillary sinus	3.1	No	Plasma cell infiltration	Right maxillectomy	No	Normocellular
2	63	M	Nasopharynx	2	No	Lambda type	Biopsy	Yes	Normocellular
3	68	M	Nasopharynx	2.3	No	Lambda type	Biopsy	No	3–5% plasma cells
4	57	M	Nasopharynx	2.3	No	Kappa type	Excisional biopsy	Yes	<5% plasma cells
5	51	M	Larynx	1	No	Lambda type	Biopsy	Yes	<5% plasma cells
6	49	M	Nasopharynx	2.2	No	Kappa type	Biopsy	Yes	3–5% plasma cells
7	83	M	Nasal cavity	6.5	Yes	Lambda type	Biopsy	Yes	3% plasma cells
8	44	M	Gingiva	2.7	Yes	Plasma cell infiltration	Biopsy	Yes	3–5% plasma cells
9	66	M	Nasopharynx	2.3	No	Kappa type	Biopsy	Yes	Normocellular
10	70	F	Nasal cavity	2.2	No	Kappa type	Biopsy	Yes	Normocellular

M: Male; F: Female; PET-CT: Positron emission tomography.

protein electrophoresis), and imaging (CT or MRI of the head and neck). PET-CT was performed in cases of clinical or radiological suspicion to assess local control or potential systemic progression.

Statistical Analysis

The data were analyzed, and categorical variables were summarized by frequency and percentage, and quantitative variables, by median and range. Statistical analyses were performed using IBM SPSS, version 26.0, program. Progression-free survival was calculated from the date of diagnosis to any type of disease progression. Overall survival was calculated from the date of diagnosis to death or the last follow-up date. Survival curves were plotted using the Kaplan–Meier method.

RESULTS

Ten patients were diagnosed with SEPs in the head and neck region, nine of whom were male. The median patient age was 60 (range: 37–83). Detailed clinicopathologic data are presented in Table 1.

The majority of cases (80%) were localized in the sinonasal area, with the nasopharynx being the most frequent site. Immunohistochemistry showed an equal distribution of kappa and lambda light-chain predominance. Systemic involvement was ruled out in all patients; PET-CT scans performed in eight patients (80%) showed no distant metastasis. Bone marrow biopsies confirmed less than 5% plasma cell infiltration in all cases.

Diagnostic biopsy was the primary surgical intervention in eight patients, while two cases required more extensive procedures: one excisional biopsy for a nasopharyngeal tumor and one maxillectomy for a maxillary sinus tumor. All 10 patients received RT as the definitive treatment, with a median dose of 45.5 Gy (range: 40–58 Gy). The majority (n=7) were treated with intensity-modulated radiation therapy (IMRT), and one patient received elective neck irradiation.

Regarding clinical outcomes, nine patients (90%) achieved CR. One patient exhibited minimal residual disease on PET-CT and MRI three months post-RT; however, the lesion remained stable during 16 months of radiological follow-up (Table 2).

The median survival time was 74 months (range: 13–187 months), with a 5-year PFS rate of 85% (Fig. 1). During the follow-up period, only one patient developed a solitary bone plasmacytoma, and treated with systemic treatment. None of the patient's condition progressed to MM.

DISCUSSION

Most plasma cell neoplasms are MM, with solitary plasmacytomas accounting for approximately 5–6% of all plasma cell neoplasms.[2] Of the solitary plasmacytomas, approximately 20–30% are extramedullary and often occur in the head and neck region.[3,18] Over the past 20 years, Istanbul University Oncology Institute and Koç University treated 10 patients with extramedullary plasmacytomas in the head and neck region. In our cohort, nine of ten patients achieved CR, with an overall survival of 100% and a five-year PFS rate of 85% at the last follow-up.

Table 2 Treatment characteristics of patients with solitary extramedullary plasmacytomas

Parameter	Subgroup	n	PR (n)	New lesion (n)	MM (n)
Tumor size	≤5 cm	9	0	1	0
	>5 cm	1	1	0	0
Bone erosion	Absent	8	0	1	0
	Present	2	1	0	0
Anatomic Site	Sinonasal	8	1	1	0
	Others	2	0	0	0
RT Dose	40–45 Gy	5	0	0	0
	>45 Gy	5	1	1	0
Treatment modality	Definitive RT	8	1	1	0
	Surgery + RT	2	0	0	0
RT technique	IMRT	7	1	1	0
	2DRT	3	0	0	0

RT: Radiotherapy; Gy: Gray; MM: Multiple myeloma; 2DRT: Two-dimensional radiotherapy; IMRT: Intensity-modulated radiotherapy; PR: Partial response.

Extramedullary plasmacytomas tend to recur locally, and progression to MM is less common in this patient group than in patients with bone plasmacytomas, affecting 10–30% of the patients over a decade.[2] Nevertheless, owing to the risk of progression to MM, these patients require ongoing hematological monitoring. Progression from a plasmacytoma to MM can take years, making long-term follow-up crucial for understanding the prognosis. In our cohort, none of the patients experienced local recurrence or progression to MM, despite 60% of our sample having a follow-up period exceeding five years. Although one patient developed a new solitary bone plasmacytoma, this was successfully managed with salvage therapy.

In a meta-analysis of 315 patients, the most common site of involvement was the sinonasal region (paranasal sinuses, 22.3%; nasal cavity, 17.5%; nasopharynx, 10.8%).[7] Furthermore, the Surveillance, Epidemiology, and End Results (SEER) analysis of 690 patients found that nasal cavity and paranasal sinus involvement accounted for 32.3% of the cases, while nasopharyngeal involvement was not reported separately.[19] In our study, eight of the 10 patients had tumors located in the sinonasal region.

For patients with SEPs, the presence of bone erosion and a tumor diameter exceeding five cm are associated with worse survival and an increased risk of progression to MM.[7,13] Large tumors, especially those involving the sinonasal region, present significant surgical challenges and are often managed primarily with RT. One patient in our cohort with a bulky tumor and extensive nasal cavity bone invasion exhibited residual anatomic and metabolic findings at the initial post-RT evaluation. Despite these features, the lesion has remained stable over 16 months of follow-up without additional intervention. Similarly, another patient with mandibular bone destruction achieved a CR despite minimal post-treatment FDG uptake and persistent minor bone erosion on imaging. These cases indicate that in highly radiosensitive tumors like SEP, post-treatment imaging findings even in the presence of initial bone destruction must be interpreted with caution to avoid unnecessary over-treatment.

For the treatment of SEPs in the head and neck region, RT is typically administered as the primary treat-

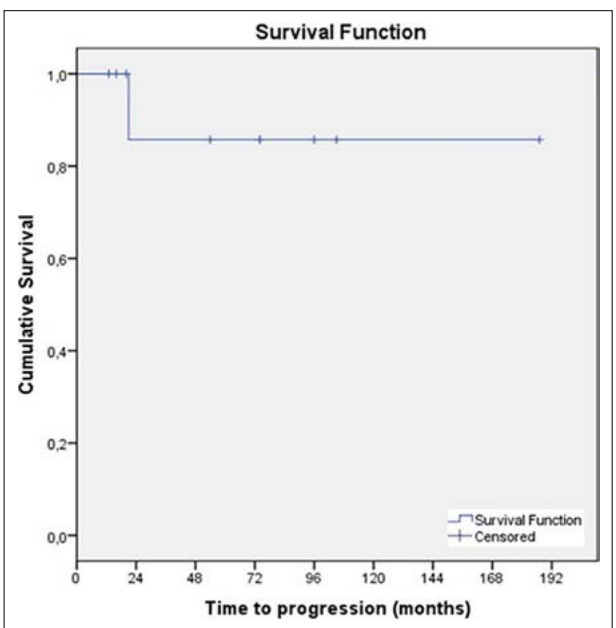


Fig. 1. Progression-free survival curve of 10 patients.

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ment option, with a local control rate of up to 80%.[8–15] Owing to the high risk of morbidity and radiosensitivity, surgery is generally not the preferred primary treatment option. Achieving clear surgical margins is challenging, and RT is often administered in addition to surgery. Some studies have reported higher local control rates when surgery and RT are combined.[7] In our series, the majority of patients (n=8) were treated with definitive RT alone, and none experienced local recurrence or progression. A recent meta-analysis by Vasudevan et al.[20] examined 742 patients with SEPs in 12 studies, including those with tumors outside the head and neck region. They found that patients who received RT had significantly lower rates of progression to MM than those treated with surgery alone. The authors attributed this finding to the ability of RT to provide sufficient coverage of microscopic residual tumor cells, which may be missed during surgical excision. Within the limitations of our small cohort, these outcomes are consistent with the view that RT can be effective as a standalone treatment for SEPs in the head and neck region.

In various studies, the radiation dose administered for treating head and neck SEPs ranges from 30 to 65 Gy.[8–10] Evidence suggests that doses exceeding 40 Gy or 45 Gy improve local control.[7,10,21] The International Lymphoma Radiation Oncology Group (ILROG) guidelines recommend a radical treatment dose of 40–50 Gy for head and neck SEPs.[2] Nevertheless, establishing RT dosing guidelines remains challenging owing to the limited number of prospective studies, and the correlation between the RT dose and PFS warrants further investigation. In our series, the median radiation dose was 45.5 Gy and radiation doses ranged from 40 to 58 Gy. Even at the minimum dose of 40 Gy, all patients (n=3) achieved a CR and maintained long-term local control. The use of higher doses (up to 58 Gy) in some cases reflected individualized treatment decisions from the earlier years of the study.

SEPs are generally localized diseases, with neck metastasis occurring in 5–20% of the cases.[7] Advances in radiological imaging technologies have facilitated the detection of neck metastases. During follow-up, neck recurrence is observed in approximately 5% of patients, and salvage treatments demonstrate a high success rate. Therefore, elective lymphatic irradiation during RT is controversial and its benefit is unclear if neck metastasis is not detected.[7] According to ILROG guidelines, elective lymphatic irradiation is not recommended unless there is a high risk of metastasis, as observed in patients with bulky tumors.[2] In our series, elective neck treatment was administered to only one patient.

Our study covers a 20-year period, which inherently introduces some heterogeneity due to advancements in RT techniques and imaging modalities. The transition from 2D-RT to modern techniques like IMRT represents a significant shift in treatment precision. Despite these technological differences, the consistently high local control rates were observed across our cohort. The outcomes observed in our study, although based on a limited number of patients, are broadly consistent with the reported literature on head and neck SEPs. However, due to the inherent limitations of a small, retrospective cohort, our results should be interpreted with caution and validated by larger, multicenter pooled analyses.

Limitations of the Study

This is a retrospective study with a small number of patients. Since patients were collected over a long period of 20 years, there is variability in the RT techniques, radiation fields and doses administered. In rare tumors like SEP, where treatment approaches are based on retrospective data, there can be significant differences in approach even among physicians in the same clinic.

CONCLUSION

This study indicates that RT provides high local control and a favorable prognosis for SEPs of the head and neck. Although no progression to MM was observed within this cohort, the potential for late systemic transformation warrants long-term multidisciplinary monitoring. Given the rarity of the disease and the limited sample size, these findings should be interpreted as exploratory, underscoring the need for larger multicenter studies to further optimize management strategies.

Ethics Committee Approval: The study was approved by the Istanbul University Ethics Committee (no: 2025/1174, date: 29/04/2025).

Informed Consent: Written informed consent was obtained from all patients.

Conflict of Interest Statement: The authors declare that there is no conflict of interest.

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REFERENCES

1. Rajkumar SV. Multiple myeloma: 2022 Update on diagnosis, risk stratification, and management. Am J Hematol 2022;97:1086–107.
2. Tsang RW, Campbell BA, Goda JS, Kelsey CR, Kirova YM, Parikh RR, et al. Radiation therapy for solitary plasmacytoma and multiple myeloma: Guidelines from the International Lymphoma Radiation Oncology Group. Int J Radiat Oncol Biol Phys 2018;101:794–808.
3. Thumallapally N, Meshref A, Mousa M, Terjanian T. Solitary plasmacytoma: Population-based analysis of survival trends and effect of various treatment modalities in the USA. BMC Cancer 2017;17:13.
4. Wiltshaw E. The natural history of extramedullary plasmacytoma and its relation to solitary myeloma of bone and myelomatosis. Medicine 1976;55:217–38.
5. Kilciksiz S, Karakoyun-Celik O, Agaoglu FY, Haydaroglu A. A review for solitary plasmacytoma of bone and extramedullary plasmacytoma. ScientificWorldJournal 2012;2012:895765.
6. Caers J, Paiva B, Zamagni E, Leleu X, Bladé J, Kristinsson SY, et al. Diagnosis, treatment, and response assessment in solitary plasmacytoma: Updated recommendations from a European Expert Panel. J Hematol Oncol 2018;11:10.
7. Venkatesulu B, Mallick S, Giridhar P, Upadhyay AD, Rath GK. Pattern of care and impact of prognostic factors on the outcome of head and neck extramedullary plasmacytoma: A systematic review and individual patient data analysis of 315 cases. Eur Arch Otorhinolaryngol 2018;275:595–606.
8. Sasaki R, Yasuda K, Abe E, Uchida N, Kawashima M, Uno T, et al. Multi-institutional analysis of solitary extramedullary plasmacytoma of the head and neck treated with curative radiotherapy. Int J Radiat Oncol Biol Phys 2012;82:626–34.
9. Susnerwala SS, Shanks JH, Banerjee SS, Scarffe JH, Farrington WT, Slevin NJ. Extramedullary plasmacytoma of the head and neck region: Clinicopathological correlation in 25 cases. Br J Cancer 1997;75:921–7.
10. Tournier-Rangeard L, Lapeyre M, Graff-Caillaud P, Mege A, Dolivet G, Toussaint B, et al. Radiotherapy for solitary extramedullary plasmacytoma in the head--and-neck region: A dose greater than 45 Gy to the target volume improves the local control. Int J Radiat Oncol Biol Phys 2006;64:1013–37.
11. Bolek TW, Marcus RB, Mendenhall NP. Solitary plasmacytoma of bone and soft tissue. Int J Radiat Oncol Biol Phys 1996;36:329–33.
12. Jyothirmayi R, Gangadharan VP, Nair MK, Rajan B. Radiotherapy in the treatment of solitary plasmacytoma. Br J Cancer 1997;70:511–6.
13. Tsang RW, Gospodarowicz MK, Pintilie M, Bezjak A, Wells W, Hodgson DC, et al. Solitary plasmacytoma treated with radiotherapy: Impact of tumor size on outcome. Int J Radiat Oncol Biol Phys 2001;50:113–20.
14. Soutar R, Lucraft H, Jackson G, Reece A, Bird J, Low E, et al. Guidelines on the diagnosis and management of solitary plasmacytoma of bone and solitary extramedullary plasmacytoma. Br J Haematol 2004;124:717–26.
15. Creach KM, Foote RL, Neben-Wittich MA, Kyle RA. Radiotherapy for extramedullary plasmacytoma of the head and neck. Int J Radiat Oncol Biol Phys 2009;73:789–94.
16. Harwood AR, Knowling MA, Bersagel DE. Radiotherapy of the extramedullary plasmacytoma of the head and neck. Clin Radiol 1981;32:31–6.
17. Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos MV, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol 2014;15:e538–48.
18. Ozsahin M, Tsang RW, Poortmans P, Belkacémi Y, Bolla M, Dinçbas FO, et al. Outcomes and patterns of failure in solitary plasmacytoma: A multicenter rare cancer Network study of 258 patients. Int J Radiat Oncol Biol Phys 2006;64:210–7.
19. Gerry D, Lentsch EJ. Epidemiologic evidence of superior outcomes for extramedullary plasmacytoma of the head and neck. Otolaryngol Head Neck Surg 2013;148:974–81.
20. Vasudevan SS, Sayed SBH, Kapartiwar P, Pang J, Asarkar AA, Olinde L, et al. Radiotherapy vs surgery for survival and locoregional control of head and neck extramedullary plasmacytoma: A systematic review and meta-analysis. JAMA Otolaryngol Head Neck Surg 2024;150:887–95.
21. Oertel M, Elsayad K, Kroeger KJ, Haverkamp U, Rudack C, Lenz G, et al. Impact of radiation dose on local control and survival in extramedullary head and neck plasmacytoma. Radiat Oncol 2019;14:63.

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ORIGINAL ARTICLE

Efficacy of Portable Bladder Ultrasound in Reducing CBCT Frequency During Pelvic Radiotherapy

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OBJECTIVE

The aim of this study was to investigate the effect of the use of bladder ultrasonography (USG) on time and workforce efficiency in patients with prostate, bladder, cervix, endometrium and rectal cancer undergoing curative pelvic radiotherapy (RT) in a radiation oncology clinic.

METHODS

The study included 142 patients who underwent pelvic RT. The prospective study group (n=71) underwent bladder USG, while the other patients included in the study (n=71) who received standard treatment were designated as the retrospective historical control group. All patients underwent planning tomography (CT), set-up verification was performed with cone beam computed tomography (CBCT) in the first 3 fractions and then evaluated with CBCT once a week. All analyses were performed using IBM SPSS Statistics Version 25 package program. A value of $P<0.05$ was determined as the significance level.

RESULTS

Patients who did not undergo USG underwent 846 CBCTs and patients who underwent USG underwent 809 CBCTs. Although not significant, fewer CBCTs were performed in the USG group. When patients with prostate cancer were analyzed; 37 patients with prostate cancer who did not undergo USG had a total of 476 CBCTs at the end of treatment. In 37 patients with prostate cancer who underwent USG, a total of 427 CBCTs were performed. The difference between these two groups was statistically significant (p=0.009).

CONCLUSION

In patients undergoing pelvic RT, both pre-planning CT and pre-treatment USG were used to determine bladder fullness.

Keywords: Cone beam computed tomography; pelvic neoplasms; radiotherapy; urinary bladder; ultrasonography.
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INTRODUCTION

Every year 150,000-300,000 people worldwide are treated with pelvic radiotherapy (RT), mostly for cancers of the rectum, bladder, prostate, cervix and endometrium.[1,2] While pelvic RT aims to eradicate cancerous tissues, it can also cause radiation-induced side effects on surrounding healthy organs and tissues. Hence, organ mobility and dose distribution should be carefully evaluated in treatment planning. In patients undergoing pelvic RT, rectum and bladder fullness are important determinants of organ doses at risk. Bladder fullness at the same volume as the planning computed tomography (CT) will ensure that the radiation dose

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received by organs at risk is at levels accepted during planning. In patients undergoing pelvic RT for curative purposes, it is recommended that the bladder be full during treatment in order to reduce intestinal doses.[3,4] For this purpose, patients who will undergo pelvic RT are asked to drink water in moderation before each treatment, and after waiting for a certain period of time and taking into account the patient's statement regarding urinary urgency, the treatment phase is started.[5] However, bladder fullness cannot always be achieved at the intended level due to many factors such as individual patient-related differences, changes occurring during the disease process, hydration level and physiologic responses to treatment, and this may prevent the lower intestinal doses provided by bladder fullness. In addition, since changes in bladder fullness may cause target organ movement, inadequate dose coverage will occur unless very large margins are used.[6] Failure to achieve adequate bladder fullness may cause undesired side effects and may present an undesirable therapeutic index with worse oncologic outcomes. With the bladder fullness protocols in clinics, pelvic RT is administered after drinking a certain amount of water and waiting for a standard period of time, taking into account the patient's statement, but in case of insufficient fullness, the completion time of each radiotherapy fraction is prolonged, more cone beam computed tomography (CBCT) is taken and this interrupts routine clinical processes and work. Especially in underdeveloped and developing countries, prolongation and delays in treatments are undesirable considering the access to RT machines and the number of patients per machine. Repeated CBCT imaging due to field mismatch will increase the total radiation dose received by patients and the risk of long-term side effects in these patients. Inadequate bladder filling may lead to increased bowel doses, while overfilling of the bladder may negatively affect patient comfort and lead to additional complications during the treatment process. In addition, the bladder volume on planning CT should be in the same position and fullness as on planning CT in each fraction for an accurate treatment. Therefore, it is of great importance to follow the bladder preparation protocol of the clinic and to measure bladder fullness with an objective assessment method and to manage the treatment process accordingly.

In our study, we evaluated bladder filling in patients undergoing curative pelvic RT using a portable handheld ultrasound (USG) device before the planning CT scan and before CBCT during RT sessions. We investigated whether the use of USG reduced the need for repeated CBCT scans when bladder filling was found to be inadequate. USG is a non-invasive and rapid method that allows for a more effective assessment of bladder fullness without negatively impacting the patient's treatment process. In our study, we aimed to evaluate whether the use of USG can be integrated into clinical practice to increase patient compliance and comfort, reduce unnecessary radiation exposure, and contribute to making treatment more efficient by shortening the treatment preparation process.

MATERIALS AND METHODS

Patient Characteristics

This non-randomized study included a total of 142 patients who underwent curative pelvic RT for prostate, endometrial, cervical, rectal, and bladder cancer. Inclusion criteria were age >18 years, Karnofsky Performance Status (KPS)>60, confirmation of a histopathologic diagnosis, and completion of curative pelvic RT. Patients with KPS<60, those who did not complete their treatment, and those who underwent palliative pelvic RT were excluded from the study.

The study utilized a prospective cohort with a retrospectively matched historical control group. The study group (n=71) undergoing pre-treatment mobile bladder USG assessment was enrolled prospectively through consecutive recruitment between January 2023 and October 2023. To form the control group without USG (n=71), medical records of patients who had previously received standard treatment between January 2022 and December 2022 were retrospectively screened.

To minimize selection bias, these historical control patients were matched 1:1 to the prospective study group based strictly on their primary diagnosis. Therefore, the distribution of the 71 patients was identical in both groups: 37 had prostate cancer, 14 had endometrial cancer, 10 had cervical cancer, 9 had rectal cancer, and 1 had bladder cancer.

Ethics committee approval was obtained from the institutional non-interventional clinical research ethics board on 18.01.2022 (Approval No: E-25403353-050.99-296077) and the study is conducted according to Declaration of Helsinki. This study was supported by an institutional scientific research project grant (Project No: TSA-2022-2416).

Set-Up and Treatment Planning

Planning CT scans were obtained using a Siemens Somatom Definition AS model with a 2.5 mm slice thick-

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ness, from the end of the liver to the middle of the femur. During treatment, patients were evaluated with CBCT in the first three fractions and subsequently once a week. According to our clinic protocol, patients were instructed to empty their bladder, drink 1 liter of water within 30 minutes, and wait for another 30 minutes before the planning CT scan. This procedure was repeated before each treatment session. Patients were treated with Varian Truebeam version 2.7 and Varian Trilogy version 9.1.1 devices.

Half of the patients included in the study (n=71) underwent a mobile bladder USG before the planning CT and each CBCT. The transverse diameter was measured by a single radiation oncologist in the outpatient treatment room just before the patient was taken to the treatment room to assess bladder fullness. A SeaMed C3 Handheld Ultrasound with a convex probe was used. If the bladder diameter measured during the planning CT was not reproduced within a tolerance limit of ±5 mm, treatment was not initiated, and the set-up process was repeated. The remaining patients (n=71), who did not undergo USG assessment, constituted the control group. The number of CBCT scans in the USG group was compared with that of the control group.

Statistical Analysis

Statistically, the conformity of continuous variables to normal distribution according to groups was evaluated by Kolmogorov-Smirnov normality test. In the comparison of continuous variables between groups, Student's t test was used for variables conforming to normal distribution and Mann-Whitney U test was used for variables not conforming to normal distribution. P<0.05 was set as the significance level. All analyses were performed using IBM SPSS Statistics Version 25 package program.

RESULTS

Our study included 142 patients who underwent pelvic RT for prostate, endometrium, cervix, rectum and bladder cancer. Of these patients, 87 (61.3%) were male and 55 (38.7%) were female. The median age of the patients was 67 years (min: 31-max: 83) The median KPS was 90 (min: 70-max: 100) Patient and tumor characteristics are summarized in Table 1. Of the 71 patients in each group with and without USG, 37 were diagnosed with prostate cancer, 14 with endometrial cancer, 10 with cervical cancer, 9 with rectal cancer and 1 with bladder cancer.

Table 1 Patient and tumor characteristics

Features	n	%
Sex	55	38.7
Female		
Male	87	61.3
KPS, median (min/max)	90 (70/100)	
Age, median (min/max)	67 (31/83)	
Diagnosis		
Prostate cancer	74	52.1
Bladder cancer	2	1.4
Cervical cancer	20	14
Endometrial cancer	28	19.6
Rectal cancer	18	12.5

KPS: Karnofsky performance score.

A total of 846 CBCT scans were performed in patients without USG and 809 CBCT scans were performed in patients with USG. The findings are available in Figure 1. Although not significant, fewer CBCTs were performed in the group that underwent USG (p=0.296). In the non-USG group, 96 CBCTs were performed due to bladder incompatibility, while 54 CBCTs were performed in the USG group.

When patients with prostate cancer were analyzed; 37 patients with prostate cancer who did not undergo USG had a total of 476 CBCTs at the end of treatment and the average number of CBCTs per person was 12.86. In 37 patients with prostate cancer who underwent USG, a total of 427 CBCTs were performed and the mean number of CBCTs was 11.54. Compared to the control group who did not undergo USG, it was observed that fewer CBCTs were performed in patients who underwent USG. The difference between these two groups was statistically significant (p=0.009). In the non-USG group, 41 CBCTs were performed due to bladder discordance. In the group that underwent USG, this value was 21. The graph is available in Figure 2.

Figure 3 shows how the bladder diameter was evaluated in the USG taken before planning CT, in the planning CT and in the CBCT image taken on the first day of treatment in a patient with prostate cancer.

DISCUSSION

Pelvic RT remains a cornerstone treatment for various pelvic malignancies including prostate, endometrial, cervical, rectal, and bladder cancers. Treating patients with a full bladder and maintaining this condition throughout the treatment is important for both treat-

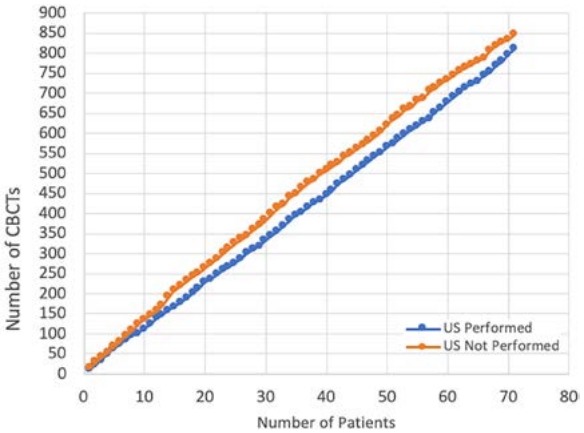


Fig. 1. Distribution of all patients.

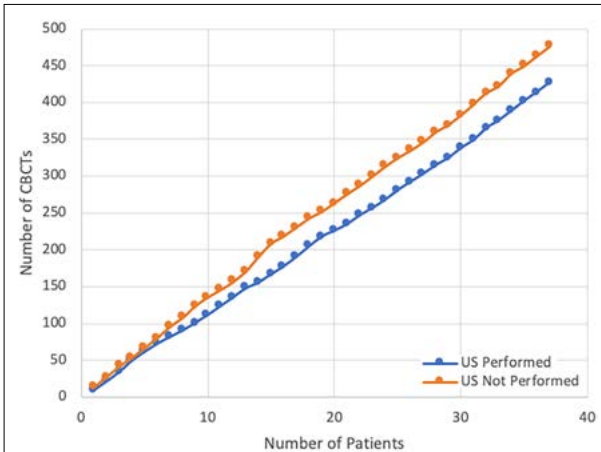


Fig. 2. Patients with prostate cancer.

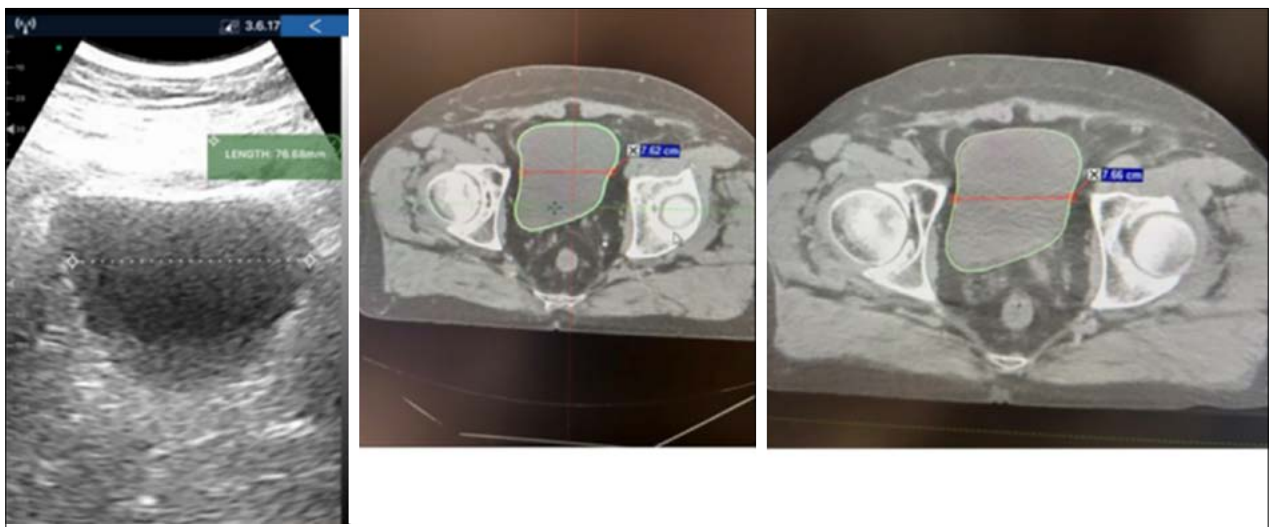


Fig. 3. Patient with prostate cancer. Bladder diameter as measured with USG: 76.6 mm; on planning CT: 76.2 mm; and on the first day of treatment with CBCT: 76.6 mm.

USG: Ultrasound; CT: Computed tomography; CBCT: Cone beam computed tomography.

ment efficacy and toxicity management. A full bladder significantly displaces the small intestine out of the radiation field, thereby reducing the risk of bowel toxicity.[7,8] Ensuring bladder fullness at the beginning of treatment and maintaining it throughout the treatment fractions is equally important. Changes in daily bladder filling can lead to intra- and inter-fraction target motion, affecting the dose delivered to the clinical target volume (CTV) and the planned target volume (PTV).[9–11] This may cause the desired ideal therapeutic index to be exceeded, resulting in worse oncological outcomes and greater toxicity.

Several studies have shown that bladder filling capacity decreases during pelvic RT.[12,13] Acute radiation-induced side effects and changes in patient habits during treatment are among the contributing factors. Radiation-induced inflammation of the bladder mucosa may lead to an increase in urinary frequency, which may make it difficult to fill the bladder to the desired level during the treatment process.[14] In addition, patients may change their fluid consumption habits while adapting to the treatment process over time, which may lead to differences in bladder filling levels between fractions. In the current literature, different methods have been investigated to assess and optimize bladder filling. Umesh et al.[15] performed bladder USG in 46 patients receiving curative RT for cervical cancer before planning CT and 45 minutes after emptying

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the bladder before treatment once a week and then at 15 minute intervals until a bladder volume of 300 ml was reached. They aimed to find the time required to reach an intermediate bladder volume by performing this procedure for 5 weeks. They demonstrated that this was reproducible by reaching intermediate bladder volume in an average of 65 minutes. This study emphasizes the importance of applying a standard bladder filling protocol to patients.

In a study by O'Doherty et al.[16] evaluating bladder filling changes in prostate cancer patients treated with RT, bladder USG was performed before planning CT and once a week before treatment. In this study, they found that bladder filling changed over the course of treatment and that smaller bladder volumes were more sustainable during planning. In this study, they also observed that providing patients with brochures with written bladder filling instructions given to the patients before treatment and practicing at home in this way were also important in maintaining bladder fullness. This finding shows that patient education and informational materials have an important place in the clinical process. In another study conducted by Luo et al.[17] with 22 patients undergoing RT, patients were divided into two groups: those who underwent pretreatment USG and those who did not. The group that received USG showed more consistent bladder fullness across fractions compared to planning CT. Another important finding of this study was that the CTV-PTV margin was reduced from 11.1 mm to 6.4 mm in the USG group by providing less displacement of the target volume. This study reveals that the use of USG is an important tool not only to assess bladder fullness but also to better establish treatment targets.

In the study by Reilly et al.[18] daily bladder ultrasound (USG) was shown to be highly effective in predicting whether target and organ doses would be met in patients receiving postprostatectomy radiotherapy. The researchers particularly emphasized that accurately estimating daily bladder volume with USG provides much of the information that would be seen on CBCT before starting treatment, thereby reducing the need for unnecessary CBCT scans. They noted that this approach both reduces the number of CBCTs performed on the patient and increases the utilization efficiency of the treatment device. Our study supports these findings and demonstrates that the use of USG not only increases dose conformity but also shortens treatment time and reduces workload by decreasing the number of CBCTs. Therefore, both studies demonstrate that integrating daily bladder USG into the pelvic radiotherapy workflow provides significant contributions in terms of both patient comfort and clinical efficiency.

Recent prospective data also support ultrasound as an effective tool for assessing bladder volume during pelvic radiotherapy. In a prospective study involving 22 patients undergoing treatment for prostate cancer, daily ultrasound measurements showed a very strong correlation (r=0.888) with bladder volume measurements obtained using CBCT. It was emphasized that daily ultrasound use could be an effective alternative to CBCT for monitoring bladder fullness during treatment, thereby reducing radiation exposure by decreasing the number of repeated CBCT scans.[19]

Interestingly, while the use of USG significantly reduced the number of CBCTs in prostate cancer patients, this effect did not reach statistical significance in the broader pelvic group. We attribute this discrepancy to the different primary sources of interfractional uncertainty among these malignancies. In prostate radiotherapy, anatomical uncertainty is predominantly driven by variations in bladder and rectal filling; therefore, verifying bladder volume with USG prior to setup effectively eliminated the main source of error, significantly reducing the need for extra CBCTs.[20] In contrast, for other pelvic tumors (particularly gynecological cases), interfractional anatomical changes are multifactorial. Even when bladder volume is strictly maintained within optimal tolerances using USG, treatment-related tumor regression, weight loss, significant soft-tissue deformation, and independent organ motion (e.g., shifts in uterine position) frequently occur.[21] Consequently, additional CBCT scans were still frequently required in this cohort to verify overall anatomical integrity and target position, entirely independent of bladder filling status. This multifactorial need for imaging overshadowed the potential benefit of USG, rendering its effect on reducing the total CBCT count statistically non-significant in the broader pelvic group.

It is thought that the use of pelvic ultrasound can reduce treatment time and costs by decreasing the use of CBCT, thereby improving patient compliance. In our clinic, an average CBCT session lasts approximately 7 minutes. The use of mobile bladder USG resulted in 42 fewer CBCT scans across the study group, saving a total of 294 minutes of treatment unit time. Since the USG procedure was briefly performed by the doctor in the outpatient room before the patient was taken to the treatment room, it did not occupy the treatment machine or disrupt the clinical workflow. Therefore, the time spent on the USG procedure itself can be considered negligible in terms of overall time efficiency.

To the best of our knowledge, our study is the first study in this field. Since USG is a noninvasive method and easy to use, its use before RT will reduce the time the patient will spend in the hospital and reduce the time to occupy the device by preventing extra CBCT.

Limitations of the study

Among the difficulties of the present study, especially in obese patients, it is difficult to accurately evaluate the bladder with USG due to subcutaneous adipose tissue. Obesity may prevent ultrasound waves from reaching deep tissues, which may decrease the quality of imaging. Especially in patients with cervical cancer, it may be difficult to accurately assess the diameter of the bladder due to compression of the bladder by the tumor. This emphasizes the effect of anatomical differences from patient to patient on the treatment process. In addition, the limited number of patients in our study suggests that the results obtained should be confirmed in a larger patient population. Future larger-scale and multicenter studies will help us better understand the efficacy and clinical benefits of mobile USG use. In particular, it is important to compare the accuracy rates of USG in different patient groups and to evaluate its effect on long-term oncologic outcomes.

CONCLUSION

In conclusion, our study demonstrates the clinical benefits of using mobile USG to assess bladder fullness in patients undergoing pelvic RT. This method has the potential to shorten treatment durations, reduce unnecessary CBCT usage, and improve patient compliance with the RT process. Specifically, our findings show a statistically significant reduction in unnecessary CBCT scans related to bladder fullness in prostate cancer patients.

Additionally, the non-invasive and easily applicable nature of USG makes it a practical tool for routine clinical use. However, further studies with larger patient cohorts are needed to evaluate the broader applicability of this method.

Ethics Committee Approval: The study was approved by the Eskişehir Osmangazi University Non-interventional Clinical Research Ethics Committee (no: E-25403353-050.99-296077, date: 18/01/2022).

Informed Consent: Written informed consent was obtained from the patients.

Conflict of Interest Statement: The authors declare that they have no conflict of interest.

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REFERENCES

1. Higham CE, Faithfull S. Bone health and pelvic radiotherapy. Clin Oncol 2015;27:668–78.
2. Andreyev J. Gastrointestinal complications of pelvic radiotherapy: Are they of any importance? Gut 2005;54:1051–4.
3. Chang JS, Yoon HI, Cha HJ, Chung Y, Cho Y, Keum KC, et al. Bladder filling variations during concurrent chemotherapy and pelvic radiotherapy in rectal cancer patients: Early experience using an ultrasound scanner. Radiat Oncol J 2013;31:41–7.
4. Buchali A, Koswig S, Dinges S, Rosenthal P, Salk J, Lackner G, et al. Impact of bladder and rectal filling on dose distribution and uterine motion in gynecologic cancer treatment planning. Radiother Oncol 1999;52:29–34.
5. Shah M, Agarwal S, Agarwal R, Subramanian B, Gupta S, De S, et al. Cone beam CT–based interfractional bladder filling variation during image-guided pelvic radiotherapy. J Cancer Res Ther 2021;17:152–6.
6. Ahmad R, Hoogeman MS, Quint S, Mens JW, de Pree I, Heijmen BJ. Inter-fraction bladder filling variations assessed with a portable 3D ultrasound scanner in cervical cancer. Radiother Oncol 2008;89:172–9.
7. Kim TH, Chie EK, Kim DY, Park SY, Cho KH, Jung KH, et al. Belly board vs. bladder filling for reducing irradiated small bowel volume in rectal cancer radiotherapy. Int J Radiat Oncol Biol Phys 2005;62:769–75.
8. Fiorino C, Foppiano F, Franzone P, Broggi S, Castellone P, Marcenaro M, et al. Rectal and bladder motion during conformal radiotherapy after prostatectomy. Radiother Oncol 2005;74:187–95.
9. Laughlin BS, Lo S, Vargas CE, DeWees TA, Van der Walt C, Tinnon K, et al. Consistent OAR management with advanced IGRT in postoperative prostate cancer radiotherapy. Cancers 2022;15:16.
10. Bell LJ, Cox J, Eade T, Rinks M, Kneebone A. Impact of rectal and bladder variability on target coverage

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doi: 10.5505/tjo.2026.4770

during post-prostatectomy IMRT. Radiother Oncol 2014;110:245–50.
11. Pinkawa M, Asadpour B, Siluschek J, Gagel B, Piroth MD, Demirel C, et al. Bladder extension variability during pelvic external radiotherapy with full or empty bladder. Radiother Oncol 2007;83:163–7.
12. Lebesque JV, Bruce AM, Kroes AP, Touw A, Shouman RT, van Herk M. Variations in rectum and bladder dose-volume parameters during conformal radiotherapy of T3 prostate cancer. Int J Radiat Oncol Biol Phys 1995;33:1109–19.
13. Stam MR, van Lin EN, van der Vight LP, Kaanders JH, Visser AG. Bladder filling variation and optimizing bladder volume with ultrasound biofeedback. Int J Radiat Oncol Biol Phys 2006;65:371–7.
14. Faithfull S, Corner J, Meyer L, Huddart R, Dearnaley D. Evaluation of nurse-led follow-up for pelvic radiotherapy patients. Br J Cancer 2001;85:1853–64.
15. Umesh M, Kumar DP, Chadha P, Choudary R, Kembhavi S, Thakur M, et al. Ultrasound-defined optimal bladder-filling protocol in cervical cancer radiotherapy. Technol Cancer Res Treat 2017;16:917–22.
16. O'Doherty UM, McNair HA, Norman AR, Miles E, Hooper S, Davies M, et al. Variability of bladder filling in radical prostate radiotherapy. Radiother Oncol 2006;79:335–40.
17. Luo H, Jin F, Yang D, Wang Y, Li C, Guo M, et al. Interfractional bladder volume variation assessed with portable bladder scanner in cervical cancer radiotherapy. Med Phys 2016;43:4412.
18. Reilly M, Ariani R, Thio E, Roh D, Timoteo M, Cen S, et al. Daily ultrasound imaging for patients undergoing postprostatectomy radiation therapy predicts and ensures dosimetric endpoints. Adv Radiat Oncol 2020;5:1206–12.
19. Bąk B, Kaczmarek K, Radoła D, Winiecki T, Bajon T. A prospective study of bladder volume assessment using ultrasound in prostate cancer radiotherapy: Comparison with cone-beam computed tomography. Radiography 2025;31:103016.
20. Wang S, Tang W, Luo H, Jin F, Wang Y. The role of image-guided radiotherapy in prostate cancer: A systematic review and meta-analysis. Clin Transl Radiat Oncol 2022;38:81–9.
21. Jadon R, Pembroke CA, Hanna CL, Palaniappan N, Evans M, Cleves AE, et al. A systematic review of organ motion and image-guided strategies in external beam radiotherapy for cervical cancer. Clin Oncol 2014;26:185–96.

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ORIGINAL ARTICLE

Evaluation of Olfactory Functions in Cancer Patients Before Radiotherapy

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OBJECTIVE

In this study,we aimed to detect olfactory functions of patients with objective method and the factors which can affect these, who referred to our department for definitive radiation therapy.

METHODS

This study included the patients without head and neck cancer. All patients functions of odor threshold, discrimination and idenfication were assessed with 'Sniffin Sticks' test before radiation therapy. The overall score is called composite threshold-discrimination-idenfication score. As these scores, ≤16 was evaluted as anosmia, 16-30 as hyposmia and >30 normal smell function.

RESULTS

This study included 48 patients with a median age of 59 years (30-76 years). With patients who had chemotherapy before radiation therapy, statistically significant olfactory disfunction (hyposmia+anosmia) was determined. 26 of 29 patients (90%) who had chemotherapy, had olfactory disfunction (p=0.02) and 7 of 10 patients (70%) who had normal smell functions had no prior chemotherapy (p=0.04). As multivariant analysis, increased age (OR:1.33, 95% CI 1.08-1.64;p=0.007) and to be treated with chemotherapy (OR:32.95, 95% CI 1.35-801.45; p=0.032) were significant factors in terms of olfactory disfunction.

CONCLUSION

In this study, we established olfactory disfunction at 79% patients who were planned definitive radiotherapy. As multivariant analysis; increasing age and to be treated with chemotherapy were statistically significant parameters as to olfactory disfunction .The patients with cancer , smell and taste disfunctions can occur frequently and to be aware of these pathologies is important for providing required treatment support.

Keywords: Chemotherapy; olfactory disfunction; radiotheraphy.
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INTRODUCTION

The senses of smell and taste are vitally important for life. These senses awaken us to dangers such as gas, fire, spolied nutrients and support oral nutrition.[1] Olfactory disfunction is seen frequently in cancer patients, these changes attract appetite and affect nutrition status adversly and and cause malnutrition.[2,3] Malnutrition occurs in great majority of cancer patients and is one of the most important cause of morbidity and mortality.[4] Thus ,it's important to apply appropriate dietary support for cancer patients.

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Olfactory disfunction can occur as the reason of oncological treatments or mechanichal or neurological damages of olfactory sites and metabolic reason as increased salivary urea concentration due to tissue catabolism.[5] The changes in smell sense can occur as change in sensitivity, distorted perception or hallucination.[1,6] Although smell and taste alterations are associated with chemotherapy and head and neck radiotheraphy, they have been reported at diagnosis and in palliative phases.[7] In the studies about olfactor disfunction in cancer patients subjective methods were often used as self reported questionaires or patients decleration.[8] Studies which used objective methods as sniffin sticks test were limited and contained complicated results.[9]

In our study, we aimed to evaluate olfactory disfunctions before radiotheraphy (RT) in cancer patients, by using objective technique as sniffin sticks test and determine the factors which can affect olfactory functions such as chemotherapy (CT), smoking, cronic disease status, using alcohol and age.

MATERIALS AND METHODS

This study included 48 cancer patients except head and neck region. All patients had locally or locally advanced disease and referred to our department for definitive RT. The patients with head and neck tumor, brain tumor or brain metastases, who had major head and neck trauma or surgery, allergic rhinitis were not included in this study. All patients functions of odor threshold, discrimination and idenfication were assessed with 'Sniffin Sticks' test before RT. For all test, the same well ventilated and silent room was used. The patients were advised for not to eat or drink something, smoking or chewing gum 15 minutes prior to the test. The sniffin sticks test was performed in three phases. At odor threshold phase, sticks which contains different dilutions of n-butanol were used and the lowest level of odor which patient can specify was determined. For discrimination phase, 16 triplets of odorants were used, every triplets contained two same and one different odorant. Patients were asked to identify different odor and got point as total odor number which they determined truly. Odor identification was assessed by means of 16 common odors, with the patients were asked to identify the odor among four possible answers presented by examiner. Patients got point as right answers number. The overall score is called 'composite threshold-discrimination-idenfication (TDI) 'score. As TDI scores, the patients olfactory status who had ≤16 TDI score was evaluted as anosmia, 16–30 as hyposmia and >30 normosmia. We determined the olfactory status of patients and investigated the factors which might be related to olfactory disfunction such as chemotherapy (CT), smoking, cronic disease status, using alcohol and age.

Ethics

This research was approved by the institutional ethic board of the Zonguldak University at 19/12/2018 (No: 2018/24) and conducted according to the ethical principles of the Declaration of Helsinki.

Statistics

Statistical Package for Social Sciences for Windows version 13 (SPSS. Inc. Chicago. IL) was used for all statistical analyses. The descriptive statistics were carried out to calculate the median value, the mean value, the range, the proportion and the standart deviation values. Categorical variables were compared using the Pearson Chi-square test. Continuous variables were compared using independent sample t-test and ANOVA test. The correlations were measured using Spearman's rho correlations. A two-sided p value <0.05 was considered as statistically significant.

RESULTS

This study included 48 patients with a median age of 59 years (30–76 years). The demographical characteristics of patients are presented in Table 1. Odor threshold scores were mean 4.5 (0–15), discrimination scores were mean 9 (4–14), identification scores were mean 9.3 (3–14) and TDI scores were mean 22.8 (9.5–37.8). 27 patients olfactory status (56%) were evaluated as hiposmia, 11 patients (23%) as anosmia and 10 patients (21%) as normal smell functions. The patient related factors which might affect olfactory functions such as smoking, cronic disease status, using alcohol and age were examined with univariant analysis and there was no statistically significant relationship between olfactory functions. With patients who had chemotherapy before RT, statistically significant olfactory disfunction (hyposmia+anosmia) was determined. 26 of 29 patients (90%) who had chemotherapy, had olfactory disfunction (p=0.02) and 7 of 10 patients (70%) who had normal smell functions had no prior chemotherapy (p=0.04) (Fig. 1). As multivariant analysis, increased age (OR:1.33, 95% CI 1.08–1.64; p=0.007) and to be treated with chemotherapy (OR:32.95, 95% CI 1.35–801.45; p=0.032) were significant factors in terms of olfactory disfunction.

Table 1 Demographics of patients

Demographics	n	%
Age, mean	59 (30–76)	
Gender		
Female	29	60.4
Male	19	30.6
HT		
Yes	14	29.2
No	34	70.8
DM		
Yes	9	18.8
No	39	81.2
CT		
Yes	29	60.4
No	19	30.6
Smoking		
Yes	14	29.2
No	34	70.8
Alcohol		
Yes	2	4.2
No	46	95.8

HT: Hypertension; DM: Diabetes mellitus; CT: Chemotherapy.

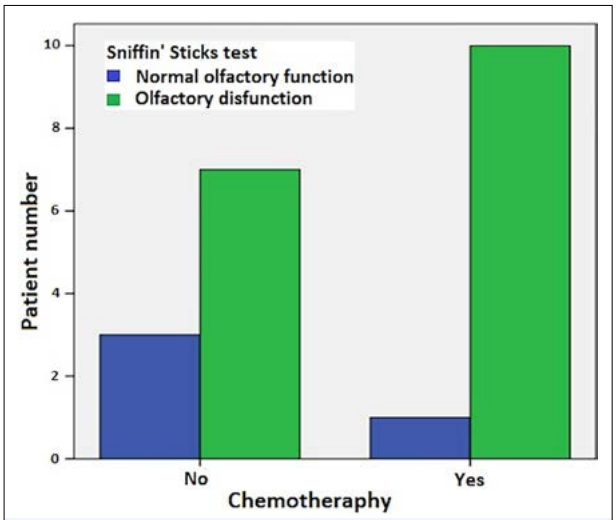


Fig. 1. The relation between chemoteraphy and olfactory disfunction.

DISCUSSION

Taste and smell changes frequently occur in oncological patients but patients can not recognize until they reach anosmia levels.[10] The patients are anable to signify these changes and due to the thought of they are not treatable, stuff and patients don't communicate about olfactory semptoms sufficiently.[9] Olfactory disfunctions are related to taste disfuctions, decrease to enjoy eating and they may be seen as semptom clusters with dry mouth, weight loss, anorexi and fatigue.[11] To treat one semptom can cure other semptoms.[12] Olfactory disfunctions affect negatively nutritional status and can cause malnutrition. It's important to determine taste and smell changes for preventing malnutrition.

In this study, 48 patients olfactory functions were evoluated before RT. 27 patients (56%) had hiposmia, 11 patients (23%) had anosmia. Olfactory disfunction frequency was 79% in our study. As the studies using self reported methods, olfactory disfunction in oncological patients was seen 5–60% after chemotherapy. As our results, 90% of patients who had chemotherapy had olfactory disfunction. Objective methods are probably more efficient to assess olfactory functions. There are different results about the relation between olfactory functions and CT. Riga et al.[10] evaluated the relation between olfactory functions and different CT drugs by using Sniffin Sticks test and they reported that, CT effects olfactory functions adversely even though they did not analyse the difference in CT regime groups. Although studies which searched different CT agents did not find any difference of effect on smell functions,[13] a recent study reported lower smell theshold after CT with 5-FU and capesitabine as compared with cisplatin and carboplatin.[10] Yakirevitch et al.[14] established any olfactory function alterations during CT or 3 weeks after cisplatin-based CT in 21 patients. Conversely, Steinbach et al.[15] reported decrease in TDI scores during carboplatinum+paclitaxel CT in 12 ovarian cancer patients, especially in threshold scores. To paralel this study we determined lower threshold scores as compared with other scores.

Many studies investigated the effect of age, gender and smoking status on smell and taste functions. Most of them reported no relation between smoking and taste and smell changes, while one smaller study disagreed.[16,17] Also, we did not find a significant relation between smoking and olfactory disfunction .

In general population, taste and smell are attracted by age. Steinbach et al.[13] reported more sensitivity to olfactory disfunction with older patients after CT. Reduction of olfactory receptor cells and their regeneration capasities, mucus secretion and epithelial thickness with older age cause smell changes.[10] According to some studies in elder patients smell changes were more severe after CT.[10,13,18] There

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are studies showed that in younger patients olfactory function was affected more severely, it might be due to their higher initial olfactory scores[19] and because of elder patients initial lower olfactory scores the reduction after CT was lesser. In this study, we determined that increased age was significant factor in terms of olfactory disfunction but we did not evaluate the initial olfactory scores before CT.

As literature, 80 % of treatment naive oncological patients had olfactory disfunction[20] and also after localize treatments such as stereotactic body radiation therapy or surgery taste and smell changes could be seen.[7] Olfactory changes in cancer patients can ocur by influencing of chemoreceptor sites for mechanichal, metabolic and neurological reasons or as the result of oncological treatments. We reported olfactory disfunction with treatment naive patients correspondingly with literature.

Olfactory and taste alterations are frequently observed in patients with cancer and can adversely affect food intake and nutritional status.[21]

CONCLUSION

We reported olfactory disfunction at 79% of patients who were planned definitive radiation therapy. These changes affect nutritional status by reducing appetite and food intake. Furthermore, smell sensation warn us against dangers such as gas, fire and spoiled food. To be aware of these pathologies before and during treatment is important for providing required supportive treatment.

Ethics Committee Approval: The study was approved by the Zonguldak University Ethics Committee (no: 2018/24, date: 19/12/2018).

Informed Consent: Written consent was obtained from the patients.

Conflict of Interest Statement: There is no of conflict of interest.

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REFERENCES

1. Brisbois TD, Hutton JL, Baracos VE, Wismer WV. Taste and smell abnormalities as an independent cause of failure of food intake in patients with advanced cancer--an argument for the application of sensory science. J Palliat Care 2006;22(2):111–4.
2. Epstein JB, Barasch A. Taste disorders in cancer patients: Pathogenesis, and approach to assessment and management. Oral Oncol 2010;46(2):77–81.
3. McLaughlin L, Mahon SM. Understanding taste dysfunction in patients with cancer. Clin J Oncol Nurs 2012;16(2):171–8.
4. Van Cutsem E, Arends J. The causes and consequences of cancer-associated malnutrition. Eur J Oncol Nurs 2005;9(Suppl 2):S51–63.
5. Kamath S, Booth P, Lad TE, Kohrs MB, McGuire WP. Taste thresholds of patients with cancer of the esophagus. Cancer 1983;52(2):386–9.
6. Hong JH, Omur-Ozbek P, Stanek BT, Dietrich AM, Duncan SE, Lee YW, et al. Taste and odor abnormalities in cancer patients. J Support Oncol 2009;7(2):58–65.
7. Belqaid K, Tishelman C, McGreevy J, Manssson-Brahme E, Orrevall Y, Wismer W, et al. A longitudinal study of changing characteristics of self-reported taste and smell alterations in patients treated for lung cancer. Eur J Oncol Nurs 2016;21:232–41.
8. Joussain P, Giboreau A, Fontas M, Laville M, Hummel T, Souquet PJ, et al. Cisplatin chemotherapy induces odor perception changes in bronchial cancer patients. Lung Cancer 2013;82(1):168–70.
9. Bernhardson BM, Tishelman C, Rutqvist LE. Chemosensory changes experienced by patients undergoing cancer chemotherapy: A qualitative interview study. J Pain Symptom Manage 2007;34(4):403–12.
10. Riga M, Chelis L, Papazi T, Danielides V, Katotomichelakis M, Kakolyris S. Hyposmia: An underestimated and frequent adverse effect of chemotherapy. Support Care Cancer 2015;23(10):3053–8.
11. Chen ML, Lin CC. Cancer symptom clusters: A validation study. J Pain Symptom Manage 2007;34(6):590–9.
12. Komurcu S, Nelson KA, Walsh D, Donnelly SM, Homsi J, Abdullah O. Common symptoms in advanced cancer. Semin Oncol 2000;27(1):24–33.
13. Steinbach S, Hummel T, Böhner C, Berktold S, Hundt W, Kriner M, et al. Qualitative and quantitative assessment of taste and smell changes in patients undergoing chemotherapy for breast cancer or gynecologic malignancies. J Clin Oncol 2009;27(11):1899–905.
14. Yakirevitch A, Talmi YP, Baram Y, Weitzen R, Pfeffer MR. Effects of cisplatin on olfactory function in cancer patients. Br J Cancer 2005;92(9):1611–3.
15. Steinbach S, Hundt W, Schmalfeldt B, Böhner C, Bek-

told S, Wolf P, et al. Effect of platinum-containing chemotherapy on olfactory, gustatory, and hearing function in ovarian cancer patients. Arch Gynecol Obstet 2012;286(2):473–80.
16. Konstantinidis I, Chatziavramidis A, Printza A, Metaxas S, Constantinidis J. Effects of smoking on taste: Assessment with contact endoscopy and taste strips. Laryngoscope 2010;120(10):1958–63.
17. McGreevy J, Orrevall Y, Belqaid K, Wismer W, Tishelman C, Bernhardson BM. Characteristics of taste and smell alterations reported by patients after starting treatment for lung cancer. Support Care Cancer 2014;22(10):2635–44.
18. Haxel BR, Berg S, Boessert P, Mann WJ, Fruth K. Olfaction in chemotherapy for head and neck malignancies. Auris Nasus Larynx 2016;43(1):74–8.
19. Eravcı FC, Ucar G, Ozcan KM, Colak M, Ergun Y, Acıkgoz Y, et al. The effect of chemotherapy on olfactory function and mucociliary clearance. Support Care Cancer 2021;29(3):1635–41.
20. Spotten L, Corish C, Lorton C, Dhuibhir PU, O'Donoghue N, O'Connor B, et al. Subjective taste and smell changes in treatment-naive people with solid tumours. Support Care Cancer 2016;24(7):3201–8.
21. O'Donoghue A, Barrett M, Dhuibhir PU, Kennedy A, O'Leary N, Walsh D. Taste and smell abnormalities in advanced cancer: Negative impact on subjective food intake. Nutr Clin Pract 2023;38:807–16.

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ORIGINAL ARTICLE

Cross-Geometry Generalisation of a Physics-Informed 3D Dose-Prediction Ensemble

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OBJECTIVE

Deep-learning dose-prediction models are often tied to their training beam configurations, limiting reusability. We tested whether an ensemble of three complementary 3D networks trained on one photon beam configuration can generalise to five unseen configurations on a held-out anatomy.

METHODS

Photon dose plans for five anatomies and six beam configurations were generated with matRad. A 13-channel input tensor (CT image, PTV/OAR masks, physics-informed per-beam ray-tracing maps) was built for every plan. Three networks (SOTA-UNet3D, Res-UNet3D, Trans-UNet3D) were trained on the training configuration (C0) of four anatomies and combined by voxel-wise mean as the Voltron ensemble. The held-out anatomy (TG-119) was evaluated under C0 and C1–C5 using the 3D gamma index (3%/3 mm) and mean absolute error (MAE).

RESULTS

Voltron achieved 51.42% gamma pass rate on C0 (MAE 8.91 Gy). Across the unseen configurations the mean was 52.49% (range 47.38%–56.94%; MAE 8.94–10.44 Gy). The largest decrease relative to C0 was 4.04 points (C1); three configurations exceeded it by 1.75–5.52 points. Performance on unseen geometries was comparable to the in-distribution baseline.

CONCLUSION

A physics-informed 3D dose-prediction ensemble trained on one beam configuration may retain its dosimetric quality on unseen co-planar geometries, suggesting an avenue for reusable models in data-scarce settings.

Keywords: Deep learning; dose distribution; generalization; neural networks; radiation dosimetry; radiotherapy.
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INTRODUCTION

Radiotherapy is a cornerstone of modern oncology, and three-dimensional dose prediction has emerged as a powerful tool for accelerating treatment planning and automating quality-assurance workflows.[1,2] Convolutional architectures based on the U-Net[3] and its three-dimensional extension[4] have become a de facto standard for voxel-wise dose prediction.[5,6] More recent work has extended these ideas with cascaded architectures,[7] structure-aware losses[8] and end-to-end planning pipelines.[2]

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Even when anatomy and prescription are fixed, the predicted dose distribution depends strongly on the beam geometry chosen by the planner. Beam-angle selection is itself a challenging combinatorial problem that has received considerable attention, including recent deep-reinforcement-learning approaches.[9] When dose-prediction networks are trained, the input representation must therefore convey the beam geometry; Barragán-Montero et al.[10] showed that encoding the beam configuration as an additional input channel allowed a single model to generalise across heterogeneous beam configurations in lung intensity-modulated radiotherapy. Beam-wise decomposition strategies further exploit the additivity of dose with respect to individual beams,[11,12] and physics-informed inputs that incorporate per-beam ray-tracing have been proposed to improve interpretability and accuracy.[12]

Despite these advances, most published dose-prediction models are trained and tested on plans that share a single beam geometry, or on data drawn from a single clinical site.[5,6] A practical question that follows is whether such models can be reused when the beam geometry departs from the one they were trained on. If the answer were yes, dose-prediction models could be more easily shared between centres that use different beam-angle conventions, which would lower the data burden on smaller centres.[13]

From a machine-learning perspective, this is a question of out-of-distribution generalisation. Recent reviews and benchmark studies in medical imaging have emphasised that deep models often degrade when the test-time distribution drifts from the training distribution.[14,15] Most published work on this problem in medical imaging concerns segmentation across scanners or hospitals, where the input distribution shifts but the task output is largely invariant. Dose prediction differs in that the output itself depends explicitly on the geometric input; the question becomes whether a network can correctly re-weight its predictions when the geometry changes.

The open-source toolkit matRad (matRad Research Group, German Cancer Research Center [DKFZ], Heidelberg, Germany) implements analytical pencil-beam algorithms for photon, scanned-proton and scanned-carbon-ion plans within a single MATLAB framework.[16] Because matRad can compute reference doses for arbitrary beam configurations under consistent algorithms, it provides a controlled testbed for studying robustness to beam-geometry variation, free of the inter-centre confounders that complicate clinical multi-institutional studies.

On the model side, residual connections[17] and attention mechanisms[18] have inspired numerous variants of the three-dimensional U-Net. Modern training recipes that combine the decoupled-weight-decay AdamW optimiser with cosine annealing and warm restarts[19] further stabilise training of large three-dimensional models. Ensembling complementary backbones is a well-known route to reduce variance and improve calibration, but to our knowledge no published study has explicitly tested an ensemble of complementary three-dimensional backbones in a controlled cross-geometry setting for dose prediction.

Building on these elements, in this study we asked a specific and previously unexplored question: can an ensemble of three complementary three-dimensional networks trained on a single beam configuration predict photon dose distributions for the same anatomy under several unseen beam configurations? We trained a Voltron ensemble, composed of SOTA-UNet3D, Res-UNet3D and Trans-UNet3D, on a single five-beam co-planar configuration (C0) and evaluated it on five unseen configurations (C1–C5) covering different beam counts and angular distributions. Reference doses were generated with matRad[16] and predictions were compared with the three-dimensional gamma index (3% / 3 mm).[20,21] To our knowledge, this is the first dosimetric study to evaluate a single three-dimensional ensemble across multiple unseen co-planar beam configurations under matched conditions. Our aim is not to deliver a clinical-grade dose calculator but to provide a transparent baseline that future cross-geometry robustness studies can compare against.

MATERIALS AND METHODS

Ethical approval

This study involved only in-silico simulations on publicly available phantoms and demonstration datasets distributed with the matRad toolkit.[16] No patient-level data, identifiers or human subjects were involved at any stage, and no ethics-committee approval or informed consent were therefore required.

Dataset and Reference Dose Generation

The overall workflow of this study is illustrated in Figure 1. All reference dose distributions were generated using the open-source treatment-planning toolkit matRad (matRad Research Group, German Cancer Research Center [DKFZ], Heidelberg, Germany), which implements analytical pencil-beam algorithms for photon plans within a single MATLAB framework

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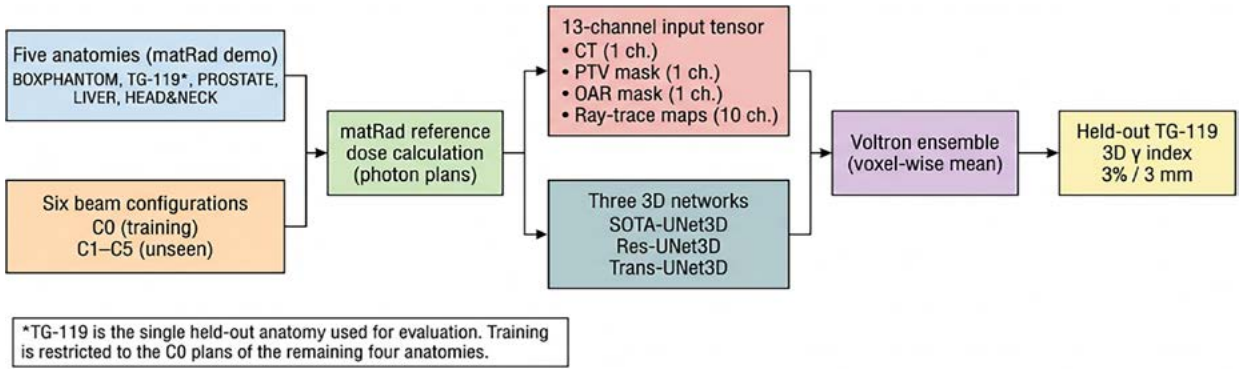


Fig. 1. Schematic overview of the study workflow. The matRad demonstration dataset (five anatomies) is combined with six beam configurations to generate reference photon dose distributions. A 13-channel input tensor (CT, PTV mask, OAR mask and per-beam ray-tracing maps) is provided to three complementary three-dimensional networks, whose voxel-wise mean defines the Voltron ensemble. The held-out anatomy (TG-119) is evaluated under the training configuration (C0) and the five unseen configurations (C1–C5) using the three-dimensional gamma index (3% / 3 mm).

CT: Computed tomography; PTV: Planning target volume; OAR: Organ at risk; MAE: Mean absolute error.

(MathWorks, Natick, MA, USA).[16] Five anatomies were used: A homogeneous water-equivalent box phantom (BOXPHANTOM), the TG-119 phantom (a synthetic concave-target benchmark), and three anthropomorphic cases (PROSTATE, LIVER and HEAD_AND_NECK) distributed with matRad as part of its demonstration dataset. The computed-tomography cubes, structure masks, voxel resolutions and isocentre coordinates supplied with each case were used without further processing.

For each anatomy, photon dose distributions were generated under six beam configurations indexed C0–C5. Configuration C0 used five equispaced co-planar beams (0°, 72°, 144°, 216°, 288°) and served as the single training configuration. The remaining configurations were: six equispaced co-planar beams (C1; 0°, 60°, 120°, 180°, 240°, 300°), seven equispaced co-planar beams (C2), nine equispaced co-planar beams (C3), six co-planar beams offset by 30° (C4; 30°, 90°, 150°, 210°, 270°, 330°) and four oblique co-planar beams (C5; 45°, 135°, 225°, 315°). All six geometries are illustrated in Figure 2. matRad inverse optimisation was run with default settings. The resulting dose cubes and structure information were exported as compressed NumPy archives (NumPy 1.26, NumPy Developers, Austin, TX, USA).

Input Tensor Construction

The input to each network was a 13-channel three-dimensional tensor (Supplementary Fig. S1). Channel 1 contained the computed-tomography image normalised to [0, 1] using the linear transformation (HU+1000)/4000, clipped to that interval. Channel 2 was the binary planning target volume (PTV) mask, defined as the union of all target structures available in matRad. Channel 3 was the binary organ-at-risk (OAR) mask, defined as the union of non-target structures excluding non-clinical labels such as BODY, SKIN, ENTRANCE, DOSE-FALLOFF, ISOCENTER and clip markers; the full exclusion list is given in Supplementary Table S1. Channels 4–13 encoded the beam geometry and physics: channel 4 held the voxel-wise sum of all per-beam ray-tracing maps, and channels 5–13 held up to nine individual per-beam maps.

For each gantry angle, a three-dimensional ray-tracing map was produced by combining a lateral Gaussian attenuation around the beam central axis (lateral standard deviation σ-lat=8.0 voxels) with a one-dimensional percent-depth-dose profile along the beam direction. For photons, the percent-depth-dose used an exponential attenuation with a soft build-up region; the functional form and parameter values are reported in Supplementary Table S2. Unused beam slots in configurations with fewer than nine beams were zero-padded. The computed-tomography image and structure masks are identical across all configurations of the same anatomy, so the only inputs that differ between configurations are channels 4–13.

Network Architectures and The Voltron Ensemble

Three complementary three-dimensional networks were used (Supplementary Fig. S2). All three were implemented in PyTorch 2.x (PyTorch Foundation, San Francisco, CA, USA) and accepted the same

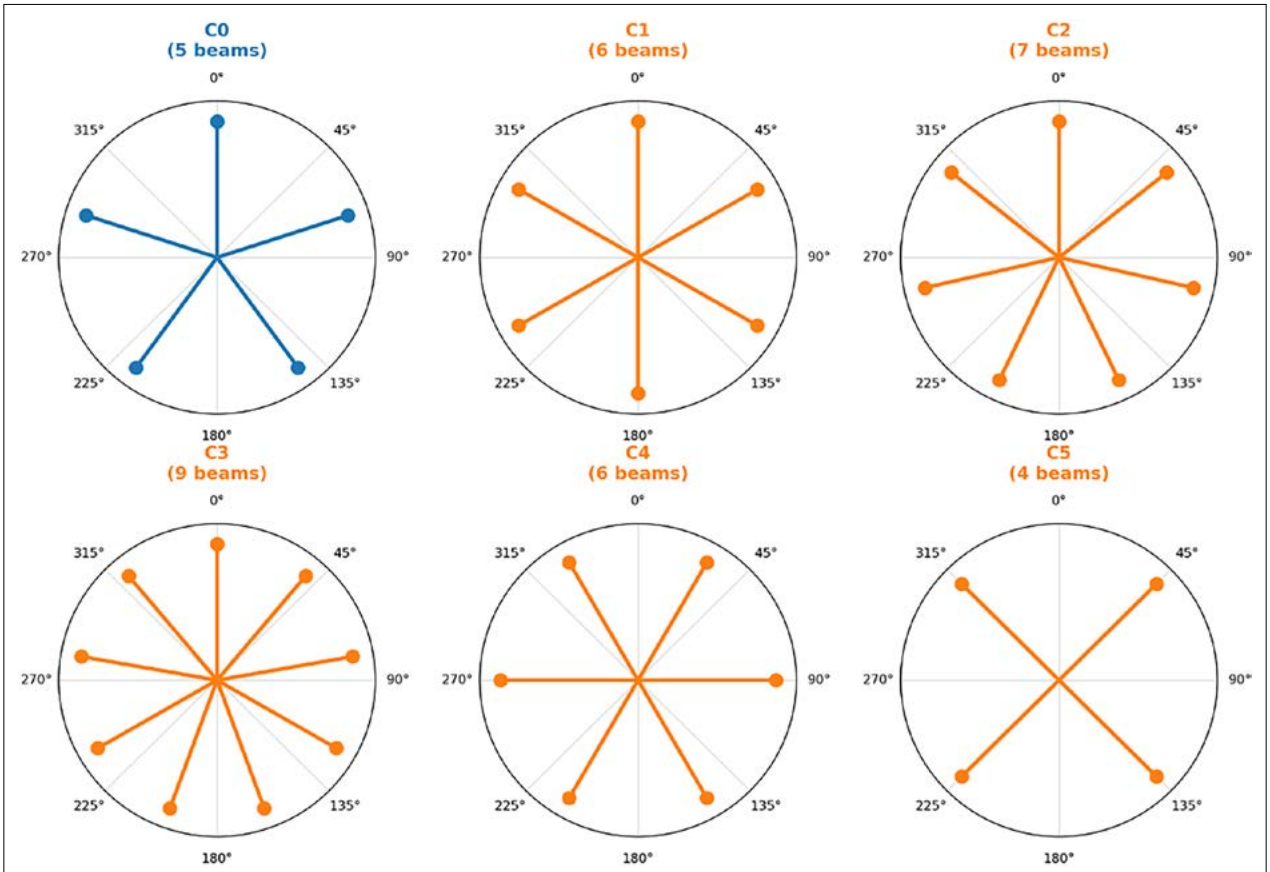


Fig. 2. Polar plots of the six beam configurations used for reference dose generation in matRad. C0 (blue) is the single training configuration; C1–C5 (orange) are used only for evaluation on the held-out anatomy. Each radial line indicates the gantry angle of a single beam. All six configurations are co-planar.

13-channel input tensor of size 128×128×128 voxels. SOTA-UNet3D is a four-level encoder–decoder with a base width of 32 channels in which each stage uses a multi-scale convolutional block (combining dilated 3×3×3 convolutions with dilation rates 1 and 2) and local–global attention-gated skip connections[22] inspired by the attention U-Net family; upsampling is performed by efficient up-convolutional blocks (trilinear upsampling followed by depthwise and pointwise convolutions).Res-UNet3D shares the same encoder–decoder topology but replaces the multi-scale block with a residual convolutional block:[17] two 3×3×3 convolutions with group normalisation and GELU activation, followed by an identity or projection shortcut. Trans-UNet3D inserts a single transformer encoder layer[18] at the bottleneck (16×16×16 spatial extent, 256 channels, four heads, feed-forward dimension 512). All three networks end in a 1×1×1 convolution followed by a sigmoid activation to anchor the output to the [0, 1] dose-fraction interval for numerical stability under mixed-precision training. The Voltron ensemble averages the three voxel-wise predictions at inference time and requires no additional training.

Training Protocol and Data Partitioning

The five anatomies were sorted alphabetically and the second anatomy (TG-119)[23] was held out as the test set; the remaining four (BOXPHANTOM, PROSTATE, LIVER and HEAD_AND_NECK) provided the training set. Crucially, training was restricted to the C0 photon plans of the four training anatomies, so the networks never saw any plan from the C1–C5 geometries at any stage of training. Training used random three-dimensional patches of size 128×128×128 voxels, with a 70% probability of being centred on a voxel inside the PTV (plus a small random jitter) and a 30% probability of being centred on a random foreground voxel; sixteen augmented patches were drawn per plan per epoch. On-the-fly augmentation was

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performed with MONAI 1.4 (Project MONAI consortium)[24] and comprised random spatial flips, random affine transformations, random Gaussian noise, random Gaussian smoothing and random intensity shifts. Each network was trained from scratch for 40 epochs with the AdamW optimiser[19] using a cosine-annealing-with-warm-restarts schedule. The loss function combined a mean-squared-error term and a mean-absolute-error term with unit weights. Random seeds were fixed to 42 throughout. Training was performed on NVIDIA A100 GPUs (NVIDIA Corporation, Santa Clara, CA, USA). Complete hyperparameter values are reported in Supplementary Table S3.

Inference and Evaluation Metrics

At inference time, the held-out anatomy was processed for each of the six beam configurations using three-dimensional sliding-window inference (MONAI 1.4) with overlapping 128×128×128 patches at 50% overlap and Gaussian importance weighting (σ-scale=0.125). The Voltron output was rescaled to physical dose units by multiplication with the maximum reference dose of the corresponding matRad plan. Predicted dose distributions were compared with the matRad references using two metrics. The first was the three-dimensional gamma index with criteria 3% / 3 mm and a 10% low-dose cut-off, computed as introduced by Low et al.[20] and following the practical guidance of Hussein et al.;[21] the dose-difference acceptance was set to 3% of the maximum reference dose, and the distance-to-agreement of 3 mm was translated into voxel radii using the actual physical voxel spacing of the anatomy. The second metric was the mean absolute error (MAE) in Gy between predicted and reference dose, computed over all voxels.

Statistical Analysis

Numerical computations and descriptive statistics were performed in Python 3.10 (Python Software Foundation, Wilmington, DE, USA) using NumPy 1.26, SciPy 1.13 and Pandas 2.2 (NumFOCUS, Austin, TX, USA). Figures were generated with Matplotlib 3.9 (Matplotlib Development Team). Because each test condition yielded a single dose volume per beam configuration on the held-out anatomy, summary measures are reported as scalar values per configuration together with the across-configuration mean and range. No formal inferential statistical testing was performed because the limited per-condition sample size (n=6 configurations on a single held-out anatomy) precludes meaningful hypothesis testing; the comparison of greatest interest in this in-silico study is the relative change of the per-configuration gamma pass rate with respect to the C0 baseline.

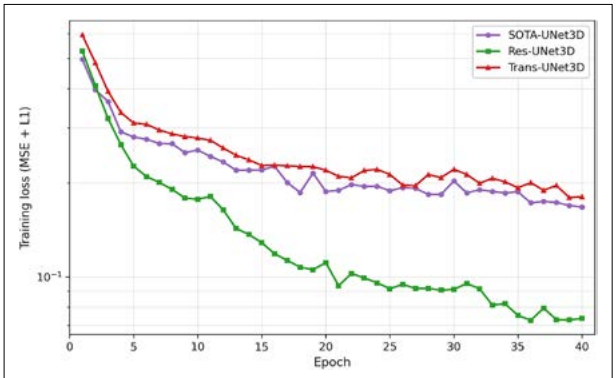


Fig. 3. Training-loss trajectories of the three networks trained from scratch on the single C0 configuration, displayed on a logarithmic vertical axis. The combined mean-squared-error + mean-absolute-error loss is shown for each of the 40 epochs. Per-network curves on a linear scale are provided in Supplementary Figure S3.

RESULTS

All three networks converged within 40 epochs of training on the single C0 configuration (Fig. 3). Res-UNet3D reached the lowest training loss (composite MSE+L1 loss=0.074 at epoch 40), while SOTA-UNet3D (0.167) and Trans-UNet3D (0.181) converged to similar values. Because the same training set, augmentation pipeline and hyperparameters were used for all three backbones, this difference is most plausibly attributed to the lower regularisation pressure of the plain residual block compared with the multi-scale and transformer-equipped blocks. Per-network training curves are shown in Supplementary Figure S3, and per-epoch loss values for all three networks are tabulated in Supplementary Table S4.

On the held-out TG-119 anatomy, the Voltron ensemble achieved a three-dimensional gamma pass rate (3% / 3 mm) of 51.42% on the training configuration C0, with a mean absolute error of 8.91 Gy (Table 1). This value is the in-distribution baseline against which the unseen-geometry predictions are compared. The full set of per-configuration values is visualised in Figure 4. A complementary scatter view of gamma versus MAE, and a distribution comparison of training versus unseen geometries, are provided in Supplementary Figure S4.

Table 1 Per-configuration three-dimensional gamma pass rate (3% / 3 mm) and mean absolute error of the Voltron ensemble on the held-out TG-119 anatomy

Configuration	Beams (gantry angles)	γ 3%/3 mm (%)	MAE (Gy)
C0 (training)	5 (0°, 72°, 144°, 216°, 288°)	51.42	8.91
C1	6 (0°, 60°, 120°, 180°, 240°, 300°)	47.38	9.17
C2	7 (equispaced)	51.34	9.08
C3	9 (equispaced)	53.17	9.11
C4	6 (offset by 30°)	53.59	8.94
C5	4 oblique (45°, 135°, 225°, 315°)	56.94	10.44
Unseen mean (C1–C5)	—	52.49	9.35

Configuration C0 was used to train the networks; C1–C5 were unseen during training. The row labelled 'Unseen mean (C1–C5)' reports the across-configuration mean for the unseen geometries. γ: Three-dimensional gamma index pass rate with 3% dose-difference criterion (relative to maximum reference dose) and 3 mm distance-to-agreement, computed under a 10% low-dose cut-off; MAE: Mean absolute error. All values were computed on the held-out anatomy (TG-119) against matRad reference plans.

Across the five unseen beam configurations, the Voltron ensemble achieved a mean gamma pass rate of 52.49% (range 47.38%–56.94%, Table 1). This value is slightly higher than the in-distribution C0 baseline (51.42%), with three of the five unseen configurations (C3, C4 and C5) producing higher gamma values than C0, while C1 and C2 were lower. The largest single deviation from baseline was a 4.0 percentage-point decrease on C1 (Fig. 4c). Configuration C5, which uses only four oblique beams and is geometrically the most different from the equispaced five-beam training geometry, in fact produced the highest gamma pass rate across all six configurations (56.94%). The heatmap in Figure 5a summarises gamma and MAE side by side,

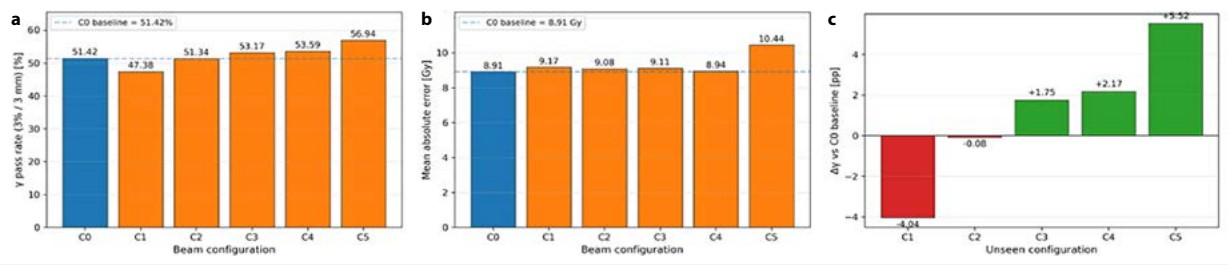


Fig. 4. Per-configuration evaluation of the Voltron ensemble on the held-out TG-119 anatomy. (a) Three-dimensional gamma pass rate (3% / 3 mm) for the six configurations; C0 (training) is shown in blue and the unseen geometries C1–C5 in orange. (b) Corresponding mean absolute error (MAE) in Gy. (c) Change in gamma pass rate of each unseen configuration relative to the C0 baseline (in percentage points; pp); positive values indicate higher gamma on the unseen geometry than on the training geometry.

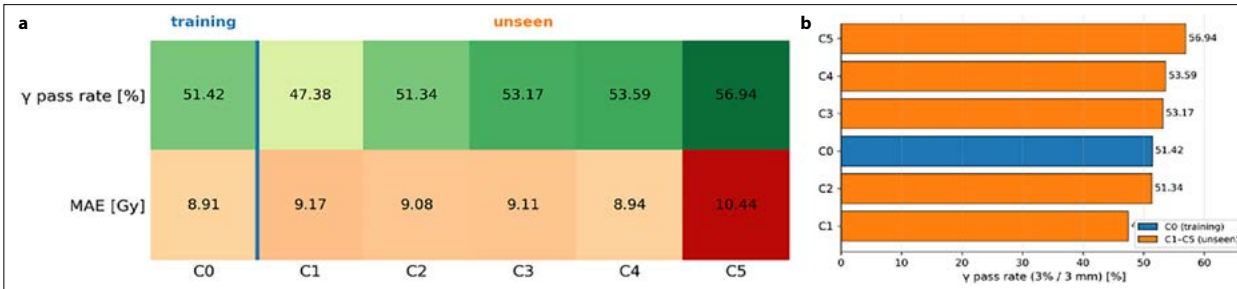


Fig. 5. Robustness summary across the six beam configurations. (a) Heatmap of the Voltron gamma pass rate (top row, green colour scale) and mean absolute error (bottom row, orange–red scale) for each configuration; the vertical blue line separates the training geometry (C0) from the five unseen geometries (C1–C5). (b) Configurations ranked by gamma pass rate, with C0 (blue) interleaved with the unseen geometries (orange).

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and the ranked view in Figure 5b orders the six configurations by gamma. Overall, the in-distribution and out-of-distribution geometries are interleaved in the ranking rather than separated.

Taken together, the per-configuration analysis indicates that the Voltron ensemble retained its dosimetric quality across the five unseen co-planar geometries: the mean gamma pass rate across C1–C5 exceeded the C0 baseline, and the largest individual decrease relative to baseline was on the order of four percentage points. MAE values stayed within approximately 8.9 to 10.4 Gy for all configurations, with no configuration producing a markedly larger error than the training geometry.

DISCUSSION

We trained a single ensemble of three complementary three-dimensional networks on one beam configuration (C0) and showed that, on a held-out anatomy, the ensemble produced dose distributions for five unseen co-planar geometries whose gamma pass rate at 3% / 3 mm was comparable to, and on average slightly higher than, the in-distribution baseline. To our knowledge, this is the first explicit dosimetric demonstration of single-configuration to multi-configuration transfer for physics-informed three-dimensional dose-prediction ensembles. The result supports the view that, when beam geometry is encoded through a small set of physically meaningful input channels rather than baked into the training distribution, much of the information a network needs to predict the dose can be shared across configurations.

Our design deliberately disentangles anatomy, geometry and the underlying photon physics. The computed-tomography image and structure masks are identical between configurations of any given plan; the only configuration-dependent inputs are the per-beam ray-tracing maps in channels 4–13. This is a much weaker form of geometric encoding than would be required if the network had to memorise each beam set from data, and is conceptually related to the beam-wise decomposition approaches proposed by other groups.[11,25] Our findings suggest that, once the geometry is supplied as an explicit input, the anatomy-conditional dose-shaping function the network has to learn is, to first approximation, invariant with respect to the number and angular distribution of co-planar beams, at least in the regimes implemented by matRad.[16]

It is interesting that several unseen configurations produced gamma pass rates above the in-distribution baseline. One plausible explanation is that, for a given anatomy, configurations with more beams or with beams that better cover the planning target volume produce smoother dose distributions that are simpler to reproduce voxel-wise, even though they were never seen during training. The lower gamma value on C1 (six equispaced beams with a different angular sampling from C0) and the higher gamma values on C3 (nine beams) and C5 (four oblique beams) hint that the local difficulty of dose reconstruction may depend more on the geometric coverage of the target than on similarity to the training geometry. Similar observations have been reported in other deep-learning dose-prediction studies that varied the input configuration.[10]

The Voltron ensemble combines a residual U-Net that converges to a very low training loss with two higher-bias estimators (a multi-scale plus attention-gate U-Net and a transformer-bottleneck U-Net). Ensembling complementary backbones is a well-established route to reduce variance and improve calibration of dose predictions.[1,7] We did not pursue weighted voting or stacking, in order to keep the pipeline reproducible and inexpensive. That this simple unweighted average already retains its dosimetric quality across multiple unseen geometries suggests that further gains from more sophisticated ensemble combinations are likely possible.

Beyond the controlled in-silico setting reported here, the broader idea that distributional differences across centres or scanners can be encapsulated in a physics-aware input layer rather than in centre-specific weights connects naturally to ongoing work on domain generalisation in medical imaging[14,15] and to the recent line of work on physics-informed dose-prediction models.[12] A particularly informative experiment would be to add a small number of plans from an additional clinical centre, with different beam-angle conventions, and to measure how much centre-specific data are needed to recover full performance; this would quantify the practical value of the cross-geometry starting point for data-scarce centres.

Limitations of the Study

Several limitations should be acknowledged. First, the reference dose distributions come from an analytical pencil-beam toolkit rather than from full Monte Carlo simulation. matRad has been validated against commercial treatment-planning systems[16], but analytical algorithms are known to be less accurate than Monte Carlo in highly heterogeneous geometries.[26,27] Our findings should therefore be read

as a controlled algorithm-to-algorithm comparison rather than an algorithm-to-clinical-truth comparison. Second, the held-out test set consists of a single anatomy, which is sufficient to demonstrate feasibility of cross-geometry transfer but does not characterise inter-patient variability rigorously. Third, the absolute gamma pass rates reported here are well below the threshold typically required for patient-specific quality assurance (commonly above 90%); the aim of this study, however, was not clinical-grade dose prediction but a transparent test of whether a single ensemble could remain robust across unseen beam configurations, and the relative change with respect to the C0 baseline is the primary outcome rather than the absolute pass rate. Fourth, our evaluation was restricted to photon plans and co-planar geometries; performance on non-co-planar geometries or on particle modalities was not assessed here. Fifth, because of the limited per-condition sample size (n=6 configurations on a single anatomy), only descriptive statistics could be reported; multi-centre, multi-patient validation against Monte Carlo references is the necessary next step before clinical translation can be considered.

CONCLUSION

An ensemble of three complementary three-dimensional networks trained on a single co-planar beam configuration produced photon dose distributions for five unseen co-planar configurations on a held-out anatomy with a mean three-dimensional gamma pass rate (3% / 3 mm) of 52.49%, compared with 51.42% for the in-distribution training configuration, and with mean absolute errors between 8.91 and 10.44 Gy across all six configurations. The largest single decrease relative to the training geometry was approximately four percentage points, while three configurations exceeded the baseline by 1.75 to 5.52 percentage points. These findings are far from clinical-grade performance, but they suggest that, when the beam geometry is encoded through a physics-informed input layer, a substantial fraction of the dose-prediction task remains transferable across co-planar beam configurations. We recommend that future cross-geometry robustness studies use this design as a reproducible baseline and explore extensions to non-co-planar geometries, Monte Carlo references and multi-centre datasets.

Informed Consent: Not applicable. This study involved only in-silico simulation on publicly available phantoms and demonstration datasets; therefore, no informed consent was required.

Conflict of Interest Statement: The authors declare that they have no conflict of interest related to this work.

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Use of AI for Writing Assistance: While the scientific focus of this research involves the development and evaluation of artificial intelligence (specifically, deep-learning models for dose prediction), this declaration concerns the use of generative AI tools in the preparation of the manuscript text. During preparation, the authors used Gemini (Google LLC, Mountain View, CA, USA) to improve language readability and to ensure grammatical correctness. After using this tool, the authors carefully reviewed and edited the content as needed. AI-assisted technologies were strictly limited to language editing and were not used in the conceptualisation, execution of the research or data generation. The authors take full responsibility for the final content of the publication.

Author Contributions: Concept – M.E.B., F.T.; Design – M.E.B., F.T.; Supervision – M.E.B., F.T.; Materials – M.E.B.; Data collection and/or processing – M.E.B., F.T.; Data analysis and/or interpretation – M.E.B., F.T.; Literature search – M.E.B., F.T.; Writing – M.E.B.; Critical review – M.E.B., F.T.

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REFERENCES

1. Babier A, Zhang B, Mahmood R, Moore KL, Purdie TG, McNiven AL, et al. OpenKBP: The open-access knowledge-based planning grand challenge and dataset. Med Phys 2021;48(9):5549–61.
2. Fan J, Wang J, Chen Z, Hu C, Zhang Z, Hu W. Automatic treatment planning based on three-dimensional dose distribution predicted from deep learning technique. Med Phys 2019;46(1):370–81.
3. Ronneberger O, Fischer P, Brox T. U-Net: Convolutional networks for biomedical image segmentation.

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doi: 10.5505/tjo.2026.4983

In Navab N, Hornegger J, Wells WM, Frangi AF, eds. Medical image computing and computer-assisted intervention - MICCAI 2015. Cham: Springer; 2015. p. 234–41.

4. Çiçek Ö, Abdulkadir A, Lienkamp SS, Brox T, Ronneberger O. 3D U-Net: Learning dense volumetric segmentation from sparse annotation. In Ourselin S, Joskowicz L, Sabuncu MR, Unal G, Wells W, eds. Medical image computing and computer-assisted intervention - MICCAI 2016. Cham: Springer; 2016. p. 424–32.
5. Kearney V, Chan JW, Haaf S, Descovich M, Solberg TD. DoseNet: A volumetric dose prediction algorithm using 3D fully-convolutional neural networks. Phys Med Biol 2018;63(23):235022.
6. Nguyen D, Jia X, Sher D, Lin MH, Iqbal Z, Liu H, et al. 3D radiotherapy dose prediction on head and neck cancer patients with a hierarchically densely connected U-Net deep learning architecture. Phys Med Biol 2019;64(6):065020.
7. Liu S, Zhang J, Li T, Yan H, Liu J. Technical note: A cascade 3D U-Net for dose prediction in radiotherapy. Med Phys 2021;48(9):5574–82.
8. Koike Y, Takegawa H, Anetai Y, Ohira S, Nakamura S, Tanigawa N. Patient-specific three-dimensional dose distribution prediction via deep learning for prostate cancer therapy: Improvement with the structure loss. Phys Med 2023;107:102544.
9. Bao P, Xia W, Yang K, Cai L, Cui Y. Beam-angle optimization for intensity-modulated radiation therapy using deep reinforcement learning. Med Phys 2024;51(5):3441–55.
10. Barragán-Montero AM, Nguyen D, Lu W, Lin MH, Norouzi-Kandalan R, Geets X, et al. Three-dimensional dose prediction for lung IMRT patients with deep neural networks: Robust learning from heterogeneous beam configurations. Med Phys 2019;46(8):3679–91.
11. Teng L, Wang B, Xu X, Zhang J, Mei L, Feng Q, et al. Beam-wise dose composition learning for head and neck cancer dose prediction in radiotherapy. Med Image Anal 2024;92:103045.
12. Wang Y, Piao Z, Gu H, Chen M, Zhang D, Zhu J. Deep learning-based prediction of radiation therapy dose distributions in nasopharyngeal carcinomas: A preliminary study incorporating multiple features including images, structures, and dosimetry. Technol Cancer Res Treat 2024;23:15330338241256594.
13. Pastor-Serrano O, Perkó Z. Millisecond speed deep learning based proton dose calculation with Monte Carlo accuracy. Phys Med Biol 2022;67(10):105006.
14. Sanner A, González C, Mukhopadhyay A. How reliable are out-of-distribution generalization methods for medical image segmentation? In Bauer S, Drechsler K, ed. Pattern recognition - DAGM GCPR 2021. Cham: Springer; 2021. p. 604–17.
15. Tajbakhsh N, Jeyaseelan L, Li Q, Chiang JN, Wu Z, Ding X. Embracing imperfect datasets: A review of deep learning solutions for medical image segmentation. Med Image Anal 2020;63:101693.
16. Wieser HP, Cisternas E, Wahl N, Ulrich S, Stadler A, Mescher H, et al. Development of the open-source dose calculation and optimization toolkit matRad. Med Phys 2017;44(6):2556–68.
17. He K, Zhang X, Ren S, Sun J. Deep residual learning for image recognition. Proc IEEE Conf Comput Vis Pattern Recognit 2016:770–8.
18. Vaswani A, Shazeer N, Parmar N, Uszkoreit J, Jones L, Gomez AN, et al. Attention is all you need. Adv Neural Inf Process Syst 2017;30:5998–6008.
19. Loshchilov I, Hutter F. Decoupled weight decay regularization. arXiv 2019;1711:05101
20. Low DA, Harms WB, Mutic S, Purdy JA. A technique for the quantitative evaluation of dose distributions. Med Phys 1998;25(5):656–61.
21. Hussein M, Clark CH, Nisbet A. Challenges in calculation of the gamma index in radiotherapy - towards good practice. Phys Med 2017;36:1–11.
22. Schlemper J, Oktay O, Schaap M, Heinrich M, Kainz B, Glocker B, et al. Attention gated networks: Learning to leverage salient regions in medical images. Med Image Anal. 2019;53:19–207.
23. Ezzell GA, Burmeister JW, Dogan N, LoSasso TJ, Mechalakos JG, Mihailidis D, et al. IMRT commissioning: Multiple institution planning and dosimetry comparisons, a report from AAPM Task Group 119. Med Phys 2009;36(11):5359–73.
24. Cardoso MJ, Li W, Brown R, Ma N, Kerfoot E, Wang Y, et al. MONAI: An open-source framework for deep learning in healthcare. arXiv 2022;2211:02701.
25. Wang B, Teng L, Mei L, Cui Z, Xu X, Feng Q, et al. Beam-wise dose composition for head-and-neck dose prediction. In Wang L, Dou Q, Fletcher PT, Speidel S, Li S, eds. Medical image computing and computer assisted intervention - MICCAI 2022. Cham: Springer; 2022. p. 575–84.
26. Newhauser WD, Zhang R. The physics of proton therapy. Phys Med Biol 2015;60(8):R155–R209.
27. Paganetti H. Range uncertainties in proton therapy and the role of Monte Carlo simulations. Phys Med Biol 2012;57(11):R99–R117.

Supplementary Materials

Cross-Geometry Generalisation of a Physics-Informed 3D Dose-Prediction Ensemble

This supplementary file accompanies the main manuscript submitted to the Turkish Journal of Oncology. It contains the supplementary figures and tables referred to in the main text, presented in the order in which they are first cited.

Contents

• Supplementary Table S1 — Structure labels excluded from the OAR mask

• Supplementary Table S2 — Functional form and parameter values of the photon depth-dose model

• Supplementary Table S3 — Complete training hyperparameters

• Supplementary Table S4 — Per-epoch training-loss values for the three networks

• Supplementary Figure S1 — Visualisation of the 13-channel input tensor

• Supplementary Figure S2 — Schematic of the three networks in the Voltron ensemble

• Supplementary Figure S3 — Per-network training-loss trajectories (linear scale)

• Supplementary Figure S4 — Complementary views of per-configuration performance

Supplementary Table S1 Structure labels excluded when building the organ-at-risk (OAR) mask (channel 3 of the input tensor). All non-target labels listed below are excluded; the remaining non-target labels are unioned into a single binary OAR mask. Matching is case-insensitive and ignores leading and trailing whitespace.

Label (case-insensitive)	**Description**
BODY	Whole patient body / external contour
SKIN	Patient skin contour
ENTRANCE	Beam entrance contour
DOSE_FALLOFF	Dose fall-off helper contour
ISOCENTER	Isocentre marker
CLIP	Generic clip marker

Couch	Treatment-couch contour
EXTERNAL	Synonym for body external
AIR	Air region inside the body contour
Lungs (combined)	Composite lungs mask when separate L/R lungs are present

OAR: organ at risk. The exclusion list is applied during matRad structure parsing and intentionally removes contours that are not clinically meaningful organs at risk (helper or marker structures).

Supplementary Table S2 Functional form and parameter values of the one-dimensional percent-depth-dose (PDD) model used to construct the per-beam ray-tracing maps in channels 4–13 of the input tensor.

Functional form (photons): $PDD(d) = (1 - exp(-\kappa \cdot d)) \cdot exp(-\mu \cdot d) \cdot (1 + \beta \cdot exp(-\alpha \cdot d))$, where d is the depth along the beam direction in voxels.

Parameter	**Value**	**Meaning**
μ (linear attenuation)	0.025 vox^{-1}	Bulk attenuation along the beam
κ (build-up rate)	0.05 vox^{-1}	Soft build-up region near beam entrance
β (build-up amplitude)	0.30	Strength of the build-up correction
α (build-up decay)	0.10 vox^{-1}	Decay of the build-up correction
σ-lateral	8.0 voxels	Lateral Gaussian width about the central axis
Max beam depth	160 voxels	Truncation depth along the beam

vox: Voxel. Parameter values were selected to give a smooth monotone PDD with a soft build-up region and were held fixed across all anatomies and beam configurations.

Supplementary Table S3 Complete training hyperparameters used for all three networks of the Voltron ensemble. The same hyperparameters were applied to SOTA-UNet3D, Res-UNet3D and Trans-UNet3D.

Hyperparameter	**Value**

Patch size	128 × 128 × 128 voxels
Patches per plan per epoch	16
Centre-on-PTV probability	0.70
Centre-on-foreground probability	0.30
Batch size (per step)	6
Gradient accumulation steps	8
Effective batch size	48
Number of epochs	40
Optimiser	AdamW
Initial learning rate	1×10^{-4}
Weight decay	5×10^{-4}
Learning-rate schedule	Cosine annealing with warm restarts
Warm-restart period (T_o)	10 epochs
Warm-restart multiplier (T_mult)	2
Loss function	MSE + L1 (unit weights)
Mixed-precision	Enabled (FP16 + dynamic loss scaling)
Gradient clipping	L2 norm 1.0
Random seed	42 (NumPy + PyTorch + Python random)
Augmentation library	MONAI 1.4 (Project MONAI consortium)
Augmentations applied	random flips, random affine, random Gaussian noise, random Gaussian smoothing, random intensity shift
Hardware	NVIDIA A100 GPU (NVIDIA Corp., Santa Clara, CA, USA)
Framework	PyTorch 2.x (PyTorch Foundation, San Francisco, CA, USA)

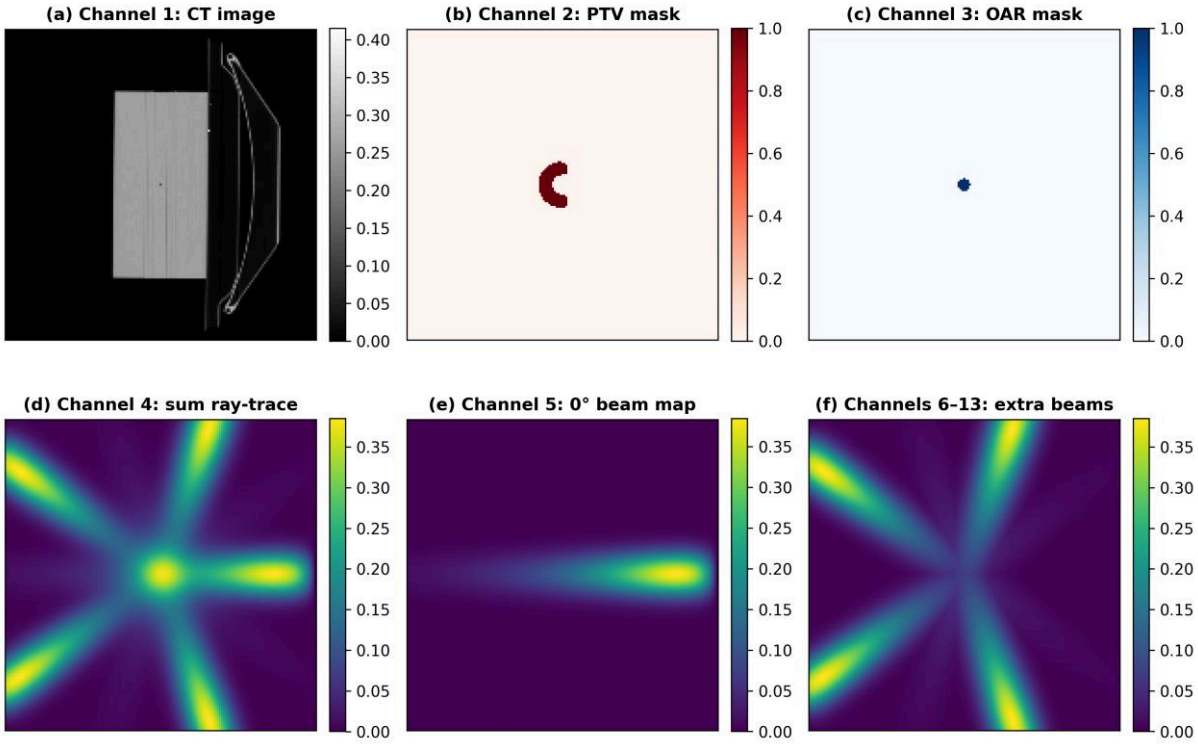
MSE: Mean squared error; L1: Mean absolute error; FP16: Half precision; T_o and T_mult are the standard parameters of the cosine-annealing-with-warm-restarts schedule.

Supplementary Table S4 Per-epoch training loss values (combined MSE + L1, unit weights) for the three networks of the Voltron ensemble. All three networks were trained for 40 epochs from scratch on the single C0 beam configuration.

Epoch	SOTA-UNet3D	Res-UNet3D	Trans-UNet3D
1	0.4967	0.5282	0.5950
2	0.3972	0.4095	0.4849
3	0.3642	0.3216	0.3927
4	0.2912	0.2651	0.3361
5	0.2804	0.2263	0.3108
6	0.2758	0.2095	0.3079
7	0.2673	0.2007	0.2953
8	0.2668	0.1905	0.2868
9	0.2499	0.1789	0.2813
10	0.2545	0.1773	0.2782
11	0.2429	0.1809	0.2735
12	0.2332	0.1639	0.2584
13	0.2195	0.1430	0.2451
14	0.2197	0.1367	0.2368
15	0.2198	0.1287	0.2274
16	0.2260	0.1187	0.2278
17	0.2003	0.1129	0.2269
18	0.1863	0.1075	0.2255
19	0.2148	0.1055	0.2254
20	0.1877	0.1111	0.2195
21	0.1892	0.0937	0.2098
22	0.1975	0.1026	0.2075
23	0.1949	0.0993	0.2190
24	0.1950	0.0958	0.2209
25	0.1887	0.0917	0.2128
26	0.1930	0.0947	0.1967
27	0.1921	0.0919	0.1958

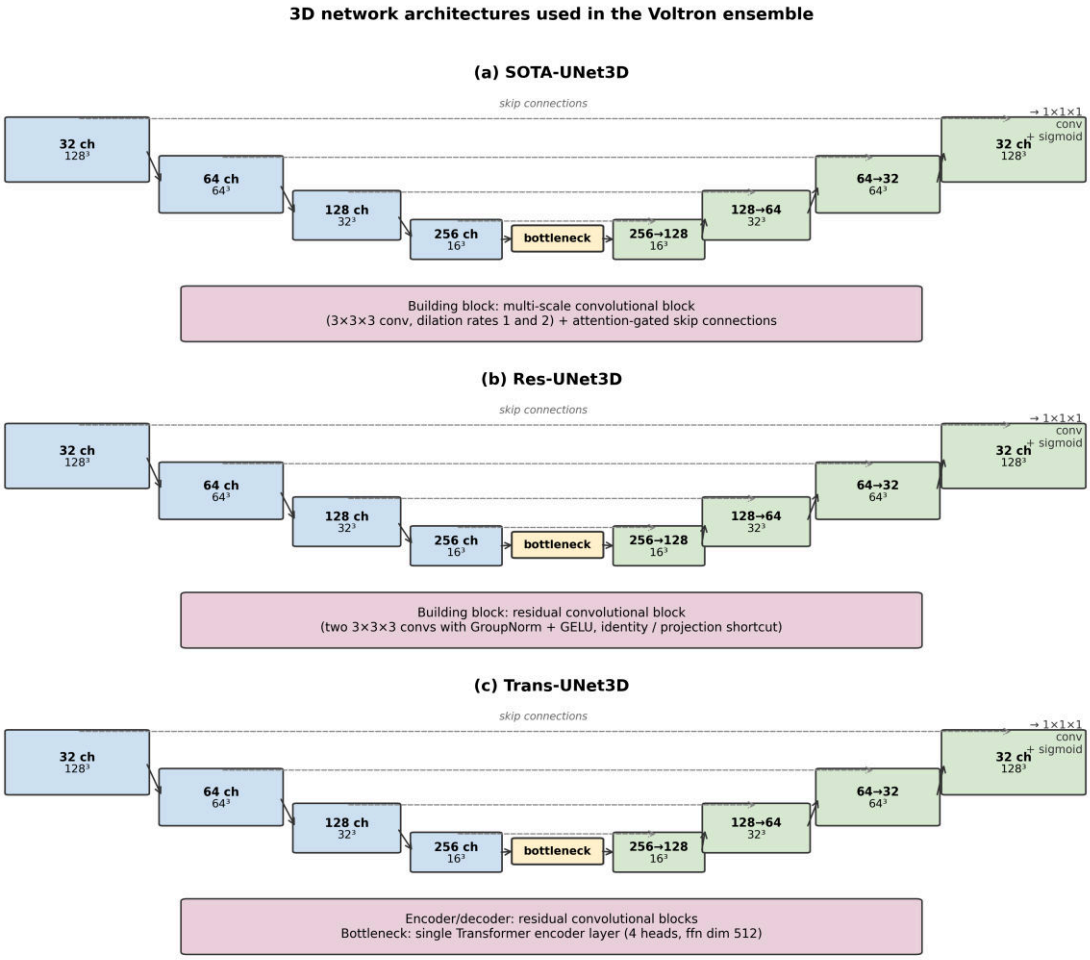
28	0.1837	0.0919	0.2127
29	0.1838	0.0907	0.2078
30	0.2027	0.0913	0.2210
31	0.1858	0.0953	0.2127
32	0.1900	0.0917	0.1994
33	0.1877	0.0813	0.2068
34	0.1856	0.0821	0.2015
35	0.1873	0.0753	0.1929
36	0.1727	0.0727	0.2003
37	0.1745	0.0795	0.1893
38	0.1732	0.0730	0.1962
39	0.1693	0.0729	0.1796
40	0.1674	0.0736	0.1806

MSE: Mean squared error; L1: Mean absolute error. Values rounded to four decimal places.



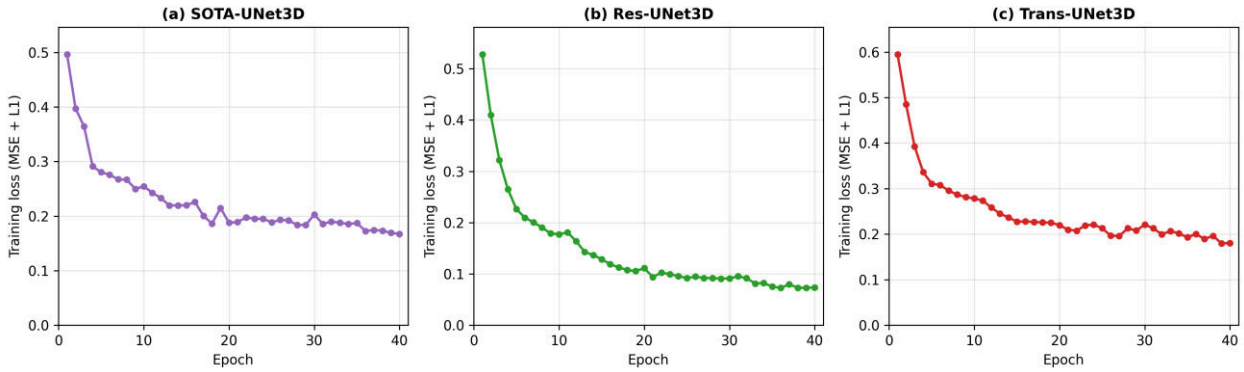
Supplementary Fig. S1. Visualisation of the 13-channel input tensor used by all three networks on a representative axial slice of the held-out TG-119 anatomy. (a) Channel 1: CT

image (Hounsfield-unit values normalised to [0, 1]). (b) Channel 2: Binary planning target volume (PTV) mask. (c) Channel 3: Binary organ-at-risk (OAR) mask. (d) Channel 4: Voxel-wise sum of all per-beam ray-tracing maps shown for the C0 configuration. (e) Channel 5: An individual per-beam ray-tracing map for the 0° beam of C0. (f) Channels 6–13: Maximum projection of the remaining per-beam maps; unused beam slots in configurations with fewer than nine beams are zero-padded. CT, computed tomography; PTV, planning target volume; OAR, organ at risk.

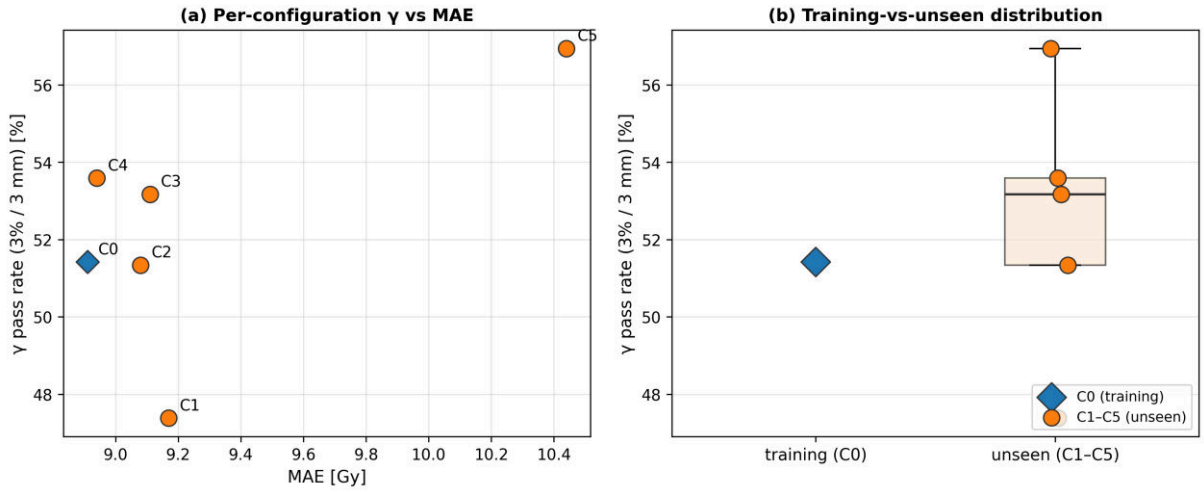


Supplementary Fig. S2. Schematic of the three three-dimensional networks that make up the Voltron ensemble. All three share a four-level encoder–decoder topology with skip connections; they differ in the type of computational block applied at each stage. (a) SOTA-UNet3D uses multi-scale convolutional blocks (dilated 3 × 3 × 3 convolutions with dilation rates 1 and 2) combined with attention-gated skip connections. (b) Res-UNet3D uses simple residual convolutional blocks (two 3 × 3 × 3 convolutions with group normalisation and

GELU, plus an identity or projection shortcut). (c) Trans-UNet3D inserts a single transformer encoder layer at the bottleneck (four heads, feed-forward dimension 512). All three networks end in a 1 × 1 × 1 convolution followed by a sigmoid activation to constrain the output to the [0, 1] dose-fraction interval. The Voltron ensemble averages the three voxel-wise predictions at inference time.



Supplementary Fig. S3. Per-network training-loss trajectories on a linear vertical axis. (a) SOTA-UNet3D. (b) Res-UNet3D. (c) Trans-UNet3D. The combined mean-squared-error + mean-absolute-error loss is shown for each of the 40 training epochs on the single C0 configuration. The combined log-scale view of all three networks is presented as Figure 3 in the main text.



Supplementary Fig. S4. Complementary views of the per-configuration Voltron ensemble performance on the held-out TG-119 anatomy. (a) Scatter plot of the three-dimensional

gamma pass rate (3% / 3 mm) against the mean absolute error (MAE) per beam configuration; C0 (training) is marked by a blue diamond and the unseen configurations C1–C5 are shown in orange. (b) Distribution comparison: the single gamma value of the training configuration (C0; blue diamond) versus the distribution of values across the five unseen configurations (orange dots; box plot drawn for reference).

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ORIGINAL ARTICLE

Demographic Variables, Clinical Characteristics, Quality of Life and Costs from Patient Perspective of Hematological Oncology Cases: A Study Conducted in Türkiye

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OBJECTIVE

To investigate the associations between socio-demographic and clinical characteristics, quality of life (QoL), and patient-borne costs among haematological oncology outpatients in Türkiye.

METHODS

This cross-sectional study included 137 adult haematological oncology outpatients treated at a public oncology centre between July and August 2024. QoL was assessed using the EQ-5D-3L and EQ VAS. Group differences were analysed using t-tests and ANOVA, while multiple linear regression identified independent predictors of QoL. Pearson correlation analysis was used to examine relationships between variables. Disease costs were calculated as total and average annual expenses per patient.

RESULTS

Respondents reported moderate QoL, with anxiety/depression being the most affected dimension. The mean EQ VAS score was 56.28±16.61. Gender and marital status were not associated with QoL ($p>0.05$). Older age was associated only with poorer self-care ($p=0.038$). Lower educational attainment, longer disease duration, and advanced cancer stage were associated with poorer QoL across several EQ-5D-3L dimensions ($p<0.05$). Regression analysis identified education ($\beta=-0.235$, $p=0.019$) and cancer detection time ($\beta=0.229$, $p=0.009$) as independent predictors of QoL. The average annual patient-borne cost was 77,378₺ ($2,353), with income loss representing the largest financial burden.

CONCLUSION

Clinical characteristics, particularly cancer stage, exert a greater influence on QoL than socio-demographic factors. Strategies promoting early diagnosis, patient education, and financial support may improve quality of life and reduce the economic burden of cancer care.

Keywords: Cancer pain; cost of illness; hematological oncology cases, outpatients; quality of life.
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INTRODUCTION

Cancer remains one of the leading causes of death and disability worldwide, imposing a substantial disease burden on societies, and its incidence continues to increase steadily on a global scale.[1] The global incidence of cancer has risen dramatically in recent decades, driven by aging populations, lifestyle factors,

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and advancements in diagnostic capabilities. In 2020 alone, an estimated 19.3 million new cases and 10 million cancer-related deaths were reported.[2] The course of cancer in Türkiye is no different from the trend in the world. According to 2022 data published by the WHO, 240.013 people were diagnosed with cancer in Türkiye in 2022, and about 129.672 (25.2%) people lost their lives.[3]

Cancer is the second leading cause of death after cardiovascular diseases, both globally and in Türkiye. Statistics indicate that approximately one in every six deaths worldwide and one in every five deaths in Türkiye are due to cancer. The five most common types of cancer globally and in Türkiye are breast, lung, prostate, colorectal, and thyroid cancers. In Türkiye, lung, prostate, and colorectal cancers are the most frequently diagnosed among men, while breast and thyroid cancers are more common among women. Each type of cancer has distinct causes, risk factors, diagnostic methods, and treatment approaches. Lifestyle factors such as tobacco use, obesity, poor nutrition, physical inactivity, and alcohol consumption significantly increase cancer risk. As such, early detection and screening strategies must be tailored to each cancer type. Moreover, implementing community-based screening programs as part of a comprehensive cancer control strategy is essential.[4]

Cancer treatment is often prolonged and poses significant physical, psychological, and socioeconomic burdens on patients. The disease and its treatment can substantially impact an individual's quality of life, which is a key factor in patient care and monitoring. Quality of life (QoL) encompasses physical, functional, psychological, and social well-being and is often diminished due to both the disease itself and its treatment.[5] Studies have highlighted that cancer patients generally experience a lower QoL due to the challenges associated with their condition.[6,7] Additionally, the financial burden of cancer is considerable. Direct medical costs, along with indirect costs such as lost productivity, long-term disability, and mortality, contribute to the overall economic impact of the disease.[8] A research indicates that indirect costs can sometimes rival or exceed direct medical expenses,[9] underscoring the need for comprehensive economic evaluations in oncology and haematological case. Taken together, survivors of cancer, especially in the early stages of their cancer journey, often face negative economic and health outcomes throughout their lives.[10]

Beyond clinical efficacy and safety, the quality of life of cancer patients and the economic burden of treatment is also crucial in decision-making processes. A holistic approach that incorporates these factors enables more informed and rational healthcare decisions while maximizing the potential value of treatments. Taking these factors into account, this study aims to examine the quality of life and costs associated with various types of hematological oncology cases from both the patient's and their companion's perspective in a sample of Türkiye.

MATERIALS AND METHODS

Study Purpose

The aim of this study is to present the disease and personal characteristics, QoL findings, and costs of hematological oncology patients receiving outpatient care from the patient perspective.

Research Type and Sampling

This descriptive cross-sectional study was conducted among individuals receiving outpatient care for cancer or suspected cancer at a public medical center in Malatya, Türkiye. The study collected data at a single point in time to describe the distribution and frequency of variables within the study population. The study was carried out between July 1, 2024, and August 31, 2024, without employing a specific sampling method; instead, it was applied to individuals who agreed to participate. As the study aimed to include all eligible cancer patients receiving outpatient care during the study period, no sampling method was employed. Questionnaires were administered to patients who voluntarily agreed to participate. For respondents who were unable to complete the questionnaire independently, assistance was provided by their relatives. A total of 137 cases who visited the relevant unit and consented to participate in the study were included.

Criteria for Inclusion

The inclusion criteria were: (1) age ≥18 years, (2) receiving outpatient treatment, (3) ability to respond to the study questions either independently or with assistance from a relative, and (4) having received treatment at the hospital for at least one year.

Data Collection and Measurements

Before data collection, verbal approval was obtained from the hospital administration. Patients were informed about the study, and those who provided informed consent completed the questionnaire administered by the researchers. Each questionnaire required approximately 10–15 minutes to complete. Data were collected at appropriate times to avoid periods of pain,

nausea, or vomiting, thereby ensuring participant comfort. For patients unable to complete the questionnaire themselves, a relative completed it on their behalf.

For data collection, the researchers utilized a Personal Information Form (including statements regarding patients' socio-demographic characteristics and cancer status) developed based on the literature, the EQ-5D-3L General Quality of Life Scale developed by EUROQOL already validated for reliability and validity in Türkiye to assess patients' quality of life, and a cost survey designed to capture patients' perspectives, based on previous studies conducted in Türkiye. It should be noted that as there is no validated value set for the EQ-5D-3L in the Turkish population, it was not possible to calculate utility index scores. Therefore, the data were analyzed using dimension-level scores – representing the frequency of reported problems across the five dimensions – and the EQ VAS, which provides a quantitative measure of the patient's self-assessed health status.

Cost-of-illness studies conducted from the patient perspective include out-of-pocket expenses incurred by patients or their caregivers for direct medical care, income losses due to morbidity and mortality, transportation costs related to healthcare access, non-medical out-of-pocket expenses, and transfer payments received due to illness.[11] Based on this reference, a 6-items form was developed through literature review in Türkiye to assess the monthly and annual cancer-related costs from the perspective of patients and their caregivers.[12–14]

The EQ-5D-3L was used to assess respondents' QoL based on the EUROQOL quality of life measurement system. The EQ-5D-3L consists of two main components: The EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D-3L general QoL scale includes five dimensions: Mobility, self-care, usual activities (ability to perform daily tasks), pain/discomfort, and anxiety/depression. Each dimension has three levels: No problems, some problems, and extreme problems. Patients were asked to indicate their health status by selecting the most appropriate statement for each dimension. This selection results in a single-digit number representing the chosen level for that dimension.

The EQ VAS (Visual Analog Scale) measures patients' self-rated current health status on a scale ranging from 0 ("the worst possible health state") to 100 ("the best possible health state"). It provides a quantitative measure of health outcomes based on patients' own perceptions. As the EQ-5D-3L is a generic health-related quality of life instrument, it is considered a valid tool for assessing quality of life in patients with cancer. [15]

Statistical Analysis

The EQ-5D-3L demonstrated excellent internal consistency, with a Cronbach's alpha (α) of 0.905. Although the Kolmogorov–Smirnov and Shapiro–Wilk tests indicated statistically significant departures from normality ($p<0.001$), the skewness (0.117) and kurtosis (-0.321) values were within the acceptable range (-1.50 to 1.50) for social science research.[16] Given the large sample size and the approximately normal distribution of the data, parametric tests were used for the analyses. The direction and strength of correlations were interpreted according to established criteria in the literature as follows:[17]

- 0.00–0.29: Weak relationship
- 0.30–0.64: Moderate relationship
- 0.65–0.84: Strong relationship
- 0.85–1.00: Very strong relationship

Data were analyzed using descriptive statistics (frequency, percentage, mean, and standard deviation). Parametric tests were used to compare QoL scores, while Pearson correlation analysis was performed to examine relationships between variables. Independent samples t-tests were used to compare the means of two groups, and one-way analysis of variance (ANOVA) was used to compare the means of more than two groups. To control for Type I error due to multiple comparisons, the Bonferroni correction was applied to the EQ-5D-3L dimension and subgroup analyses. Multiple linear regression analysis was performed to identify factors associated with QoL, as measured by the EQ-5D-3L index score. Cost analysis included total and mean costs per patient. As the hospital did not authorize access to direct treatment costs (e.g., radiotherapy, chemotherapy, and surgical interventions), the cost analysis was conducted from the patient's perspective. Statistical analyses were performed using IBM SPSS Statistics version 27.0. Statistical significance was set at $p<0.05$, with a 95% confidence level.

Ethical Declaration

Ethical approval for the study was derived from the Bingöl University Social and Human Sciences Scientific Research and Publication Ethics Committee (Date: 13/08/2024, No: E.166497). Additionally, verbal informed consent was obtained from the patients included in the study after explaining the study's purpose to them. Moreover, this research was conducted in ac-

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cordance with the principles of the Declaration of Helsinki (www.wma.net/e/policy/b3.htm).

RESULTS

Among the respondents, 59.9% were male, 76.6% were married, and 72.3% were unemployed. The largest age group was ≥60 years (40.9%), followed by 53–59 years (19.7%). Illiteracy and postgraduate education were uncommon, with most respondents having completed either primary school or university (Table 1). Monthly income was categorized according to the minimum wage established by public authorities in Türkiye at the time of the study. The largest proportion of respondents (43.8%) reported a monthly income of 10.000–20.000₺ ($306–613). Given the universal health insurance system in Türkiye, most respondents (90.5%) were covered by public health insurance.

Table 2 summarizes the cancer-related characteristics of the respondents. Overall, 39.4% had been diagnosed within the previous 2 years, 41.6% had lived with the diagnosis for 3–5 years, and 19.0% for 6 years or longer, with the distribution differing significantly across categories (t=28.439, p<0.001). Most respondents (68.6%) had an unknown cancer stage. This high proportion is largely attributable to the predominance of hematological malignancies in the study sample, for which conventional staging systems are often not applicable. In addition, incomplete medical records, unavailable staging information for patients referred from other institutions, ongoing diagnostic evaluations at the time of data collection, and the retrospective nature of data retrieval may have contributed to the high proportion of cases with unknown stages.

Among patients with known disease stage, Stage I was the second most common category (12.4%), and the distribution of cancer stages differed significantly across categories (t=32.515, p<0.001). Acute Myeloid Leukemia (AML) was the most common cancer type (24.8%), followed by Multiple Myeloma (MM) (14.6%) and lymphoma (11.7%). The distribution of cancer types was also statistically significant (t=20.319, p<0.001). The cancer profile observed in this study differs from national and global epidemiological patterns, in which breast, lung, and colorectal cancer are the most prevalent. However, the study was not intended to represent all patients with cancer in Türkiye; rather, it reflects the characteristics of patients receiving care at the study center. Therefore, deviations from the overall epidemiological distribution of cancer types were expected. Additionally, detailed data on cancer types and frequencies are given in Table 2 and Figure 1.

Table 1 Socio-demographic characteristics of the respondents

Characteristics of respondents	n	%
Gender		
Female	55	40.1
Male	82	59.9
Marital status		
Single	32	23.4
Married	105	76.6
Age		
18–25	12	8.8
26–34	11	8.0
35–43	13	9.5
44–52	18	13.1
53–59	27	19.7
≥60	56	40.9
Education		
Illiterate	10	7.3
Primary school	35	25.5
Secondary school	26	19.0
High school	37	27.0
University	27	19.7
Postgraduate	2	1.5
Work status		
Employed	38	27.7
Non-employed	99	72.3
Income		
≤10.000 ₺ (≤$306)	32	23.4
10.000-20.000 ₺ ($306-$613)	60	43.8
20.000 TL-30.000 ₺ ($613-$919)	24	17.5
≥30.000 TL (≥$919)	21	15.3
Insurance		
Universal health insurance (UHI)	124	90.5
Private health insurance	3	2.2
No health insurance	10	7.3

Table 3 presents the respondents' EQ-5D-3L scores. Across all five dimensions, most respondents reported some degree of impairment, indicating reduced health-related quality of life. The highest mean score was observed for anxiety/depression (2.09±0.66), with 82.5% of respondents reporting moderate or extreme problems, followed by pain/discomfort (1.99±0.55; 84.7%), usual activities (1.94±0.60; 78.8%), self-care (1.80±0.70; 63.5%), and mobility (1.79±0.61; 68.6%). The mean EQ VAS score was 56.28±16.61, indicating a moderate level of self-perceived health status.

Table 2 Respondents' findings regarding the case of cancer

Characteristics of respondents	n	%	Mean	SD	t	p
Cancer detection time						
Initial stage	54	39.4	1.80	0.739	28.439	<0.001
3–5 years	57	41.6				
≥6	26	19.0				
Cancer stage						
Stage I	17	12.4	4.10	1.477	32.515	<0.001
Stage II	11	8.0				
Stage III	7	5.1				
Stage IV	8	5.8				
Unknown	94	68.6				
Cancer type						
AML	34	24.8	6.22	3582	20.319	<0.001
MM	20	14.6				
Lymphoma	16	11.7				
ALL	13	9.5				
KLL	10	7.3				
Lung	8	5.8				
MDS	7	5.1				
ITP	6	4.4				
KML	5	3.6				
Breast	5	3.6				
Colon	3	2.2				
Anemia	3	2.2				
Bladder	2	1.5				
Pancreatic	2	1.5				
Prostate	2	1.5				
Stomach	1	0.7				

AML: Acute myeloid leukemia; MM: Multiple myeloma; ALL: Acute lymphoblastic leukemia; KLL: Chronic lymphocytic leukemia; MDS: Myelodysplastic syndrome; İTP: Immune thrombocytopenic purpura; KML: Chronic myeloid leukemia.

Table 4 presents the associations between respondents' socio-demographic and disease-related characteristics and the EQ-5D-3L dimensions and EQ VAS scores. Gender and marital status were not significantly associated with any EQ-5D-3L dimension or the EQ VAS (p>0.05). Age was significantly associated only with self-care (F=2.433, p=0.038), with respondents aged ≥60 years reporting greater impairment.

Educational level was significantly associated with self-care (F=2.633, p=0.026), usual activities (F=3.784, p=0.003), and pain/discomfort (F=2.473, p=0.035), indicating poorer QoL among respondents with lower educational attainment. Cancer detection time was significantly associated with self-care (F=4.895, p=0.009) and usual activities (F=3.656, p=0.028), with longer disease duration corresponding to greater impairment.

Cancer stage showed the strongest associations with QoL. Significant differences were observed for mobility (F=3.925, p=0.005), self-care (F=2.588, p=0.040), usual activities (F=2.710, p=0.033), and pain/discomfort (F=6.966, p=0.001), with progressively poorer scores from Stage I to Stage IV. Although anxiety/depression (p=0.063) and EQ VAS scores (p=0.050) also worsened with advancing stage, these associations did not reach statistical significance. Overall, disease-related characteristics, particularly cancer stage, were more strongly associated with QoL than socio-demographic characteristics. Lower educational attainment, longer cancer detection time, and advanced cancer stage were associated with poorer outcomes across multiple EQ-5D-3L dimensions.

Multiple linear regression analysis was performed to identify factors associated with QoL, as measured

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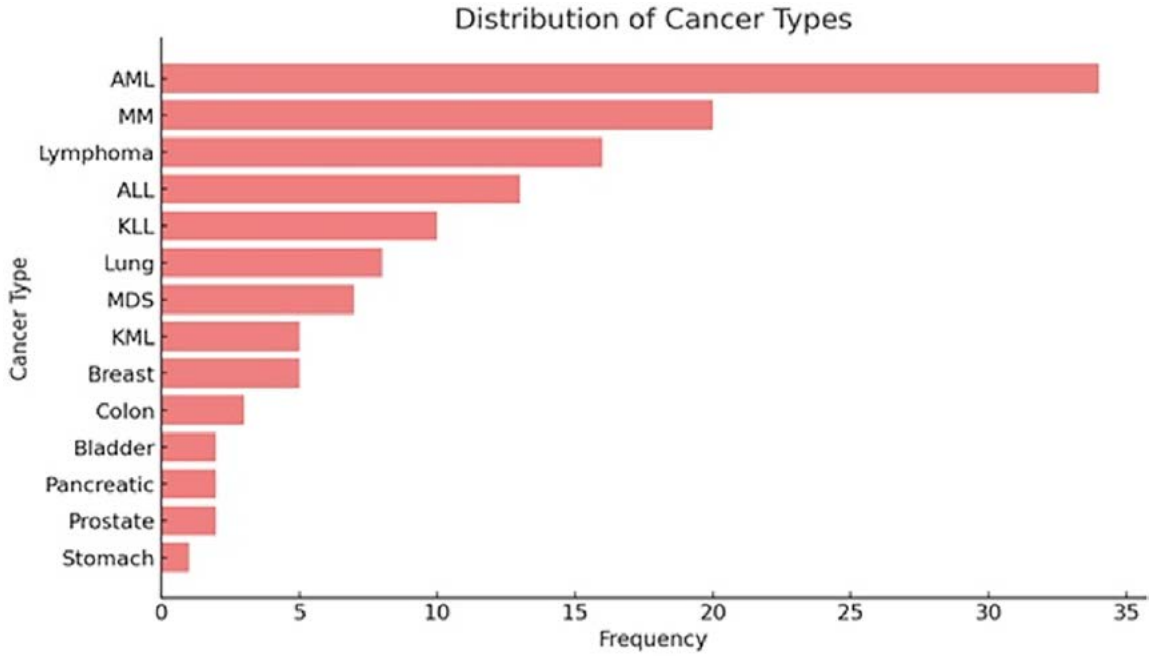


Fig. 1. Cancer types detected in patients.

Table 3 Respondents' quality of life assessment scale (EQ-5D-3L) scores

EQ-5D-3L Sub-dimensions	Statistical tests			
	n	%	Mean	SD
Mobility				
I have no problems in walking about	43	31.4	1.79	0.612
I have some problems in walking about	80	58.4		
I am confined to bed	14	10.2		
Self-care				
I have no problems with self-care	50	36.5	1.80	0.698
I have some problems washing and dressing myself	65	47.4		
I am unable to wash or dress myself	22	16.1		
Usual activities				
I have no problems with performing my usual activities	29	21.2	1.94	0.603
I have some problems with performing my usual activities	87	63.5		
I am unable to perform my usual activities	21	15.3		
Pain-discomfort				
I have no pain or discomfort	21	15.3	1.99	0.549
I have moderate pain or discomfort	96	70.1		
I have extreme pain or discomfort	20	14.6		
Anxiety-depression				
I am not anxious or depressed	24	17.5	2.09	0.663
I am moderately anxious or depressed	76	55.5		
I am extremely anxious or depressed	37	27.0		
Average VAS score	137	100.0	56.28	16.61

SD: Standard deviation; VAS: Visual analogue scale.

Table 4 Association of some socio-demographic variables of respondents with quality of life

Demographic variables	Sub-dimensions of EQ-5D-3L					
	Mobility mean±SD	Self-care mean±SD	Usual activities mean±SD	Pain-discomfort mean±SD	Anxiety-depression mean±SD	VAS score mean±SD
Gender						
Female	1.89±0.72	1.91±0.82	2.06±0.68	2.11±0.68	2.23±0.69	54.86±19.49
Male	1.75±0.57	1.75±0.65	1.90±0.57	1.95±0.50	2.05±0.65	56.76±15.56
Tests	t=1.093	t=1.167	t=1.316	t=1.313	t=1.387	t=-0.574
p	p=0.276	p=0.245	p=0.190	p=0.195	p=0.183	p=0.602
Marital status						
Married	1.76±0.61	1.81±0.69	1.94±0.59	1.99±0.56	2.10±0.64	56.05±15.72
Single	1.88±0.61	1.75±0.72	1.94±0.67	2.00±0.51	2.09±0.74	57.03±19.50
Tests	t=-0.915	t=0.421	t=0.044	t=-0.086	t=0.011	t=-0.292
p	p=0.362	p=0.674	p=0.965	p=0.932	p=0.991	p=0.770
Age						
18–25	1.83±0.58	1.67±0.65	1.83±0.72	1.83±0.58	1.92±0.67	61.67±17.88
26–34	1.91±0.54	1.82±0.75	2.00±0.63	2.00±0.63	2.18±0.87	54.55±18.64
35–43	1.54±0.52	1.54±0.52	1.85±0.56	2.08±0.49	2.23±0.60	61.15±17.34
44–52	1.56±0.71	1.50±0.71	1.72±0.67	1.94±0.42	1.94±0.64	59.17±15.07
53–59	1.81±0.56	1.70±0.54	1.93±0.47	1.96±0.59	2.11±0.64	56.30±16.21
≥60	1.88±0.63	2.02±0.75	2.05±0.62	2.04±0.57	2.13±0.66	53.59±16.46
Tests	F=1.304	F=2.433	F=1.029	F=0.367	F=0.523	F=0.946
p	p=0.266	p=0.038	p=0.403	p=0.870	p=0.759	p=0.454
Education						
Illiterate	2.10±0.57	2.30±0.82	2.50±0.53	2.50±0.53	2.30±0.68	50.50±16.24
Primary school	1.91±0.62	1.97±0.75	2.11±0.63	2.03±0.51	3.20±0.68	50.57±16.62
Secondary school	1.69±0.62	1.72±0.65	1.81±0.57	1.92±0.63	2.04±0.66	56.73±15.55
High school	1.84±0.64	1.73±0.65	1.89±0.62	1.97±0.60	2.22±0.67	58.11±16.76
University	1.56±0.51	1.52±0.58	1.74±0.45	1.89±0.32	1.81±0.56	62.41±15.90
Postgraduate	1.50±0.71	1.50±0.71	1.50±0.71	1.50±0.71	1.50±0.71	62.50±17.68
Tests	F=1.928	F=2.633	F=3.784	F=2.473	F=2.011	F=2.028
p	p=0.094	p=0.026	p=0.003	p=0.035	p=0.081	p=0.079
Cancer detection time						
Initial stage	1.63±0.59	1.57±0.60	1.78±0.54	1.89±0.54	2.04±0.64	58.80±15.78
3–5 years	1.89±0.62	1.91±0.71	2.02±0.64	2.04±0.57	2.09±0.72	54.82±16.96
≥6	1.88±0.59	2.00±0.75	2.12±0.59	2.12±0.52	2.23±0.59	54.23±17.48
Tests	F=3.096	F=4.895	F=3.656	F=1.806	F=0.752	F=1.037
p	p=0.058	p=0.009	p=0.028	p=0.168	p=0.473	p=0.357
Cancer stage						
Stage I	1.47±0.51	1.53±0.72	1.71±0.59	1.53±0.51	1.82±0.81	63.24±18.02
Stage II	1.82±0.41	1.73±0.47	1.91±0.30	2.09±0.54	2.18±0.60	55.45±13.69
Stage III	2.14±0.69	2.14±0.69	2.14±0.54	2.43±0.54	2.29±0.49	49.29±22.07
Stage IV	2.38±0.52	2.38±0.52	2.50±0.54	2.50±0.54	2.63±0.52	43.13±14.13
Unknown	1.77±0.61	1.78±0.71	1.93±0.61	1.99±0.50	2.07±0.64	56.76±15.91
Tests	F=3.925	F=2.588	F=2.710	F=6.966	F=2.289	F=2.436
p	p=0.005	p=0.040	p=0.033	p=0.001	p=0.063	p=0.050

SD: Standard deviation.

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Table 5 Factor affecting quality of life of cancerous patients

Variables	B	SE	β	t	p	VIF
(constant)	1.202	0.600		2.005	**0.047**	
Gender	-0.114	0.101	-0.118	-1.424	0.157	1.052
Marital status	0.136	0.140	0.108	0.967	0.335	1.918
Age	-0.015	0.040	-0.047	-0.369	0.713	2.485
Education	-0.097	0.041	-0.235	-2.379	**0.019**	1.500
Work status	0.252	0.145	0.212	1.742	0.084	2.281
Income	0.076	0.070	0.140	1.080	0.282	2.576
Insurance	0.135	0.095	0.136	1.424	0.157	1.404
Cancer detection time	0.165	0.062	0.229	2.645	**0.009**	1.148
Cancer stage	0.040	0.032	0.109	1.222	0.224	1.232
Cancer type	-0.005	0.012	-0.031	-0.370	0.712	1.232

B: Unstandardized Coefficient; SE: Standard error; VIF: Visual analogue scale.

Table 6 Estimated monthly costs incurred by patients due to illness

Cost statements	Status	n	%	Total annual costs (¤/$)	Average annual cost per patient (¤/$)
Medications related to the disease but not covered by insurance	Yes	39	28.5	1,230,000 (37,403)	31,538 (959)
	No	98	71.5		
Special nutrition and diet recommended by the doctor for the disease in question	Yes	39	28.5	220,000 (6,690)	5,641.03 (172)
	No	98	71.5		
External food consumption due to illness during health care services	Yes	100	73.0	611,750 (18,603)	6,118 (186)
	No	37	27.0		
Transportation fee commuting to hospital due to disease	Yes	102	74.5	333,450 (10,140)	3,237 (98)
	No	35	25.5		
Compulsory accommodation related to the disease	Yes	12	8.8	67,700 (2,059)	5,270 (160)
	No	125	91.2		
Other disease-related expenses (personal care, etc.)	Yes	63	45.99	520,000 (15,813)	8,253 (251)
	No	74	54.01		
Average income loss in the last one year due to treatment of the disease		137	100.0	10,715,500 (325,819)	77,378 (2,353)

by the EQ-5D-3L index score (Table 5). The model included sociodemographic and clinical variables (gender, age, marital status, education, employment status, income, insurance status, cancer type, cancer stage, and cancer detection time). Among these, only educational level (β=−0.235, p=0.019) and cancer detection time diagnosis (β=0.229, p=0.009) were significant independent predictors of QoL. Collinearity diagnostics indicated no evidence of multicollinearity, with all variance inflation factors (VIF) values ranging from 1.052 to 2.576. In addition, the model was statistically significant (F=2.777, p<0.004) and explained 11.6% of the variance in QoL (adjusted R^2=0.116). On the other hand, longer cancer detection time was associated with higher EQ-5D-3L index scores, whereas higher educational attainment was associated with lower index scores in this cohort. None of the remaining sociodemographic or clinical variables, including age, sex, cancer stage, and cancer type, showed statistically significant independent associations with QoL.

We calculated the monthly costs for patients who answered 'yes' to the cost statements in Table 6, then

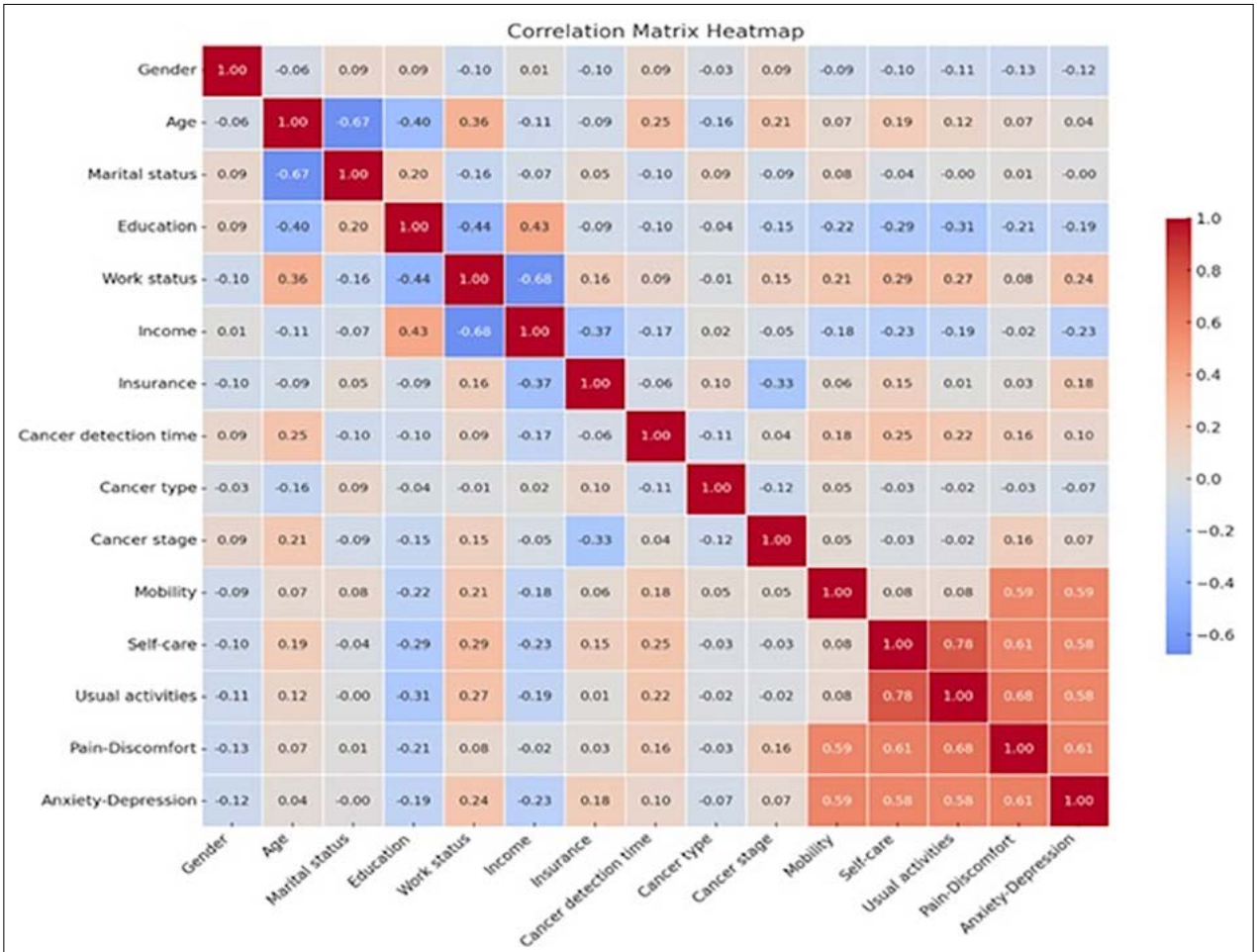


Fig. 2. Correlation matrix head map.

determined their total annual costs. Next, we divided the total annual costs by the number of these patients to find the average annual cost per patient. The table presents the financial burden of disease-related expenses on patients, focusing on various cost factors such as medication, special nutrition, transportation, and income loss. The total annual costs for each category were calculated, and the average annual cost per affected patient was determined. The total income loss amounted to 10.714,500 ₺ ($325.819). The average income loss per patient was 77.378 ₺ ($2.353), making it the most significant financial impact among all categories.

The highest financial burden comes from income loss, followed by medications not covered by insurance and other disease-related expenses. A large portion of patients also faced costs related to transportation, external food consumption, and special diets, which add to the overall economic strain of managing the disease. The data highlights the need for financial support mechanisms, insurance coverage expansions, or policy changes to mitigate these costs for patients.

The heatmap illustrates (Fig. 2) the correlation among the variables. The colors visually represent the strength and direction of the relationships: Dark red indicates a strong positive correlation, whereas dark blue signifies a strong negative correlation. The numerical values in each cell represent the Pearson correlation coefficients. This matrix demonstrates how each variable is related to the others. For example, there is a positive correlation between education level and income (r=0.428), indicating that higher levels of education are generally associated with higher income. Additionally, a strong positive correlation is observed between self-care and usual activities (r=0.783), suggesting that individuals with better self-care abilities are typically more capable of performing daily activities.

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DISCUSSION

Cancer care illustrates that the value of healthcare extends beyond clinical outcomes alone.[18] Traditionally, the quality of cancer care has been assessed using indicators such as morbidity, mortality, and readmission rates. However, comprehensive evaluation also requires consideration of patient-reported outcomes, including QoL, perceived health status, functional impairment, and financial burden.[19] Oncology remains one of the most resource-intensive areas of healthcare because of increasingly complex diagnostic and therapeutic approaches.[18] Accordingly, an estimated 28–48% of cancer survivors experience financial hardship due to direct (e.g., out-of-pocket expenses) and indirect (e.g., income loss) costs, which has consistently been associated with psychological distress and poorer QoL.[20,21] As a multidimensional construct encompassing physical, psychological, and social well-being, QoL has become a key outcome for evaluating cancer care.[22] Consequently, patient characteristics, treatment costs, and patient-reported outcomes should all be considered when assessing the value of cancer care interventions.

Evidence simultaneously examining patient-reported QoL and patient-borne costs across heterogeneous cancer populations remains limited both in Türkiye and internationally. Most previous studies have focused on a single cancer type, restricting the generalizability of their findings. By including patients with both solid tumors and hematological malignancies and assessing both QoL and patient-reported costs, the present study provides a broader perspective on the factors associated with health outcomes in routine oncology practice. The predominance of older adults and hematological malignancies in our cohort distinguishes this study from many population-based investigations. Although 68.6% of respondents had an unknown cancer stage, this primarily reflects the inclusion of hematological malignancies, for which conventional TNM staging is often not applicable. Nevertheless, caution is warranted when interpreting stage-specific findings because incomplete staging information may have reduced statistical precision.

In this study, respondents reported a moderate overall QoL, while anxiety/depression emerged as the most impaired EQ-5D-3L dimension, followed closely by pain/discomfort. This pattern is consistent with studies from Malaysia and Türkiye, which likewise identified psychological distress and pain as the domains most frequently affected among patients with cancer.[22–26] These findings reinforce growing evidence that psychological well-being remains insufficiently addressed during cancer care despite advances in medical treatment. The strong correlations observed between pain, impaired daily functioning, and anxiety/depression further support the bidirectional relationship between physical symptoms and psychological distress reported in previous studies. [21–29]

Consistent with studies conducted in India and Türkiye, older respondents in our study experienced greater impairment in self-care, suggesting that age-related functional decline compounds the physical effects of cancer and its treatment.[22,23] Similarly, lower educational attainment was associated with poorer QoL across several EQ-5D-3L dimensions, supporting evidence that education influences health literacy, access to health information, self-management skills, and healthcare utilization.[23,26] However, these findings differ from Canadian valuation research and a systematic review reporting no association between education and health-state preferences.[24,25] This discrepancy may reflect methodological differences. Whereas those studies evaluated societal preferences or utility valuations, our study examined patients who lived through health experiences during active cancer care. Educational attainment may therefore exert a greater influence on patient-reported outcomes than on societal health-state valuations.

An unexpected finding was that longer cancer detection time was associated with better self-care, usual activities, and overall QoL. This contrasts with studies[22,26] reporting progressive deterioration over time but may reflect survivor adaptation, improved symptom management, successful completion of intensive treatment, or the exclusion of patients with the poorest prognoses from longer-term follow-up. Similar adaptation effects have been observed in longitudinal studies[26–33] showing that patients often adjust psychologically and functionally following the initial treatment period. Nevertheless, because of the cross-sectional design, this finding should be interpreted cautiously and confirmed in prospective studies.

Cancer stage was strongly associated with physical dimensions of QoL, particularly mobility, self-care, usual activities, and pain/discomfort, which agrees with findings from Türkiye, Malaysia, Spain, and the United Kingdom demonstrating poorer functional outcomes and greater healthcare utilization among patients with advanced disease. [22,26,33–35] Interestingly, cancer stage was not independently associated with anxiety/depression in our study. This may indicate that psychological distress is influenced not only by disease severity but also by uncertainty, coping mecha-

nisms, social support, and financial concerns. Similar observations have been reported in psycho-oncology research, where emotional well-being is only moderately correlated with clinical disease indicators.

The multivariable analysis further demonstrated that educational level and cancer detection time were the only independent predictors of QoL after adjustment for demographic and clinical characteristics. Neither cancer type nor stage remained significant in the adjusted model, suggesting that socioeconomic and adaptive factors may explain more variation in perceived health than disease characteristics alone. These findings complement previous systematic reviews indicating that psychosocial determinants frequently contribute to patient-reported QoL independently of clinical variables.[25,29]

Financial burden emerged as another important finding. Income loss represented the largest patient-reported cost, followed by uninsured medication expenses and other disease-related expenditures. These observations are consistent with evidence from the United States and other countries showing that indirect costs frequently exceed direct medical expenses and continue despite insurance coverage.[30–32] Although Türkiye provides universal health insurance, our findings suggest that substantial financial toxicity persists because of non-medical expenses, productivity losses, and treatments not fully covered by insurance. This highlights the importance of evaluating cancer care from the patient's perspective rather than relying exclusively on healthcare system expenditures.

Overall, the present findings support the growing body of evidence that improving cancer outcomes requires more than advances in diagnosis and treatment. Interventions aimed at early diagnosis, effective symptom control, psychological support, patient education, and reduction of financial burden are likely to improve both health-related quality of life and the overall value of cancer care. Future multicenter longitudinal studies including more representative distributions of cancer types and complete staging information are needed to confirm these findings and better understand changes in QoL over the disease trajectory.

Strengths and Limitations

This study has several strengths. It was conducted at a tertiary medical center serving patients with cancer from multiple provinces, thereby enhancing the heterogeneity of the study population and the potential generalizability of the findings. Unlike many previous studies focusing on a single cancer type, it evaluated patients with diverse cancer diagnoses and disease stages while simultaneously examining health-related quality of life, patient-borne costs, and sociodemographic characteristics. Data was collected through direct patient interviews, with assistance from relatives when respondents were unable to complete the questionnaire independently, thereby minimizing missing data. Furthermore, the analysis of individual EQ-5D-3L dimensions provided a comprehensive understanding of the specific domains of health-related quality of life most affected in this population.

Despite its strengths, this study has several limitations. First, its single-center design and relatively small sample size may limit the generalizability of the findings to the broader population of patients with cancer. Second, the cross-sectional design provides only a snapshot of patients' health status and precludes conclusions regarding causality or changes in health-related quality of life over time. Third, cancer stage information was unavailable for a substantial proportion of respondents (68.6%). This largely reflects the inclusion of both solid tumors and hematological malignancies, for which conventional staging systems are often not applicable, although incomplete clinical documentation may also have contributed. Fourth, the heterogeneous study population, comprising both hematological malignancies (e.g., Acute Myeloid Leukemia [AML] and Multiple Myeloma [MM]) and solid tumors, limited disease-specific analyses because these conditions differ in their clinical course, treatment, and prognosis. Accordingly, the findings should be interpreted with caution. Future multicenter, longitudinal studies with larger samples and more comprehensive clinical data are needed to validate and extend these findings.

CONCLUSION

Cancer care evaluation should extend beyond survival and safety outcomes to include health-related quality of life and patient-borne costs, supporting more patient-centered and value-based care. This study provides evidence on QoL, financial burden, and the sociodemographic and clinical factors associated with patient-reported outcomes among patients with cancer. The findings highlight the need for policies promoting health education, employment support, timely cancer screening and diagnosis, and equitable access to healthcare. Future multicenter longitudinal studies are warranted to further inform evidence-based, patient-centered cancer care.

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REFERENCES

1. Malhan S, Göksel T, Karadurmuş N, Kavaklı K, Savaş R, Şendur MAN, et al. The cost-effectiveness of national lung cancer screening in Türkiye. Turk J Oncol 2025;40(1):30–42.
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71(3):209–49.
3. World Health Organization. Global cancer observatory. 2025. Available at: https://gco.iarc.who.int/media/globocan/factsheets/populations/792-turkiye-fact-sheet.pdf. Accessed Mar 3, 2025.
4. The Ministry of Health of Türkiye. Health statistic yearbook 2023. 2023. Available at: https://dosyasb.saglik.gov.tr/Eklenti/50208/0/siy2023ingilizce31012025pdf.pdf. Accessed Feb 2, 2025.
5. Jitender S, Mahajan R, Rathore V, Choudhary R. Quality of life of cancer patients. J Exp Ther Oncol 2018;12:217–21.
6. Arboe B, Goerloev JS, Olsen MH, Dalton SO, Nielsen KF, Nielsen SR, et al. Social outcomes after high dose chemotherapy with autologous stem cell transplant. Blood 2016;128(22):1193.
7. Smyth EN, Shen W, Bowman L, Peterson P, John W, Melemed A, et al. Patient-reported pain and other quality of life domains as prognostic factors for survival in a phase III clinical trial of patients with advanced breast cancer. Health Qual Life Outcomes 2016;14(1):1–10.
8. Torun P, Kutlar A. Economic costs of cancer: A computable general equilibrium model approach. Hacettepe J Health Adm 2018;21(1):87–101.
9. Yabroff KR, Lamont E, Mariotto A, Warren J, Topor M, Meekins A. Economic burden of cancer in the United States: Estimates, projections, and future research. Cancer Epidemiol Biomarkers Prev 2008;7(1):3–14.
10. Zakaria. Sociodemographic and health characteristics of cancer survivors in Canada between 2015 and 2018. J Public Health 2023;31:849–67.
11. Afroz A, Alramadan MJ, Hossain MN, Romero L, Alam K, Magliano DJ, et al. Cost-of-illness of type 2 diabetes mellitus in low and lower-middle income countries: A systematic review. BMC Health Serv Res 2018;8(1):1–10.
12. Arslan DT. Cost-effective analysis of robotic and open radical prostatectomy methods applied in prostate cancer surgeries [Doctoral dissertation]. Ankara: Ankara University; 2022.
13. Işıkçelik F. Evaluation of the cost of illness and quality of life in acute myocardial infarction [Doctoral dissertation]. Ankara: Ankara University; 2023.
14. Saygılı M. An evaluation of three different palliative care service models in terms of patients with cancer diagnosis-their family caregivers and cost-effectiveness analysis [Doctoral dissertation]. Ankara: Hacettepe University; 2016.
15. Glick H, Doshi J, Sonnad SS, Polsky D. Economic evaluation in clinical trials. United Kingdom: Oxford University Press; 2015.
16. Tabachnick BG, Fidell LS. Using multivariate statistics. Boston: Pearson; 2013.
17. Ural A, Kılıç İ. Scientific research process and data analysis with SPSS. Ankara: Detay Publishing; 2013.
18. Adelson KB, Velji S, Patel K, Chaudhry B, Lyons C, Lilenbaum R. Preparing for value-based payment: A stepwise approach for cancer centers. J Oncol Pharm Pract 2016;12(10):e924–32.
19. Martin D, Demartines N, Hübner M. Patient perspectives in cancer surgery. J Clin Med 2022;11:789.
20. Gordon LG, Merollini KM, Lowe A, Chan RJ. A systematic review of financial toxicity among cancer survivors: We can't pay the co-pay. Patient 2017;10(3):295–309.
21. Fitch MI, Longo CJ, Chan RJ. Cancer patients' perspectives on financial burden in a universal healthcare system: Analysis of qualitative data from participants from 20 provincial cancer centers in Canada. Patient Educ Couns 2021;104(4):903–10.

22. Toptaş T, Yıldız I, Yıldız M, Varol U, Bayoglu IV, Ozguroglu M. Quality-of-life in Turkish cancer patients: The impact of sociodemographic characteristics, medical history, and management. Int J Hematol Oncol 2014;24(1):23–9.
23. Dixit J, Gupta N, Kataki A, Roy P, Mehra N, Kumar L, et al. Health-related quality of life and its determinants among cancer patients: Evidence from 12,148 patients of Indian database. Health Qual Life Outcomes 2024;22:26.
24. Sayah FA, Bansback N, Bryan S, Ohinma A, Poissant L, Pullenayegum E, et al. Determinants of time trade-off valuations for EQ-5D-5L health states: Data from the Canadian EQ-5D-5L valuation study. Qual Life Res 2016;25:1679–85.
25. Shrestha A, Martin C, Burton M, Walters S, Collins K, Wyld L. Quality of life versus length of life considerations in cancer patients: A systematic literature review. Psychooncology 2019;28:1367–80.
26. Puteh SEW, Razali H, Ismail A, Zulkifli M. Health status based on EQ-5D-5L for the cancer patient population in Malaysia. Sci Rep 2024;14:8152.
27. Hirose C, Fujii H, Iihara H, Ishihara M, Nawa-Nishigaki M, Kato-Hayashi H, et al. Real-world data of the association between quality of life using the EuroQol 5 Dimension 5 Level utility value and adverse events for outpatient cancer chemotherapy. Support Care Cancer 2020;28:5943–52.
28. Tripathy S, Hansda U, Seth N, Rath S, Rao PB, Mishra TS, et al. Validation of the EuroQol five-dimensions-three-level quality of life instrument in a classical Indian language (Odia) and its use to assess quality of life and health status of cancer patients in eastern India. Indian J Palliat Care 2015;21(3):282–8.
29. Fukushima T, Suzuki K, Tanaka T, Okayama T, Inoue J, Morishita S, et al. Global quality of life and mortality risk in patients with cancer: A systematic review and meta-analysis. Qual Life Res 2024;33:2631–43.
30. Islam N, Atreya A, Nepal S, Uddin KJ, Kaiser R, Menezes RG, et al. Assessment of quality of life (QOL) in cancer patients attending oncology unit of a teaching hospital in Bangladesh. Cancer Rep 2023;6:e1829.
31. Gelin D, Ulus B. The life quality of the patients receiving chemotherapy in the hospital and the influencing factors. Acıbadem Univ Health Sci J 2015;6(1):31–5.
32. Mudaranthakam DP, Wick J, Calhoun E, Gurley T. Financial burden among cancer patients: A national-level perspective. Cancer Med 2023;12:4638–46.
33. Hall PS, Hamilton P, Hulme CT, Meads DM, Jones H, Newsham A, et al. Costs of cancer care for use in economic evaluation: A UK analysis of patient-level routine health system data. Br J Cancer 2015;112:948–56.
34. Doğan MD, Kurt S, Ertin. The correlation between individuals' attitudes toward cancer screening, cancer information overload, and healthy life awareness: A cross-sectional study. J Public Health 2024;32:759–64.
35. Rodríguez-Gonzalez A, Carmona-Bayonas A, Hernandez San Gil R, Cruz-Castellanos P, Antoñanzas-Basa M, Lorente-Estelleset D, et al. Impact of systemic cancer treatment on quality of life and mental well-being: A comparative analysis of patients with localized and advanced cancer. Clin Transl Oncol 2023;25:3492–500.

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ORIGINAL ARTICLE

Impact of Internal Mammary Node Irradiation and Thoracic Lateral Diameter on Organ-at-Risk Doses and Normal Tissue Complication Probability in Free-Breathing Right Breast Volumetric Modulated Arc Therapy

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OBJECTIVE

To evaluate the independent impact of internal mammary node irradiation (IMNI) and thoracic morphology on organ-at-risk (OAR) doses and normal tissue complication probability (NTCP) in free-breathing right breast volumetric modulated arc therapy (VMAT), and to identify computed tomography (CT)-based markers of higher OAR dose.

METHODS

Fifty consecutive right-sided breast cancer patients treated with free-breathing VMAT were retrospectively analyzed. Doses were converted to the equivalent dose in 2-Gy fractions (EQD2; α/β=3 Gy). Pulmonary NTCP (Lyman-Kutcher-Burman model) and major adverse cardiac event risk (Darby model) were calculated. Multivariate analysis identified independent OAR-dose predictors.

RESULTS

IMNI (13 patients, 26%) significantly increased lung Dmean, pulmonary NTCP, and cardiac Dmean on univariate analysis (all $p<0.001$). After adjustment, IMNI independently predicted lung Dmean (β=+0.97 Gy; p=0.029), lung V5 (β=+8.28%; p=0.024), cardiac Dmean (β=+0.43 Gy; p=0.027), and NTCP (β=+0.60%; p=0.020). Thoracic lateral diameter independently correlated with lung Dmean (ρ=0.368; p=0.009) and cardiac Dmean (ρ=0.311; p=0.028). The Haller Index showed no significant correlation with OAR doses.

CONCLUSION

IMNI independently increases lung and cardiac doses and thoracic lateral diameter independently predicts OAR dose in free-breathing right-breast VMAT. These markers may identify higher-risk patients who could be prioritized for deep inspiration breath-hold (DIBH) evaluation, pending confirmation in paired planning studies.

Keywords: Breast cancer radiotherapy; internal mammary node irradiation; normal tissue complication probability; organ-at-risk dose; volumetric modulated arc therapy.

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INTRODUCTION

Breast cancer is the most common malignancy among women worldwide, with approximately 2.3 million incident cases annually.[1] Adjuvant radiotherapy (RT) substantially reduces locoregional recurrence and improves breast cancer-specific survival following breast-conserving surgery and mastectomy.[2] However, irradiation of the thoracic region inevitably exposes the ipsilateral lung and heart to incidental radiation, with the potential for long-term cardiopulmonary complications.

The landmark study by Darby et al.[3] demonstrated that the risk of major adverse cardiac events (MACE) increases linearly with the mean heart dose by 7.4% per gray, commencing within five years of irradiation and persisting for decades. Radiation-induced pneumonitis, a clinically relevant dose-limiting toxicity, has been quantitatively characterized through dose-volume metrics, with lung mean dose and V20 serving as principal predictors within the Lyman-Kutcher-Burman (LKB) modelling framework.[4]

Internal mammary node irradiation (IMNI) has been increasingly incorporated into locoregional RT protocols for node-positive and high-risk breast cancer following randomized evidence of survival benefits from comprehensive regional nodal irradiation.[5] However, incorporating internal mammary targets substantially expands the irradiated volume, raising concerns about elevated OAR dose exposure.[6] In right-sided breast cancer, the cardiac anatomy results in comparatively lower baseline mean heart doses than in left-sided irradiation; nevertheless, the incremental OAR dose burden attributable to IMNI remains clinically relevant, particularly given the proximity of the right coronary artery, lung base, and liver to the internal mammary chain.

Deep-inspiration breath-hold (DIBH) is an established respiratory gating technique that reduces cardiac and pulmonary doses by increasing thoracic volume and creating greater geometric separation between the irradiated target and critical structures.[7] Recent dosimetric studies have demonstrated meaningful OAR sparing with DIBH in right-sided breast cancer, particularly when IMNI is included.[8] Despite these findings, DIBH requires additional institutional </w:t>< w:lastRenderedPageBreak/><w:t>resources, extended simulation times, and patient cooperation. Identifying pretreatment CT-based morphological features associated with higher free-breathing OAR dose could, in principle, help flag patients for whom more advanced dose-sparing approaches merit prospective evaluation.

This study aimed to assess the independent impact of IMNI and thoracic morphological parameters, including lateral diameter, AP diameter, longitudinal diameter, the Vertical-Transverse Lung Ratio, and the Haller Index, on OAR dose-volume indices and NTCP in a homogeneous free-breathing right breast VMAT cohort and to identify determinants of free-breathing OAR dose that may serve as candidate criteria for prospective DIBH evaluation.

MATERIALS AND METHODS

Patients and Ethics

This retrospective single-institution study enrolled 50 consecutive patients with right-sided breast cancer who were treated with adjuvant RT at the Batman Training and Research Hospital Department of Radiation Oncology between August 2025 and May 2026. Ethical approval was obtained from the Non-Interventional Research Ethics Committee of the Batman Training and Research Hospital (No: 481, Date: 14/05/2026). This study was conducted in accordance with the Declaration of Helsinki. All patients received free-breathing VMAT, and those planned with DIBH were excluded to ensure cohort homogeneity. Written consent was obtained from the patients.

Treatment Planning

Treatment plans were generated using the Monaco 6.2 planning system (Elekta AB, Stockholm, Sweden) and delivered using an Elekta Versa HD linear accelerator. Contouring was performed by a single radiation oncologist according to the ESTRO consensus guidelines.[9] Hypofractionated schedule: 40.05 Gy in 15 fractions (simultaneous integrated boost 48 Gy/15 fr for breast-conserving surgery patients). Conventional schedule: 50 Gy in 25 fractions with a sequential boost of 10 Gy/5 fractions. IMNI was selectively applied based on the axillary nodal status and medial tumor location.

Dosimetric Parameters and EQD2 Conversion

DVH parameters were extracted for the ipsilateral lung (Dmean, V5, and V20) and heart (Dmean and V5). All doses were converted to EQD2 using a linear-quadratic model (α/β=3 Gy). For the hypofractionated plans, the V20 threshold was adjusted to V16 and V5 to V4 in the physical dose, corresponding to 20 Gy and 5 Gy EQD2, respectively.

Thoracic Morphological Measurements

Thoracic dimensions were measured on planning CT, including the AP, lateral, and longitudinal diameters. The Haller Index (HI = lateral^2 / (AP × sagittal)) was

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Table 1 Patient and thoracic morphological characteristics by internal mammary node irradiation status

Parameter	Total (n=50)	No IMNI (n=37)	IMNI (n=13)	p
Surgery, n (%)				
Breast-conserving surgery	28 (56)	21 (56.8)	7 (53.8)	0.851
Mastectomy	22 (44)	16 (43.2)	6 (46.2)	–
Fractionation, n (%)				
Hypofractionated (40.05 Gy/15 fr)	22 (44)	19 (51.4)	3 (23.1)	0.149
Conventional (50 Gy/25 fr)	28 (56)	18 (48.6)	10 (76.9)	–
Nodal Irradiation, n (%)				
Peripheral lymphatic RT	35 (70)	22 (59.5)	13 (100)	0.003**
Internal mammary RT	13 (26)	–	13 (100)	–
Thoracic measurements				
AP diameter (cm)	10.26±1.41	10.31±1.39	10.10±1.50	0.664
Lateral diameter (cm)	21.96±1.19	21.84±1.20	22.38±1.12	0.185
Longitudinal diameter (cm)	14.30±1.62	14.27±1.68	14.38±1.45	0.834
Haller index	2.18±0.35	2.19±0.36	2.16±0.34	0.820
Right lung volume (cc)	1341±186	1335±191	1357±176	0.704
Cardiac volume (cc)	625±104	618±110	644±87	0.419
Breast/mastectomy volume (cc)	722±484	700±464	786±545	0.602

**: p<0.01. Continuous data are presented as mean ± SD, and categorical data are presented as n (%). Group comparisons: independent samples t-test or Fisher's exact test as appropriate. AP: Anterior-posterior; BCS: Breast-conserving surgery; GTV: Gross tumor volume; HI: Haller Index; IMNI: Internal mammary node irradiation; RT: Radiotherapy.

calculated. The right lung, cardiac, and breast/GTV volumes were derived from CT-based contours. All measurements were performed by a single observer using a digital caliper.

NTCP Modelling

Pulmonary NTCP was calculated using the LKB model (TD50=30.5 Gy, m=0.37, n=0.99).[10] Cardiac MACE risk was estimated using the Darby linear model: MACE risk=3%×(1+0.074×cardiac Dmean).[3]

Statistical Analysis

Normality was assessed using the Shapiro-Wilk test. Normally distributed continuous variables are expressed as mean ± standard deviation (SD) and compared using the independent-samples t-test. Non-normally distributed variables are expressed as medians (25^{th}–75^{th} percentile) and were compared using the Mann-Whitney U test. Categorical variables were compared using Fisher's exact test. Spearman's rank correlation was used to assess the bivariate associations between the morphological parameters and the OAR dose metrics, given the non-normal distribution of several dose parameters. Multivariate linear regression, adjusted for fractionation schedule, surgical type, right lung volume, and peripheral nodal irradiation, identified independent predictors of OAR dose. Multicollinearity was assessed using variance inflation factors (VIFs), with values <5 considered acceptable. The robustness of the IMNI associations was further evaluated by restricting the analysis to patients who received regional nodal irradiation, by modelling nodal treatment as a three-level ordinal variable (breast/chest-wall only, regional nodal irradiation without IMNI, and regional nodal irradiation with IMNI), and by re-estimating the primary model using a non-parametric bootstrap (percentile confidence intervals over 2000 resamples), which makes no distributional assumption while targeting the same conditional-mean estimand. Linear regression was used descriptively to quantify explained variance and independent associations rather than for formal parametric inference. Cohen's d quantified effect sizes. Analyses were performed using Python 3.11 (pandas 2.1, scipy 1.11, statsmodels 0.14) and SPSS 26.0 (IBM Corp., Armonk, NY, USA). Statistical significance was set at p<0.05 (two-tailed).

RESULTS

Patient and Treatment Characteristics

The cohort comprised 50 patients with right-sided breast cancer who were treated with free-breathing VMAT. Breast-conserving surgery was performed in 28 (56.0%) patients and mastectomy in 22 (44.0%) patients. Hypofractionated RT was used in 22 (44.0%) and conventional fractionation in 28 (56.0%). Peripheral lymphatic RT was administered to 35 (70.0%) patients and IMNI to 13 (26.0%). Patient characteristics and between-group comparisons are shown in Table 1.

Table 2 OAR dose parameters and NTCP estimates by internal mammary node irradiation status (EQD2, α/β=3 Gy)

Parameter (EQD2, α/β=3 Gy)	Total (n=50)	No IMNI (n=37)	IMNI (n=13)	p
Ipsilateral lung				
Dmean (Gy)†	9.95 (8.43–11.00)	8.95 (6.80–10.50)	11.00 (10.20–11.00)	<0.001***
V20 (%)†	15.5 (12.0–19.0)	13.0 (11.0–17.0)	18.0 (17.0–20.0)	0.003**
V5 (%)	45.30±11.64	42.11±9.99	54.38±10.71	<0.001***
NTCP Pneumonitis (%)†	2.97 (1.64–4.20)	2.81 (1.79–3.82)	4.20 (3.60–4.20)	<0.001***
Heart				
Dmean (Gy)	2.15±0.64	1.97±0.56	2.64±0.56	<0.001***
V5 (%)†	1.35 (0.10–7.60)	1.09 (0.10–6.00)	8.70 (5.48–10.00)	0.002**
MACE Risk (%)‡	3.48±0.14	3.44±0.13	3.59±0.13	<0.001***

†: Non-normally distributed (Shapiro-Wilk p<0.05): median (25th–75th percentile); Mann-Whitney U test. Normally distributed: mean±SD; independent-samples t-test. ‡: MACE risk: Darby model (baseline 3%×[1+0.074×Dmean]). **: p<0.01; ***: p<0.001. Spearman's rank correlation coefficients are denoted as r. EQD2: Equivalent dose in 2-Gy fractions; IMNI: Internal mammary node irradiation; MACE: Major adverse cardiac event; NTCP: Normal tissue complication probability.

No significant differences were observed between the IMNI and non-IMNI groups in terms of surgical type, fractionation, thoracic measurements, or anatomical volumes (all p>0.05); the only significant difference was a higher peripheral RT rate in the IMNI group (100% vs. 59.5%; p=0.003). Fifteen patients received breast or chest-wall irradiation alone, 22 received comprehensive regional nodal irradiation without IMNI, and all 13 IMNI patients also received regional nodal irradiation; the 22 patients who received regional nodal irradiation without IMNI served as the reference stratum enabling the effect of IMNI to be separated from that of comprehensive regional nodal irradiation.

OAR Dose Distribution and NTCP

Overall, the median ipsilateral lung Dmean was 9.95 (IQR: 8.43–11.00) Gy, median lung V20 was 15.5 (IQR: 12.0–19.0) %, lung V5 was 45.30±11.64%, cardiac Dmean was 2.15±0.64 Gy, and median cardiac V5 was 1.35 (IQR: 0.10–7.60) %. The median pulmonary NTCP was 2.97 (IQR: 1.64–4.20) % (range 1.39–5.54%), and the mean MACE risk was 3.48±0.14%.

Impact of Internal Mammary Node Irradiation

Univariate analysis demonstrated that IMNI was significantly associated with higher values for all OAR dose endpoints, with large effect sizes (Cohen's d=1.27, 1.18, and 1.18 for lung Dmean, lung V5, and cardiac Dmean, respectively) (Table 2). The rate of lung V20 exceeding 15% was 92% in patients with IMNI versus 46% in patients without IMNI (p=0.004). Cardiac Dmean exceeded 2.5 Gy in 54% of IMNI patients versus 14% of non-IMNI patients (p=0.007).

After multivariate adjustment, IMNI remained an independent predictor of lung Dmean (β=+0.97 Gy, 95% CI: +0.10 to +1.85; p=0.029; R^2=0.616), lung V5 (β=+8.28%, 95% CI: +1.14 to +15.41; p=0.024; R^2=0.338), cardiac Dmean (β=+0.43 Gy, 95% CI: +0.05 to +0.81; p=0.027; R^2=0.372), and pulmonary NTCP (β=+0.60%, 95% CI: +0.10 to +1.11; p=0.020; R^2=0.625). Lung V20 and cardiac V5 did not retain significance after adjustment (Table 3). No evidence of problematic multicollinearity was observed among the regression covariates (all VIF values <2; IMNI VIF=1.21, peripheral RT VIF=1.72).

Table 3 Multivariate linear regression: Independent effect of IMNI on OAR doses after adjustment for fractionation, surgical type, right lung volume, and peripheral nodal irradiation

Outcome	IMNI β (Gy or %)	95% CI	p
Lung Dmean (Gy)	+0.97	+0.10 to +1.85	0.029*
Lung V20 (%)	+1.81	-0.45 to +4.07	0.114
Lung V5 (%)	+8.28	+1.14 to +15.41	0.024*
Heart Dmean (Gy)	+0.43	+0.05 to +0.81	0.027*
Heart V5 (%)	+2.95	-1.30 to +7.20	0.168
NTCP Pneumonitis (%)	+0.60	+0.10 to +1.11	0.020*

*: p<0.05. Covariates: IMNI, fractionation (hypofractionated vs. conventional), surgery (BCS vs. mastectomy), right lung volume, and peripheral lymphatic RT. CI: Confidence interval; IMNI: Internal mammary node irradiation; NTCP: Normal tissue complication probability.

Because all IMNI patients also received comprehensive regional nodal irradiation, additional analyses were performed to separate the two effects. When the analysis was restricted to the 35 patients receiving regional nodal irradiation, IMNI remained independently associated with cardiac Dmean (β=+0.48 Gy; p=0.047), while lung Dmean (β=+0.99 Gy; p=0.054) and lung V5 (β=+8.07%; p=0.052) showed similar effect sizes with borderline statistical significance. Mod-

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Table 4 Robustness of the independent effect of IMNI on organ-at-risk doses: Primary OLS model and non-parametric bootstrap

Outcome	Model	IMNI β (Gy or %)	95% CI	p
Lung Dmean (Gy)	OLS (primary)	+1.03	+0.09 to +1.97	0.032*
	Bootstrap (2000 resamples)	+1.01	+0.23 to +1.82	0.013*
Lung V5 (%)	OLS (primary)	+8.28	+1.14 to +15.41	0.024*
	Bootstrap (2000 resamples)	+8.00	+0.45 to +16.67	0.035*
Heart Dmean (Gy)	OLS (primary)	+0.47	+0.06 to +0.89	0.026*
	Bootstrap (2000 resamples)	+0.45	-0.03 to +0.95	0.068

*: p<0.05. β denotes the adjusted IMNI coefficient (increment attributable to internal mammary node irradiation) from the primary covariate set (IMNI, fractionation, surgery, right lung volume, and peripheral lymphatic RT; n=50). Because several dose parameters were non-normally distributed and the sample was modest, the ordinary least-squares (OLS) estimates were re-evaluated using a non-parametric bootstrap (percentile confidence intervals over 2000 resamples), which makes no distributional assumption while targeting the same conditional-mean estimand. Doses are expressed in EQD2 (alpha/beta=3 Gy). The IMNI associations for the lung endpoints were preserved under bootstrap resampling; the cardiac Dmean association was directionally consistent but attenuated to borderline significance, consistent with the modest sample size and the exploratory nature of the analysis. CI: confidence interval; IMNI: internal mammary node irradiation.

elling nodal treatment as a three-level ordinal variable demonstrated a stepwise dose gradient, with IMNI adding an incremental dose burden beyond regional irradiation alone (lung Dmean: +2.96 Gy vs. +1.93 Gy; cardiac Dmean: +0.96 Gy vs. +0.48 Gy, relative to breast/chest-wall irradiation). Re-estimation of the primary model using a non-parametric bootstrap (2000 resamples; Table 4) confirmed the robustness of the IMNI associations for the lung endpoints (lung Dmean p=0.013; lung V5 p=0.035), whereas the association with cardiac Dmean remained directionally consistent (β=+0.45 Gy) but did not reach conventional statistical significance (p=0.068), consistent with the modest sample size and exploratory nature of the analysis.

Thoracic Geometry as a Predictor of OAR Dose

Among the morphological parameters, the lateral thoracic diameter correlated significantly with lung Dmean (ρ=0.368, p=0.009), pulmonary NTCP (ρ=0.368, p=0.009), cardiac Dmean (ρ=0.311, p=0.028), and MACE risk (ρ=0.311, p=0.028). These associations were retained in the multivariate models after adjusting for IMNI and fractionation. The Haller Index showed no significant correlation with any OAR dose parameter (all p>0.05; |ρ| range: 0.016–0.076). The longitudinal diameter showed no significant correlation with lung V5 (ρ=-0.226, p=0.114).

DISCUSSION

This study demonstrates that IMNI independently increases the ipsilateral lung dose, pulmonary NTCP, and cardiac mean dose in free-breathing right breast VMAT, even after adjusting for the fractionation schedule and other treatment-related confounders. Additionally, the thoracic lateral diameter independently predicted the lung and cardiac OAR dose, providing a readily measurable pretreatment CT parameter associated with higher OAR dose under free-breathing treatment. Because the regression analyses were exploring and performed in a relatively small cohort, the observed associations should be interpreted as hypothesis-generating.

Our finding of elevated OAR doses with IMNI is consistent with the published dosimetric evidence. Refsgaard et al.[11] reported a mean ipsilateral lung dose increase of 2.7 Gy and an approximately 20% increase in irradiated volume with IMNI versus non-IMNI locoregional RT plans. Regional nodal irradiation, including IMNI, has consistently been shown to increase cardiac and lung dose-volume parameters compared with breast or chest wall irradiation alone.[12] Our data confirm these findings in a right-sided free-breathing VMAT-specific cohort with EQD2 normalization, a methodological refinement enabling valid cross-comparison across mixed fractionation schedules, which is a common limitation of prior dosimetric studies.

The independent predictive value of IMNI for cardiac Dmean (β=+0.43 Gy after multivariate adjustment) has a direct clinical significance. Applying the Darby model,[3] this increment corresponds to an approximate 3.2% relative increase in MACE risk attributable specifically to IMNI. While the absolute cardiac risks associated with right-sided breast RT are lower than those associated with left-sided irradiation, the cumulative lifetime risk — particularly in younger patients, those with pre-existing cardiovascular comorbidities, or those receiving anthracycline-based chemotherapy — may reach clinical relevance.[13] Given

that the right coronary artery passes through the anterior aspect of the heart near the medial fields, minor increases in mean heart dose driven by IMNI cannot be dismissed as clinically negligible.

The IMNI-related lung dose elevation has important implications for pneumonitis-risk stratification. Consistent with QUANTEC recommendations,[14] an institutional lung V20 threshold of 15% was used as a practical risk boundary in the breast RT context, which is a lower threshold than the 30–35% recommended for lung cancer RT, reflecting the expectation of lower lung doses in adjuvant breast irradiation. The fact that 92% of IMNI patients exceeded this threshold versus only 46% of non-IMNI patients (p=0.004) identifies IMNI candidates as the highest-risk free-breathing subgroup, in whom prospective evaluation of DIBH benefit is warranted.

DIBH has been shown to meaningfully reduce OAR doses in right-sided breast cancer RT, particularly when IMNI is included. Yoo et al.[15] demonstrated reductions in ipsilateral lung Dmean from 15.9 to 12.6 Gy and cardiac Dmean from 2.5 to 1.6 Gy with DIBH in right-sided patients receiving regional nodal irradiation. A treatment planning study by Brown et al.[8] similarly confirmed considerable OAR sparing with DIBH in right-sided locoregional RT plans, including IMNI. Our data identified patients with IMNI as the highest-risk free-breathing subgroup, in whom the potential benefit of more advanced dose-sparing techniques would be worth evaluating prospectively.

To our knowledge, the identification of the lateral thoracic diameter as an independent predictor of lung and cardiac OAR dose is novel in the right-sided breast RT setting. The mechanistic basis is straightforward: A wider thorax necessitates wider tangential beam apertures that intercept a proportionally larger volume of the ipsilateral lung. Critically, the lateral diameter remained significant after adjustment for lung volume, indicating that thoracic width conveys distinct geometric information beyond volumetric parameters. The lateral diameter is directly measurable from any planning CT without specialized software, making it a readily available candidate parameter for pretreatment risk assessment, pending external validation. External validation is required before adopting specific lateral-diameter thresholds for routine clinical decision-making.

The Haller Index, a thoracic deformity index derived from the AP, sagittal, and lateral diameters, showed no significant correlation with OAR doses in our right-sided cohort (all p>0.05). This differs from the findings of left-sided breast cancer studies, in which thoracic shape may influence cardiac proximity to the irradiated chest wall. In right-sided RT, cardiac exposure is predominantly determined by the medial field extent (IMNI inclusion) rather than thoracic deformity, explaining the lack of HI predictive value. These findings argue against the use of thoracic shape indices as OAR dose predictors in right-sided breast RT.

The LKB-derived pulmonary NTCP estimates (median, 2.97%) and Darby-model MACE estimates (mean, 3.48%) reflect the low OAR doses characteristic of adjuvant breast RT.[16] Their principal utility in this study lies in their use as continuous quantitative outcome variables for multivariate analysis and as individualized risk communication tools, enabling explicit, patient-centered quantification of the incremental OAR risk attributable to IMNI, which may support the informed consent process and facilitate risk-adapted planning decisions.

Limitations of the Study

This study had several limitations. As this was a retrospective single-center analysis, selection bias cannot be excluded. The sample size of 50 patients limited the statistical power of the subgroup analyses. Accordingly, multivariable modelling should be considered exploratory and requires confirmation in larger external datasets. Demographic variables, including patient age and cardiovascular comorbidity profiles, were not available in the dosimetric dataset and could not be included as covariates. The absence of clinical toxicity data precludes the direct validation of NTCP estimates against observed outcomes, and a prospective cohort study with long-term toxicity endpoints is warranted. Because all patients who received IMNI also underwent peripheral lymphatic irradiation, these two variables were strongly associated, which may introduce collinearity into the multivariate models; the IMNI estimates should therefore be interpreted as reflecting comprehensive regional nodal irradiation that included the internal mammary chain. In addition, p-values were not adjusted for multiple comparisons, so borderline associations warrant cautious interpretation. DIBH planning was not performed in this cohort; a paired dosimetric comparison of free-breathing and DIBH plans for individual patients is required to directly quantify patient-specific DIBH benefits. Consequently, the proposed DIBH selection criteria remain inferential and should be validated in paired free-breathing and DIBH planning studies.

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CONCLUSION

In free-breathing right breast VMAT, IMNI independently increased the ipsilateral lung dose, pulmonary NTCP, and cardiac mean dose after multivariate adjustment. The thoracic lateral diameter independently predicted lung and cardiac OAR exposure beyond lung volume, whereas the Haller Index did not predict OAR doses in the right-sided context. Patients requiring IMNI, particularly those with a wide lateral thoracic diameter, represent the highest-risk subgroup under free-breathing treatment and may be candidates for prospective DIBH evaluation. These pretreatment CT-based criteria may assist patient stratification for DIBH evaluation; however, external validation and paired DIBH-free-breathing planning studies are required before routine clinical implementation.

Ethics Committee Approval: The study was approved by the Batman Training and Research Hospital Non-Interventional Research Ethics Committee (no: 481, date: 14/05/2026).

Informed Consent: Written consent was obtained from the patients.

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REFERENCES

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2024;74(3):229–63.
2. Darby S, McGale P, Correa C, Taylor C, Arriagada R, Clarke M, et al; Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: Meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet 2011;378(9804):1707–16.
3. Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Brønnum D, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med 2013;368(11):987–98.
4. Marks LB, Yorke ED, Jackson A, Ten Haken RK, Constine LS, Eisbruch A, et al. Use of normal tissue complication probability models in the clinic. Int J Radiat Oncol Biol Phys 2010;76(3 Suppl):S10–9.
5. Whelan TJ, Olivotto IA, Parulekar WR, Ackerman I, Chua BH, Nabid A, et al. Regional nodal irradiation in early-stage breast cancer. N Engl J Med 2015;373(4):307–16.
6. Poortmans PM, Collette S, Kirkove C, Van Limbergen E, Budach V, Struikmans H, et al. Internal mammary and medial supraclavicular irradiation in breast cancer. N Engl J Med 2015;373(4):317–27.
7. Haussmann J, Corradini S, Nestle-Kraemling C, Bölke E, Tamaskovics B, Djiepmo-Njanang FJ, et al. Recent advances in radiotherapy of breast cancer. Radiat Oncol 2020;15(1):71.
8. Brown S, Kügele M, Edvardsson A, Berg L, Alkner S, Andersson Ljus C, et al. Dose reduction to organs at risk with deep-inspiration breath-hold during right breast radiotherapy: A treatment planning study. Radiat Oncol 2019;14(1):223.
9. Offersen BV, Boersma LJ, Kirkove C, Hol S, Aznar MC, Biete Sola A, et al. ESTRO consensus guideline on target volume delineation for elective radiation therapy of early stage breast cancer. Radiother Oncol 2015;114(1):3–10.
10. Seppenwoolde Y, Lebesque JV, de Jaeger K, Belderbos JS, Boersma LJ, Schilstra C, et al. Comparing different NTCP models that predict the incidence of radiation pneumonitis. Int J Radiat Oncol Biol Phys 2003;55(3):724–35.
11. Refsgaard L, Buhl ES, Nielsen AWM, Thomsen MS, Andersen K, Jensen I, et al. Internal mammary node irradiation in early breast cancer — target coverage and implications on dose to organs at risk. Acta Oncol 2025;64:795–802.
12. Overgaard M, Hansen PS, Overgaard J, Rose C, Andersson M, Bach F, et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. N Engl J Med 1997;337(14):949–55.
13. Taylor CW, Wang Z, Macaulay E, Jagsi R, Duane F, Darby SC. Exposure of the heart in breast cancer radiation therapy: A systematic review of heart doses

published during 2003 to 2013. Int J Radiat Oncol Biol Phys 2015;93(4):845–53.
14. Kwa SL, Lebesque JV, Theuws JC, Marks LB, Munley MT, Bentel G, et al. Radiation pneumonitis as a function of mean lung dose: An analysis of pooled data of 540 patients. Int J Radiat Oncol Biol Phys 1998;42(1):1–9.
15. Yoo S, Jung H, Kim S, Jeong J, Lim YK, Kim JY, et al. Comprehensive analysis of the role of deep inspiration breath-hold in right-sided breast cancer radiotherapy: A focus on cardiac substructures and right coronary artery. J Appl Clin Med Phys 2025;26(7):e70067.
16. Gagliardi G, Constine LS, Moiseenko V, Correa C, Pierce LJ, Allen AM, et al. Radiation dose-volume effects in the heart. Int J Radiat Oncol Biol Phys 2010;76(3 Suppl):S77–85.

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ORIGINAL ARTICLE

Quality of Life Analysis in Anal Squamous Cell Carcinoma Cases Treated with IMRT: A Single-Center Cross-Sectional Study

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OBJECTIVE

The standard treatment for anal cancer involves chemoradiotherapy (CRT), often resulting in long-term side effects that impact patients' quality of life (QoL). The present study aimed to analyse the long-term QoL in anal squamous cell carcinoma (SCC) cases treated with intensity-modulated radiation therapy (IMRT).

METHODS

Between January 2007 and January 2022, 27 anal SCC cases were treated with definitive radiotherapy (RT) or CRT with IMRT. The EORTC QLQ-C30 and EORTC QLQ-CR29 scales were used for data collection.

RESULTS

The mean score for Global Health status/QoL was 72±22.9 and functional scales (range, 84.5-93.8) were generally high, indicating a favourable QoL in the EORTC QLQ-C30 scale. The highest symptom scores were observed for fatigue, insomnia, and financial difficulty. Notably, age (<65 vs. ≥65) was identified as a factor influencing Global Health status/QoL, with patients <65 years of age experiencing a more positive impact. In EORTC QLQ-CR29, although functional scales showed favourable outcomes in body image, anxiety and weight, sexual interest for males (24.8±34.4) and females (10.4±15.7) was impaired, while symptoms like impotence (37.2±32.9) and dyspareunia (31.3±34) scored high. The third-highest symptom was urinary frequency (20.7±27.1). Age ≥65 years was associated with increased symptoms of buttock pain, flatulence and anxiety.

CONCLUSION

Among anal SCC survivors treated with IMRT, functional scores were generally high, whereas clinically relevant sexual function problems were observed. Given the limited sample size and the multiple QoL domains examined, these exploratory findings should be considered hypothesis-generating rather than confirmatory.

Keywords: Anus neoplasms; intensity-modulated radiotherapy; quality of life.
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INTRODUCTION

Anal region cancers are less prevalent compared to other types of gastrointestinal cancer, however, unfavorable trends in anal cancer incidence have been observed over time.[1] Incidence patterns varied by geography and population characteristic, attributed to the distribution of risk factors causing anal cancer in dif-

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ferent regions.[2] In the latest report, age-standardised incidence rates were less than 2.2/100 000 person-years across selected countries worldwide. Germany exhibited the highest incidence rates for both sexes (1.65/100 000 men and 2.16/100 000 women) during 2008–2012, while the lowest rates were found in the Philippines (0.25/100 000 men and 0.18/100 000 women). Notably, female incidence rates remained higher than male rates across nearly all analysed countries.[3] According to another report, anal SCC incidence increased by 2.7% annually from 2001 to 2015. Among white men, incidence steadily rose until age 65–69 years, while white women showed sharp increases from age 30 to 54 years, followed by gradual increases. In contrast, among black men, steep increases occurred at younger ages, whereas among black women, increases persisted until age 65–69 years. Statistically significant increases in incidence were observed for all age groups aged 50 years and older. Among men, the average annual percentage changes for the age groups 50–59, 60–69, and 70 years and older were 4.2%, 2.7%, and 3.8%, respectively. For women, the corresponding changes for the same age groups were 5.0%, 5.3%, and 2.5%, respectively.[4] With the aging global population, the burden of anal cancer is expected to persistently increase and continue to have an impact.

Anal cancer has unique anatomical and histological features that play a pivotal role in their diagnosis, treatment and monitoring. The standard treatment for local-regional disease involves definitive chemoradiotherapy (CRT), as supported by prospective randomized studies.[5,6] The primary goal of treatment is to achieve a complete response while minimizing toxicity. Throughout treatment history, various concurrent chemotherapy (CT) regimens, radiotherapy (RT) techniques and dose applications have been explored to reduce toxicity.[7–9] Despite efforts to minimize toxicity, a significant number of patients still receive high doses of RT as the standard treatment.[10] Consequently, the long-term side effects become inevitable, significantly impacting patients' quality of life (QoL).[11]

In addition, the evaluation of long-term side effects lacks a gold standard method and often tends to provide assessments more aligned with clinicians' perspectives.[12–14] Therefore, QoL scales containing subjective assessments based on the patient's personal experiences play a crucial role. The EORTC core quality of life questionnaire (EORTC QLQ-C30) version 3.0 stands out as the most widely used QoL scale, applicable across various cancer types.[15] Specifically designed for the colorectal region, the EORTC Quality of Life Questionnaire-Colorectal Cancer (EORTC QLQ-CR29) has been recognized as a suitable scale for assessing QoL functions.[16,17] Retrospective and cross-sectional studies conducted up to 2015 and examining the EORTC QLQ-C30 and EORTC QLQ-CR29 scales have reported a decline in QoL and an increase in symptoms.[18] These studies primarily focused on patient populations treated with three-dimensional conformal radiotherapy (3D-CRT) until 2007. Subsequently, the widespread adoption of intensity-modulated radiation therapy (IMRT) has led to a reduction in side effect profiles, albeit with continued effects on QoL.[19,20] Up to date, limited research has assessed the QoL effects of IMRT; therefore, the present study aimed to analyse the QoL of anal squamous cell carcinoma (SCC) cases treated with IMRT and to identify clinical factors associated with QoL.

MATERIALS AND METHODS

Between January 2007 and January 2022, 27 cases of local/local-advanced anal SCC treated with definitive RT/CRT at the Department of Radiation Oncology, Ege University Hospital, were evaluated in the present study. The patient data was accessed retrospectively from archive files. Individuals aged 18 years or older who had a minimum follow-up of 2 years after diagnosis and showed no signs of recurrence were included. Exclusion criteria included metastatic disease at diagnosis, multiple sclerosis, Parkinson's disease, external rectal prolapse, inflammatory bowel disease, diabetic neuropathy, prior RT at diagnosis, and a history of other cancers within the last 3 years. Patients lost to follow-up or unreachable at the time of survey administration were excluded. To assess the QoL of the patients, interviews were conducted using The EORTC QLQ-C30 and EORTC QLQ-CR29 questionnaires in a cross-sectional manner. No serial or prospective PRO collection during treatment was available. This was a cross-sectional survivorship assessment rather than a longitudinal QoL study.

Treatment and Follow-up

Using the sequential boost technique, high-risk clinical target volume (CTV) included gross disease CTV, mesorectum, presacral nodes and bilateral internal and external iliac nodes below the sacroiliac joint.[21] Additional inguinal nodes were included if there was gross inguinal nodal involvement. Low-risk CTV encompassed gross disease CTV, high-risk CTV, presacral, bilateral internal and external iliac nodes above the sacroiliac joint to the L5/S1 vertebral body junction.

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Bilateral inguinal nodes were included if there was no obvious involvement. The dose consisted of 45 Gy at 1.8 Gy per fraction, followed by a 5.4–9 Gy boost at 1.8 Gy per fraction for the high-risk CTV. An additional 5.4–9 Gy boost was administered for the gross disease CTV, reaching a total of 59.4 Gy or 64.8 Gy for stable or progressive cases. Using the Simultaneous Integrated Boost (SIB) technique, single CTV included gross disease CTV, bilateral inguinal nodes, mesorectum, presacral nodes, and bilateral internal and external iliac nodes above the sacroiliac joint to the L5/S1 vertebral body junction.[22] The dose was targeted at 45–54 Gy for single CTV, with a specific 54–59.4 Gy range for gross disease CTV. Concurrent CT was administered with a continuous infusion of 5-Florourasil (5-FU) at a dose of 1,000 mg/m^2/day given intravenously on days 1–4 and 29–32, and Mitomycin C (MMC) as a 10 mg/m^2 intravenous bolus on days 1 and 29 (maximum 20 mg). None of the cases received induction chemotherapy.

Patients underwent regular follow-up after their treatment, which involved digital rectal

examinations every 3 months for the first 2 years, biannually from year 3 to 5, and yearly thereafter. Females underwent gynecological examinations, and imaging was conducted as necessary.

Data Collection

The EORTC QLQ-C30 and EORTC QLQ-CR29, which have undergone Turkish validations, were utilized in the present study. Permission to use these questionnaires was obtained from the appropriate authorities. All patients were treated and followed at Ege University Hospital, Department of Radiation Oncology, which is also the institution that provided ethics approval for this study (Approval Code: 2024-KAEK-04, No: 24-10/6). The study was performed in line with the principles of the Declaration of Helsinki. Patients treated between 2007 and 2022 were identified retrospectively from institutional archives, and in 2024 the ethics committee approved retrospective contact and administration of the survey. QoL questionnaires were administered once per patient during survivorship follow-up after ethics approval in 2024. A consent form and information sheet, detailing the study's purpose, procedures, risks, benefits, confidentiality measures, and voluntary nature, were obtained from each patient.

The EORTC QLQ-C30 questionnaire was developed by Aaronson et al.[23] and later validated and tested in Turkish by Guzelant et al.[24]. This comprehensive questionnaire comprises 30 questions grouped into three main categories: i) Global health status and QoL; ii) functional scales; iii) and symptom scales. Functional scales assess physical, role, emotional, cognitive and social functions, while symptom scales evaluate fatigue, nausea-vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea and financial difficulty, each with a single question. The first 28 of 30 questions are on a 4-point Likert-type scale (not at all: 1 Point; a little: 2 Points; quite a bit: 3 Points; very much: 4 Points). The final two questions inquire about general well-being, with a scoring range of 1 to 7 (1 point: Very poor; 7 points: Excellent). The overall scoring for subgroups is measured on a scale ranging from 0 to 100, following the EORTC scoring guidelines.[25] A higher score on the global health status/QoL, and functional scales indicates a higher QoL or high functional levels, while a higher score on the symptom scales represents a high level of symptoms or low functional levels.

EORTC QLQ-CR29 was developed by Gujral et al.[16] and Whistance et al.,[17] and the validation and reliability of the Turkish version of the questionnaire were performed by Akduran and Durna.[26] It consists of 29 questions specifically designed for colorectal disease-related complaints, including subheadings for patients with or without stomas. The scale uses a 4-point Likert-type scale for responses (not at all: 1 Point; a little: 2 Points; quite a bit: 3 Points; very much: 4 Points). Additionally, it includes questions about urinary symptoms, pain, hair loss, dry mouth, self-image, health concerns, worries and sexual symptoms.

The EORTC QLQ-CR29 questionnaire is complementary to the EORTC QLQ-C30. It starts with question 31 and ends with question 59. The questions 31–47 cover gastrointestinal symptoms, pain, urinary symptoms, self-image and health concerns. Question 48, a yes-or-no question about the presence of a stoma, is not included in the analysis. The subsequent questions are tailored for patients with a stoma bag, with questions 49–55, and for those without a stoma bag, with questions 49–54. The last four questions inquired about sexual QoL in the past 4 weeks, with two separate questions for each gender (questions 56 and 57 for males, 58 and 59 for females). The overall scoring for subscales is measured on a scale ranging from 0 to 100 according to the EORTC scoring guidelines.[25] Higher scores obtained from the functional scales represent high QoL or high functional levels. For symptom scales, higher scores represent a high level of symptoms or low functional levels.

Statistics

Statistical analysis was performed using IBM SPSS Statistics version 25 (IBM Corp.). The mean values of

QoL scores were examined along with their standard deviations. The relationship between QoL scores and clinical factors was assessed using the Mann-Whitney U test or t-test after normality analysis. P<0.05 was considered to indicate a statistically significant difference. Given the limited sample size and the large number of QoL subscales analyzed, we framed all comparisons as exploratory to avoid overinterpretation. For clarity, only statistically significant mean differences are presented, along with their corresponding 95% confidence intervals and exact p-values. Additionally, time since RT (months) was analyzed as a continuous variable in relation to each EORTC QLQ-C30 and EORTC QLQ-CR29 domain using simple linear regression. Domain scores were treated as dependent variables, while months since RT was the independent variable. Regression coefficients (B), 95% confidence intervals, standardized coefficients (Beta), and p-values were reported.

RESULTS

The patient and tumor characteristics are outlined in Table 1. The median RT dose was 59.4 Gy, with a range of 50.4–64.8 Gy. A total of 85.2% of patients received ≤59.4 Gy, while 14.8% received >59.4 Gy. Regarding boost technique, 70.4% of patients underwent a simultaneous integrated boost (SIB), whereas 29.6% received a sequential boost. The median time since RT was 87 months (range, 12–188 months).

Table 1 The patient and tumour characteristics

Characteristic	n (%)
Gender	
Female	19 (70.4)
Male	8 (29.6)
Age, median, years (range)	59 (26–75)
T stage	
T1	3 (11.1)
T2	6 (22.2)
T3	14 (51.9)
T4	4 (14.8)
N Stage	
N0	13 (48.2)
N1a	11 (40.7)
N1b	0 (0)
N1c	3 (11.1)
Stage	
I	2 (7.4)
IIA	4 (14.8)
IIB	7 (26)
IIIA	3 (11.1)
IIIB	0 (0)
IIIC	11 (40.7)
Radiotherapy, median total dose, Gy (range)	59.4 (50.4–64.8)
Median time since radiotherapy, months (range)	87 (12–188)
Radiotherapy dose, Gy	
≤59.4	23 (85.2)
>59.4	4 (14.8)
Radiotherapy boost technique	
Simultaneous integrated boost (SIB)	19 (70.4)
Sequential boost	8 (29.6)
Concurrent chemotherapy	
Yes	25 (92.6)
No	2 (7.4)

EORTC QLQ-C30

The mean scores for global health status/QoL (mean±SD) and functional scales (mean±SD) are high, indicating a good QoL for most cases. The global health status/QoL score was 72±22.9. Among the functional scales, cognitive function had the highest score (93.8±11.5) (Table 2). When assessing the overall health for the past week (question 29), 22.2% of cases scored 7, 33.3% scored 6 and 22.2% scored 5 points. In the symptom scales (mean±SD), the highest symptom score was observed for fatigue (18.7±18.2), followed by insomnia (18.4±28). Financial difficulty ranked third (11.1±20.6). Other symptom scores were 10 or below (Table 2). Regarding diarrhea, 7.4% of cases reported experiencing it 'quite a bit' or 'very much'. For constipation, all cases responded with 'not at all' or 'a little,' and no cases reported severe constipation.

According to the association between clinical characteristics and the EORTC QLQ-C30, not the median age of 59 but the cut-off value of 65 years (<65 vs. ≥65) was identified as the sole factor related to the Global health status/QoL, indicating a deterioration, especially in the elderly population. Being <65 years old was associated with a positive impact on Global health status/QoL (p=0.029; Mann-Whitney U test) (Table 3).

In regression analyses evaluating time since RT as a continuous variable, no significant associations were observed across global health, the five functional scales, and the eight symptom scales (all p>0.10). Only minor, non-significant trends were noted, suggesting slightly lower physical and social functioning and somewhat higher fatigue and pain with longer follow-up intervals. Effect sizes were modest (e.g., global health B=-0.035, 95% CI -0.219 to 0.150; physical functioning B=-0.139,

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Table 2 EORTC QLQ-C30 mean scores

	Scale	Mean score	Min-max	SD	Total
QLQ-C30	Global Health status / QoL *	72.2	16–100	22.9	27
	Functional scales*				
	Physical	84.5	20–100	22	27
	Role	86.4	17–100	25.6	27
	Emotional	85.8	34–100	17.7	27
	Cognitive	93.8	66–100	11.5	27
	Social	88.3	34–100	21.9	27
	Symptom scales**				
	Fatigue	18.7	0–45	18.2	27
	Nausea and vomiting	0.5	0–16	3	27
	Pain	9.2	0–66	18.1	27
	Dyspnoea	0	0	0	27
	Insomnia	18.4	0–66	28	27
	Appetite	5	0–34	12.3	27
	Constipation	6.2	0–34	13.4	27
	Diarrhea	9.9	0–100	24.1	27
	Financial impact	11.1	0–66	20.6	27

*: Scores range from 0 to 100, with a higher score representing a higher level of functioning or better functioning; **: Scores range from 0 to 100, with a higher score representing a greater degree of symptoms or less functioning. SD: standard deviation.

Table 3 The relationship between EORTC QLQ-C30 and clinical characteristics

Characteristic	n	Global health status / QoL mean (SD) score (0–100)	Physical mean (SD) score (0–100)	Role mean (SD) score (0–100)	Emotional mean (SD) score (0–100)	Cognitive mean (SD) score (0–100)	Social mean (SD) score (0–100)	Fatigue* mean (SD) score (0–100)	Insomnia* mean (SD) score (0–100)
Gender									
Female	19	73.1 (22)	83.4 (22)	84 (26)	85.5 (18)	92 (16)	88.7 (21)	20.1 (18)	24.4 (30)
Male	8	70.3 (24)	87 (22)	91 (23	86.6 (15)	98 (5)	87.5 (4)	15.5 (19)	4.2 (12)
Age									
<65	19	78 (17)**	85.7 (22)	90 (21)	86.1 (14)	95.3 (11)	91.6 (18)	16.2 (18)	20.2 (30)
≥65	8	56 (26)	79.7 (22)	76.8 (34)	83.5 (25)	89.7 (12)	79.5 (28)	26.7 (14)	16.7 (25)
T stage									
T1-2	9	76.5 (16)	92.2 (13)	96 (12)	94.4 (11)	92.6 (12)	98.2 (5)	11.2 (14)	14.6 (29)
T3-4	18	70.1 (25)	80.6 (24)	81.7 (29)	81.5 (18)	94.4 (11)	83.4 (25)	22.5 (18)	20.3 (28)
N status									
N-	13	73.4 (25)	85.4 (26)	89.8 (24)	91.7 (14)	93.6 (10)	87.2 (25)	13.7 (18)	7.6 (19)
N+	14	71.2 (21)	83.6 (17)	83.5 (26)	80.3 (19)	94 (12)	89.4 (19)	23.3 (16)	28.4 (31)
Stage									
I-II	13	73.4 (25)	85.4 (26)	89.8 (24)	91.7 (14)	93.6 (10)	87.7 (25)	13.7 (18)	7.6 (19)
III	14	71.2 (21)	83.6 (17)	83.7 (26)	80.3 (19)	94 (12)	89.2 (19)	23.5 (16)	28.4 (31)

*: Higher scores indicate higher levels of symptoms or less functioning; **: Mean difference (95% CI): 23.2 (5.2 – 41.1), and p=0.029. SD: Standard deviation; QoL: Quality of life.

-0.307 to 0.030; social functioning B=-0.131, -0.299 to 0.037; fatigue B=0.076, –0.067 to 0.219; pain B=0.087, -0.054 to 0.228), indicating no clear pattern of late recovery or late decline in this survivor cohort.

EORTC QLQ-CR29

Regarding the functional scales (mean±SD), the highest scores were observed in the body image, anxiety and weight subscales, suggesting a favorable QoL. However,

Table 4 EORTC QLQ-CR29 mean scores

	Scale	Mean score	Min-max	SD	Total
QLQ-CR29	Functional scales*				
	Body image	88.4	56–100	15.3	27
	Anxiety	76.1	33–100	20.5	27
	Weight	86.2	33–100	21.4	27
	Sexual interest (male)	24.8	0–100	34.4	8
	Sexual interest (female)	10.4	0–33	15.7	19
	Symptom scales**				
	Urinary frequency	20.7	0–100	27.1	27
	Blood and mucus in stool	6	0–66	14.5	27
	Stool frequency	6	0–100	19.6	27
	Urinary incontinence	12.2	0–100	24.6	27
	Dysuria	1.2	0–33	6.3	27
	Abdominal pain	15.9	0–100	26.6	27
	Buttock pain	11	0–100	24.3	27
	Bloating	8.5	0–100	21.8	27
	Dry mouth	0	0	0	27
	Hair loss	2.4	0–33	8.8	27
	Taste	1.2	0–33	6.3	27
	Flatulence	13.4	0–66	22.8	27
	Faecal incontinence	8.5	0–100	23.6	27
	Sore skin	3.6	0–66	13.9	27
	Embarrassment	7.3	0–100	21.3	27
	Stoma care problems	22	0–33	19	3
	Impotence	37.2	0–100	32.9	8
	Dyspareunia	31.3	0–100	34	19

*: Scores range from 0 to 100, with a higher score representing a higher level of functioning or better functioning; **: Scores range from 0 to 100, with a higher score representing a greater degree of symptoms or less functioning. SD: Standard deviation.

sexual interest for both males and females was associated with impaired function (Table 4). Out of 8 male patients, 4 answered 'not at all' and 3 answered 'a little,' indicating that 87.5% had little to no sexual interest. For female patients, out of 19, 13 answered 'not at all,' and 6 answered 'a little,' indicating that all had little to no sexual interest. Impotence received the highest score (37.2±32.9), followed by dyspareunia (31.3±34) on the symptom scales (mean±SD) (Table 4). Among male patients, 25% reported 'quite a bit' or 'very much' for erection problems. For female patients, 26.3% answered 'quite a bit' or 'very much' regarding pain or discomfort during intercourse. The third-highest symptom was urinary frequency (20.7±27.1). During the day or night, 22.2% of cases reported 'quite a bit' or 'very much' for frequent urination. Abdominal pain was reported as 'quite a bit' by 11.1%, and flatulence by 11.1%. Severe fecal incontinence was reported in 7.4% of cases. Overall, the symptom scales showed favourable outcomes except for impotence, dyspareunia and urinary frequency (Table 4). Three cases had stomas, but the impact of stoma and non-stoma presence on QoL could not be assessed due to the limited number of cases.

Regarding the relationship between clinical characteristics and the EORTC QLQ-CR29, age (<65 vs. ≥65) was the only factor influencing symptoms of buttock pain (p=0.037) and flatulence (p=0.017). Additionally, there was a statistically significant association between age ≥65 and increased anxiety (p=0.049; Mann-Whitney U test) (Table 5).

In regression analyses assessing time since RT as a continuous variable, no significant associations were found for the majority of CR29 domains, including body image, anxiety, weight, urinary and bowel symptoms, embarrassment, and female sexual functioning (all p>0.10). Non-significant positive trends were observed for abdominal pain (p=0.084) and bloating (p=0.127), while other domains such as dysuria and buttock pain also showed mild but non-significant increases with longer follow-up. Importantly, male impotence demonstrated a significant positive association with time since RT (B=0.499, 95% CI 0.155–0.843,

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Table 5 The relationship between EORTC QLQ-CR29 and clinical characteristics

Characteristic	n	Body Image mean (SD) score (0–100)	Anxiety mean (SD) score (0–100)	Weight mean (SD) score (0–100)	Urinary frequency* mean (SD) score (0–100)	Abdominal pain* mean (SD) score (0–100)	Flatulence* mean (SD) score (0–100)	Urinary incontinence* mean (SD) score (0–100)	Buttock pain* mean (SD) score (0–100)
Gender									
Female	19	87.6 (15)	76.7 (19)	85.7 (20)	20.8 (30)	19.1 (29)	13.8 (22)	17.4 (27)	13.9 (27)
Male	8	90.3 (16)	74.6 (23)	87.3 (24)	20.5 (17)	8.2 (15)	12.3 (24)	0 (0)	4.1 (11)
Age									
<65	19	85.8 (17)	80.3	82.2 (23)	23.4 (29)	12.4 (27)	6.9 (17)	10.4 (24)	7 (23)
≥65	8	94.5 (5)	(20)** 66.1 (17)	95.7 (12)	14.3 (18)	24.7 (23)	28.8 (27)**	16.5 (24)	20.6 (24)**
T stage									
T1-2	9	90 (14)	81.1 (17)	88.8 (17)	14.6 (25)	11 (23)	11 (23)	22.1 (37)	11 (23)
T3-4	18	87.6 (16)	73.6 (21)	85 (23)	23.8 (28)	18.3 (28)	14.6 (23)	7.3 (14)	11 (25)
N status									
N-	13	87.2 (17)	79.2 (25)	89.5 (16)	10 (12)	7.6 (14)	12.6	10.1 (20)	5 (12)
N+	14	89.5 (13)	73.2 (14)	83.1 (25)	30.7 (33)	23.6 (32)	14.1	14.2 (28)	16.5 (31)
Stage									
I-II	13	87.2 (17)	79.2 (25)	89.5 (16)	10 (12)	7.6 (14)	12.6 (21)	10.1 (20)	5 (12)
III	14	89.5 (13)	73.2 (14)	83.2 (25)	30.7 (33)	23.6 (32)	14.1 (26)	14.2 (28)	16.5 (31)

*: Higher scores indicate higher levels of symptoms or less functioning; **: Anxiety: Mean difference (95% CI): 21.1 (6.1-31.2), and p=0.049 / Buttock pain: Mean difference (95% CI): -16.2 (-34.4–7.2), and p=0.037/ Flatulence: Mean difference (95% CI): -21.9 (-40.1–-3.8), and p=0.017. SD: Standard deviation; QoL: Quality of life.

p=0.012), indicating a progressive worsening of erectile dysfunction over time. No variability was present for dry mouth, precluding analysis. Overall, these findings suggest that while most quality-of-life domains remain stable over long-term follow-up, male sexual dysfunction may increase with time after RT.

DISCUSSION

In this study, we conducted an analysis of the long-term QoL in cases of anal SCC treated with IMRT. Previous studies investigating EORTC QLQ-C30 in long-term anal cancer survivors before IMRT showed that Global health status/QoL scores ranged from 60 to 71, with functional scales exhibiting variability between 56 and 87. Frequently reported symptoms in the symptom scales were fatigue (range, 27–40), insomnia (range, 23.5–40), and diarrhea (range, 27–35) (Supplementary 1). [11,27–31]

In the IMRT period, the global health status/QoL reported by Yerramilli et al.[32] showed a score of 86.5. This contrasts with scores in other series,[10,33–37] which ranged from 70 to 77.6, consistent with the 3D-CRT period. The present study similarly observed this trend, revealing a Global health status/QoL score of 72.2. Functional scales in our analysis demonstrated favourable outcomes of 85 and above, aligning with Yerramilli's results.[32] Studies mostly reported scales of 80 and above for role, emotional, physical and social functions. [10,33–37] Particularly, cognitive function consistently scored higher than other functional scales in various reports, ranging from 82.5 to 95.8.[33–35] A similar result in cognitive function was also evident in the present study. While no study has directly compared QoL outcomes between IMRT and 3D-CRT, the findings of the present study appear broadly consistent with and comparable to those reported in historical 3D-CRT and IMRT series (Supplementary 1). However, the absence of baseline QoL assessments and a contemporaneous comparison group precludes causal conclusions regarding a QoL advantage associated with IMRT. Notably, previous longitudinal IMRT studies reported that Global health status/QoL and several functional scales returned toward baseline values during follow-up (Supplementary 2).[10,33] However, QoL significantly worsened in the acute period, emphasizing the importance of employing the EORTC QLQ-C30 during this phase. In the late period, focusing on site- or treatment-specific questionnaires may be more logical; however, several of these scales are inevitable extensions of the EORTC QLQ-C30.

Reports indicated that most symptoms in the EORTC QLQ-C30 are commonly observed in the general population,[33,37] similar to the findings reported

in some 3D-CRT studies.[28,29] The two most prevalent symptoms in present data, fatigue and insomnia, pose a significant challenge. Additionally, the EORTC QLQ-C30 addresses only two specific regional issues, namely diarrhea and constipation. Although the present study reported lower scores for diarrhea (9.9±24.1) compared with both the 3D-CRT and IMRT periods, the issue persists. Other studies have reported scores ranging from 14.3 to 22.8,[32–34,36,37] with some reporting higher scores and others lower,[10,35] highlighting the ongoing challenge of effectively managing this side effect, even with IMRT implementation (Supplementary 1).

The EORTC QLQ-CR29, though not specifically designed for the anal region, encompasses the colorectal area and conducts a comprehensive inquiry. Previous studies on anal cancer have consistently reported a decline in sexual interest and an increase in sexually related symptoms.[27,28,38–40] Benztzen et al.[30] reported 24% dyspareunia and 67% impotence with 3D-CRT. Another analysis also revealed a severe decrease in sexual desire in 58% [20 of 33 women (60%) and 3 of 7 men (42.8%)], along with severe dyspareunia in 60% (21 of 35 women) and erection problems in 71% (5 of 7 men) with 3D-CRT.[40] Despite the application of IMRT, significant reports of sexual impairment persisted.[41] Koerber et al.[42] reported a lower incidence of chronic G3 dyspareunia (32% for IMRT vs. 58% for 3D-CRT) and vaginal dryness (41% for IMRT vs. 83% for 3D-CRT) with IMRT. In addition, the same authors identified these issues as major concerns for women undergoing CRT. In the present study, although EORTC QLQ-CR29 function and symptom scores were deemed acceptable, noticeable decreases in sexual interest and an increase in sexual symptoms were also observed with IMRT. Sexual interest severely decreased in 92.2% [19 of 19 in females (100%) and 7 of 8 in males (87.5%)]. While severe dyspareunia was observed in 26.3% (5 of 19), impotence was less frequent at 25% (2 of 8) compared with the previous data. This emphasizes the ongoing challenge of managing sexual side effects. Yet, it should be noted that impotence was evaluated in only 8 patients in our series; therefore, the results should be interpreted with caution.

In terms of EORTC QLQ-CR29 scores with IMRT, a previous study indicated the highest QoL scores; however, they also reported the highest scores for dyspareunia (48.5±38.1) and impotence (50±39.8).[32] Dyspareunia scores varied between 26.6 and 42, and impotence scores were in the range of 39.4 to 52 in other studies (Supplementary 3).[10,33,34,36,37] Across all studies, it was found that males had more sexual symptoms than females, but conversely, females had higher levels of sexual aversion. Our findings revealed that both male and female sexual interest was lower than reported in the literature. While the dyspareunia score (31.3±34) was consistent with ranges reported in previous data, impotence (37.2±32.9) was less pronounced, despite higher scores in preliminary data. Most patients expressed satisfaction with their bodies.

Contradictory data in various studies suggested that sexual scores either returned to the pre-treatment baseline or worsened in the 12th month after treatment (Supplementary 2). [10,33,34,36] When compared with the general population, Bentzen et al.[30] reported lower levels of dyspareunia (28±34) but higher levels of impotence (69±37) in anal SCC cases with 3D-CRT. It should be noted that in several series, patient age negatively affects sexual desire.[43] It is possible that similar symptoms were present before treatment. A prospective observational survey of non-institutionalized men aged 40–70 years found that 52% of men reported erectile dysfunction and erectile dysfunction is observed more frequently with increasing age.[44] In addition, most reports emphasize the physical aspects of sexuality (dyspareunia, changes in the vagina and decreased sexual activity) and may not adequately represent the psychological (decreased libido, alterations in body image, anxiety related to sexual performance) and social (difficulty maintaining previous sexual roles, emotional distancing from partners, perceived change in partner's level of sexual interest) aspects of female cancer survivors.[45] Although EORTC QLQ-CR29 addresses physical aspects and psychological effects, including decreased libido and alterations in body image, it does not inquire about anxiety related to sexual performance. The question about anxiety addresses concerns related to the future. Additionally, social aspects are overlooked.

Clinicians, primarily focused on survival, often disregard the evaluation of sexual function. Gender differences and social norms also contribute to this phenomenon. Consequently, patients are typically examined by gynecologists and urologists in the late period. Although complementary medical strategies in the post-treatment phase (e.g., guidance on the use of vaginal dilators and lubricants) are recommended, efficacy has been the subject of controversial discussion in the literature.[38]

Nevertheless, a more effective approach remains elusive at present. Clinicians, therefore, should adopt the approach known as pre-rehabilitation, or 'pre-hab,' as a pre-treatment strategy. While pre-hab research often centers on nutrition and exercise, it could also involve teaching pelvic floor exercises, starting moisturizer regimens, and recommending lubricant use before

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treatment.[46] Psychological evaluation should not be overlooked both before and after the treatment process. Future studies are required to explore the role of supportive care (including more intensive approaches and/or new agents) during and after CRT.

Based on these findings and in line with current survivorship recommendations, routine screening for sexual dysfunction should be integrated into follow-up visits, with structured referral pathways (urology, gynecology, pelvic floor physiotherapy, psycho-oncology) when indicated. Counseling should cover both physical (e.g., dyspareunia, erectile dysfunction) and psychosocial (e.g., libido, body image, partner communication) aspects. Furthermore, pre-habilitation should be expanded to include sexual health interventions prior to CRT, such as pelvic floor exercises, moisturizers, and lubricants, delivered by a multidisciplinary team.

In the current study, the present authors observed that urinary frequency (20.7±27.1) emerged as the most prevalent symptom, following impotence and dyspareunia regarding the EORTC QLQ-CR29 symptom scales. This aligns with frequencies reported in other IMRT studies, ranging from 14 to 32.7 (Supplementary 3).[10,32–34,36,37] In comparison with baseline values, it is observed that urinary symptoms mostly improve after treatment, except for the result reported by Joseph et al.[33] (Supplementary 2). Management of urinary tract symptoms after pelvic RT involves lifestyle modifications, such as fluid intake adjustments and avoiding bladder irritants like caffeine and alcohol. Pelvic floor muscle training has shown efficacy in improving symptoms, especially when combined with counseling and physical therapy. Hyperbaric oxygen therapy is promising for managing urinary tract symptoms after pelvic RT, particularly for patients who completed pelvic RT more than 6 months prior.[47] Initial management strategies include behavioral modifications and keeping a 72-hour voiding diary. Anticholinergic and beta-3 agonist medications are options for managing irritative symptoms in female patients post-RT, while third-line treatments like a botulinum toxin A, percutaneous tibial nerve stimulation or sacral neuromodulation may be considered for those with uninhibited bladder contractions. In cases of decreased bladder compliance, more invasive treatments like catheterization or urinary diversion may be necessary, with regular upper urinary tract monitoring recommended.[48]

On the other hand, the present results indicated lower rates of fecal incontinence (8.5±23.6) and flatulence (13.4±22.8) compared with previous data, which reported fecal incontinence in the range of 14–29 and flatulence between 17.2 and 40.2 (Supplementary 3).[10,31–33,35,36] Severe fecal incontinence, reported by Lefevre et al.[37] at 7%, was also found in the present study at the same rate. However, the prevalence of flatulence was lower in the present study at 11.1%, compared with the reported 25%.

Regarding the RT dose, the median value was 59.4 Gy in the current series. Notably, some reports suggest an increase in side effects with doses exceeding >60 Gy.[49,50] Therefore, the adherence of the present study to a lower dose may have contributed to the positive QoL outcomes observed.

When analysing the clinical factors influencing EORTC QLQ-C30 and QLQ-CR29 in anal SCC, limited studies are available. Allal et al.[27] reported lower physical scale scores in elderly patients without a significant relationship with the EORTC QLQ-C30 scale and clinical factors. Sauter et al.[35] also found favourable scores for Global health status/QoL, physical and role functioning with EORTC QLQ-C30 in patients under 70 years old, however, observed no significant relationship with treatment-related factors and functional and symptom scales. By contrast, Das et al.[39] identified a trend toward lower QoL scores in patients under 51 years old. In the present analysis of EORTC QLQ-C30, individuals <65 years old exhibited improved Global health status/QoL. For EORTC QLQ-CR29, cases aged ≥65 showed a tendency for anxiety. Additionally, hip/anal pain and flatulence symptoms were statistically higher in cases aged ≥65 years again indicating age is an important factor for a patient's well-being. These age-related differences may reflect a combination of treatment-related late effects, age-related physiological changes, and a greater burden of comorbidities in older survivors. Age-associated changes in bowel function, pelvic floor function, musculoskeletal symptoms, and psychological well-being may produce symptoms similar to those associated with pelvic treatment. Because pretreatment QoL and detailed comorbidity data were not available, the relative contributions of treatment, aging, and comorbidity could not be determined. Therefore, these findings should be interpreted cautiously and regarded as exploratory.

The present study has several limitations that need consideration. Firstly, the inability to compare the present patient population with the general population, coupled with the small number of cases, are notable drawbacks. In addition, the study population consisted exclusively of recurrence-free survivors who remained available for follow-up and completed the questionnaires. Therefore, survivorship and potential nonresponse bias

may have contributed to the relatively favourable QoL scores observed. Patients who developed recurrence, experienced greater morbidity, were lost to follow-up, or were otherwise unavailable for survey completion were not represented, which may limit the generalizability of the findings to the entire treated population. Due to the cross-sectional nature of the study, baseline values at the time of diagnosis are unknown. However, it is essential to recognize that anal cancer is a rare malignancy, and the analysis of long-term QoL with IMRT is inherently limited. Given the distinctive nature of the anal region and its treatment differing from other colorectal cancers, a specific QoL scale, the EORTC Quality of Life Questionnaire-Anal Cancer (EORTC QLQ-ANL27), has been developed. This scale comprises 27 questions addressing ongoing gastrointestinal symptoms, skin symptoms, lifestyle adjustments, stoma concerns, and sexual symptoms, following the EORTC QLQ-C30 scale.[51] Notably, the lack of Turkish validation and reliability analysis for this scale and its non-utilization in the present study poses additional limitations. Therefore, it should not be concluded that the sexual function items in the CR29 are direct and sole indicators of anal function.

It is crucial to acknowledge that QoL is a result of side effects, and QoL questionnaires play a valuable role in assessing patients individually, shedding light on the symptoms experienced by cases. However, every individual's perception of QoL varies significantly. Additionally, functional conditions and symptoms are not directly observed in real life. Scales based on individual responses given during visits may mask some functional losses and symptoms. Recognizing that symptoms can develop over time underscores the importance of repeatable assessments during visits. A comprehensive analysis of the patient's symptoms at the time of diagnosis is crucial for evaluating long-term outcomes after treatment.

CONCLUSION

In conclusion, the long-term QoL outcomes of anal SCC survivors treated with IMRT presented a mixed profile, with relatively high functional scores and persistent challenges in selected symptom domains. Given the limited sample size and the multiple QoL domains examined, these exploratory findings should be interpreted as hypothesis-generating rather than confirmatory. Future research should focus on addressing the specific needs of this patient population, incorporating targeted interventions, and developing comprehensive, culturally validated assessment tools to enhance the understanding and management of long-term effects.

Ethics Committee Approval: The study was approved by the Ege University Hospital Clinical Research Ethics Committee (no: 24-10/6, date: 14.10.2024).

Informed Consent: Written informed consent was obtained from all individual participants included in the study.

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REFERENCES

1. Shiels MS, Kreimer AR, Coghill AE, Darragh TM, Devesa SS. Anal cancer incidence in the United States, 1977–2011: Distinct patterns by histology and behavior. Cancer Epidemiol Biomarkers Prev 2015;24(10):1548–56.
2. Daling JR, Madeleine MM, Johnson LG, Schwartz SM, Shera KA, Wurscher MA, et al. Human papillomavirus, smoking, and sexual practices in the etiology of anal cancer. Cancer 2004;101(2):270–80.
3. Mignozzi S, Santucci C, Malvezzi M, Levi F, La Vecchia C, Negri E. Global trends in anal cancer incidence and mortality. Eur J Cancer Prev 2024;33(2):77–86.
4. Deshmukh AA, Suk R, Shiels MS, Sonawane K, Nyitray AG, Liu Y, et al. Recent trends in squamous cell carcinoma of the anus incidence and mortality in the United States, 2001–2015. J Natl Cancer Inst 2020;112(8):829–38.
5. Nigro ND, Vaitkevicius VK, Considine B. Combined therapy for cancer of the anal canal: A preliminary report. Dis Colon Rectum 1974;17:354–6.
6. James RD, Glynne-Jones R, Meadows HM, Myint AS, Saunders MP, Maughan T, et al. Mitomycin or cisplatin chemoradiation with or without maintenance chemotherapy for treatment of squamous-cell carcinoma of the anus (ACT II): A randomised, phase 3, open-label, 2×2 factorial trial. Lancet Oncol 2013;14(6):516–24.
7. Oliveira SC, Moniz CM, Riechelmann R, Alex AK, Braghirolli MI, Bariani G, et al. Phase II study of capecitabine in substitution of 5-FU in the chemoradiotherapy regimen for patients with localized squamous cell carcinoma of the anal canal. J Gastrointest Cancer 2016;47(1):75–81.

Turk J Oncol 2026;41(3):228–239
doi: 10.5505/tjo.2026.4944

8. ISRCTN Registry. PLATO—PersonaLising Anal cancer radioTherapy dOse—incorporating Anal Cancer Trials (ACT) ACT3, ACT4 and ACT5, ISRCTN88455282. Available at: https://www.isrctn.com/ISRCTN88455282. Accessed Aug 26, 2026.
9. Peiffert D, Giovannini M, Ducreux M, Michel P, François E, Lemanski C, et al. High-dose radiation therapy and neoadjuvant plus concomitant chemotherapy with 5-fluorouracil and cisplatin in patients with locally advanced squamous-cell anal canal cancer: Final results of a phase II study. Ann Oncol 2001;12(3):397–404.
10. Han K, Cummings BJ, Lindsay P, Skliarenko J, Craig T, Le LW, et al. Prospective evaluation of acute toxicity and quality of life after IMRT and concurrent chemotherapy for anal canal and perianal cancer. Int J Radiat Oncol Biol Phys 2014;90(3):587–94.
11. Jephcott CR, Paltiel C, Hay J. Quality of life after non-surgical treatment of anal carcinoma: A case–control study of long-term survivors. Clin Oncol (R Coll Radiol) 2004;16:530–5.
12. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys 1995;31(5):1341–6.
13. Rubin P, Constine LS, Fajardo LF, Phillips TL, Wasserman TH; RTOG Late Effects Working Group. Overview: Late Effects of Normal Tissues (LENT) scoring system. Int J Radiat Oncol Biol Phys 1995;31(5):1041–2.
14. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. National Cancer Institute. US Department of Health and Human Services, National Institutes of Health.
15. Fayers P, Bottomley A; EORTC Quality of Life Group; Quality of Life Unit. Quality of life research within the EORTC—the EORTC QLQ-C30. Eur J Cancer 2002;38(Suppl 4):S125–33.
16. Gujral S, Conroy T, Fleissner C, Sezer O, King PM, Avery KN, et al.; European Organisation for Research and Treatment of Cancer Quality of Life Group. Assessing quality of life in patients with colorectal cancer: An update of the EORTC quality of life questionnaire. Eur J Cancer 2007;43(10):1564–73.
17. Whistance RN, Conroy T, Chie W, Costantini A, Sezer O, Koller M, et al.; European Organisation for Research and Treatment of Cancer Quality of Life Group. Clinical and psychometric validation of the EORTC QLQ-CR29 questionnaire module to assess health-related quality of life in patients with colorectal cancer. Eur J Cancer 2009;45(17):3017–26.
18. Sodergren SC, Vassiliou V, Dennis K, Tomaszewski KA, Gilbert A, Glynne-Jones R, et al.; EORTC Quality of Life Group. Systematic review of the quality of life issues associated with anal cancer and its treatment with radiochemotherapy. Support Care Cancer 2015;23(12):3613–23.
19. Gul SK, Tepetam H, Yildiz F, Er I, Oksuz DC, Parvizi M, et al. Revisiting the radical radiotherapy–radiochemotherapy results in anal canal cancers: (TROD Gastrointestinal Group Study 02-005). Clin Colorectal Cancer 2023;22(3):318–26.
20. Neibart SS, Manne SL, Jabbour SK. Quality of life after radiotherapy for rectal and anal cancer. Curr Colorectal Cancer Rep 2020;16(1):1–10.
21. Glynne-Jones R, Nilsson PJ, Aschele C, Goh V, Peiffert D, Cervantes A, et al.; ESMO–ESSO–ESTRO. Anal cancer: ESMO–ESSO–ESTRO clinical practice guidelines for diagnosis, treatment and follow-up. Radiother Oncol 2014;111:330–9.
22. Kachnic LA, Winter K, Myerson RJ, Goodyear MD, Willins J, Esthappan J, et al. RTOG 0529: A phase 2 evaluation of dose-painted intensity-modulated radiation therapy in combination with 5-fluorouracil and mitomycin-C for the reduction of acute morbidity in carcinoma of the anal canal. Int J Radiat Oncol Biol Phys 2013;86(1):27–33.
23. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85(5):365–76.
24. Guzelant A, Goksel T, Ozkok S, Tasbakan S, Aysan T, Bottomley A. The European Organization for Research and Treatment of Cancer QLQ-C30: An examination into the cultural validity and reliability of the Turkish version of the EORTC QLQ-C30. Eur J Cancer Care (Engl) 2004;13(2):135–44.
25. Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A; on behalf of the EORTC Quality of Life Group. EORTC QLQ-C30 scoring manual. 3rd ed. Brussels: EORTC; 2001.
26. Akduran F, Durna Z. Turkish validation and reliability of the EORTC QLQ-CR29 quality of life scale for colorectal cancer. Turk J Gastroenterol 2021;32(4):357–64.
27. Allal AS, Sprangers MA, Laurencet F, Reymond MA, Kurtz JM. Assessment of long-term quality of life in patients with anal carcinomas treated by radiotherapy with or without chemotherapy. Br J Cancer 1999;80(10):1588–94.
28. Provencher S, Oehler C, Lavertu S, Jolicoeur M, Fortin B, Donath D. Quality of life and tumor control after short split-course chemoradiation for anal canal carcinoma. Radiat Oncol 2010;5:41.
29. Welzel G, Hagele V, Wenz F, Mai SK. Quality of life outcomes in patients with anal cancer after combined radiochemotherapy. Strahlenther Onkol 2011;187(3):175–82.

30. Bentzen AG, Balteskard L, Wanderas EH, Frykholm G, Wilsgaard T, Dahl O, et al. Impaired health-related quality of life after chemoradiotherapy for anal cancer: Late effects in a national cohort of 128 survivors. Acta Oncol 2013;52(4):736–44.
31. Knowles G, Haigh R, McLean C, Phillips H. Late effects and quality of life after chemo-radiation for the treatment of anal cancer. Eur J Oncol Nurs 2015;19(5):479–85.
32. Yerramilli D, Drapek L, Nipp RD, Horick N, Moran SMC, Noé B, et al. Sexual function, quality of life, and mood after radiation therapy in patients with anal cancer. J Gastrointest Cancer 2020;51(1):204–10.
33. Joseph K, Vos LJ, Warkentin H, Paulson K, Polkosnik LA, Usmani N, et al. Patient-reported quality of life after helical IMRT-based concurrent chemoradiation of locally advanced anal cancer. Radiother Oncol 2016;120(2):228–33.
34. Gilbert A, Drinkwater K, McParland L, Adams R, Glynne-Jones R, Harrison M, et al. UK national cohort of anal cancer treated with intensity-modulated radiotherapy: One-year oncological and patient-reported outcomes. Eur J Cancer 2020;128:7–16.
35. Sauter C, Peeken JC, Borm K, Diehl C, Münch S, Combs SE, et al. Quality of life in patients treated with radiochemotherapy for primary diagnosis of anal cancer. Sci Rep 2022;12(1):4416.
36. Hosni A, Ringash J, Han K, Liu ZA, Brierley JD, Wong RKS, et al. Impact of definitive chemoradiation on quality-of-life changes for patients with anal cancer: Long-term results of a prospective study. Dis Colon Rectum 2022;65(5):642–53.
37. Lefèvre AC, Serup-Hansen E, Storm KS, Wind KL, Kronborg C, Spindler KG. One-year treatment-related side effects and quality of life after chemoradiotherapy in squamous cell carcinoma of the anus. Int J Radiat Oncol Biol Phys 2023;115(5):1165–77.
38. Fakhrian K, Sauer T, Dinkel A, Klemm S, Schuster T, Molls M, et al. Chronic adverse events and quality of life after radiochemotherapy in anal cancer patients: A single-institution experience and review of the literature. Strahlenther Onkol 2013;189(6):486–94.
39. Das P, Cantor SB, Parker CL, Zampieri JB, Baschnagel A, Eng C, et al. Long-term quality of life after radiotherapy for the treatment of anal cancer. Cancer 2010;116(4):822–9.
40. Sunesen KG, Nørgaard M, Lundby L, Havsteen H, Buntzen S, Thorlacius-Ussing O, et al. Long-term anorectal, urinary and sexual dysfunction causing distress after radiotherapy for anal cancer: A Danish multicentre cross-sectional questionnaire study. Colorectal Dis 2015;17(11):O230–9.
41. Corrigan KL, Rooney MK, De B, Ludmir ED, Das P, Smith GL, et al. Patient-reported sexual function in long-term survivors of anal cancer treated with definitive intensity modulated radiation therapy and concurrent chemotherapy. Pract Radiat Oncol 2022;12(5):e397–405.
42. Koerber SA, Seither B, Slynko A, Haefner MF, Krug D, Liermann J, et al. Chemoradiation in female patients with anal cancer: Patient-reported outcome of acute and chronic side effects. Tumori 2019;105(2):174–80.
43. Bober SL, Varela VS. Sexuality in adult cancer survivors: Challenges and intervention. J Clin Oncol 2012;30(30):3712–9.
44. Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB. Impotence and its medical and psychosocial correlates: Results of the Massachusetts Male Aging Study. J Urol 1994;151:54–61.
45. Mirabeau-Beale KL, Viswanathan AN. Quality of life in women treated for gynecologic malignancies with radiation therapy: A literature review of patient-reported outcomes. Gynecol Oncol 2014;134(2):403–9.
46. Canty J, Stabile C, Milli L, Seidel B, Goldfrank D, Carter J. Sexual function in women with colorectal/anal cancer. Sex Med Rev 2019;7(2):202–22.
47. Uberoi P, Smith CA, Lucioni A. Management of lower urinary tract symptoms after prostate radiation. Curr Urol Rep 2021;22:37.
48. Leddy LS. Management of lower urinary tract symptoms after pelvic radiation in females. Curr Urol Rep 2018;19:106.
49. Pan YB, Maeda Y, Wilson A, Glynne-Jones R, Vaizey CJ. Late gastrointestinal toxicity after radiotherapy for anal cancer: A systematic literature review. Acta Oncol 2018;57(11):1427–37.
50. Engineer R, Mallik S, Mahantshetty U, Shrivastava S. Impact of radiation dose on locoregional control and survival in squamous cell carcinoma of the anal canal. Radiother Oncol 2010;95(3):283–7.
51. Sodergren SC, Johnson CD, Gilbert A, Tomaszewski KA, Chu W, Chung HT, et al.; EORTC Quality of Life Group. Phase I–III development of the EORTC QLQ-ANL27, a health-related quality of life questionnaire for anal cancer. Radiother Oncol 2018;126(2):222–8.

Supplementary 1. Comparison of mean scores in studies utilizing EORTC QLQ-C30 for 3D-CRT and IMRT

	3D-CRT						IMRT							
QLQ-C30	Allal (27) (1999) n=41	Jephcott (11) (2004) n=50	Provencher (28) (2010) n=30	Welzel[§] (29) (2011) n=52	Bentzen (30) (2013) n=128	Knowles[†] (31) (2015) n=42	Han[#] (10) (2014) n=58	Joseph[#] (33) (2016) n=54	Yeramilli (32) (2020) n=42	Gilbert[#] (34) (2020) n=57[‖]	Sauter[††] (35) (2022) n=52	Hosni[#] (36) (2022) n=72	Lefèvre[#] (37) (2023) n=232[‖]	Balci Topuz (current study) n=27
Global Health status / QoL *	71 (21)	66 (28)	70 (25)	60 (n/a)	68 (25)	66.7 (n/a)	70 (20)	72.2 (18.3)	86.5 (16.3)	72.8 (19.5)	77.6 (13)	72.7 (n/a)	71.6 (21.6)	72.2 (22.9)
Functional scales*														
Physical	79.5 (22)	74 (29)	87 (14)	70 (n/a)	77 (22)	86.7 (n/a)	88 (15)	84.9 (17.2)	91 (12.9)	84 (20.7)	82.3 (17)	85.5 (n/a)	84.8 (19.3)	84.5 (22)
Role	85 (21)	76 (33)	77 (26)	60 (n/a)	69 (31)	66.7 (n/a)	86 (25)	79.4 (23.1)	91.7 (16)	81 (24.1)	70.5 (22)	82.9 (n/a)	80 (26.7)	86.4 (25.6)
Emotional	77 (25)	74 (28)	77 (26)	56 (n/a)	77 (25)	66.7 (n/a)	78 (21)	77 (21.9)	87.3 (12.1)	80.3 (23.1)	70.5 (15)	79.2 (n/a)	81.9 (18.7)	85.8 (17.7)
Cognitive	76 (23)	75 (24)	85 (25)	75 (n/a)	77 (26)	83.3 (n/a)	79 (18)	82.5 (23.9)	90.9 (12.3)	84.8 (20.9)	95.8 (12.5)	82.9 (n/a)	84.5 (21.6)	93.8 (11.5)
Social	82 (28)	73 (35)	74 (34)	60 (n/a)	71 (29)	66.7 (n/a)	83 (20)	81.1 (22.3)	90.5 (15.2)	76.6 (27.1)	83.0 (11)	83.8 (n/a)	84.8 (23.6)	88.3 (21.9)
Symptom scales**														
Fatigue	27 (22)	36 (30)	28 (29)	40 (n/a)	38 (28)	33.3 (n/a)	24 (18)	27.2 (19.6)	15.6 (16.1)	26.2 (22.8)	21.1 (18)	26 (n/a)	26.3 (24.6)	18.7 (18.2)
Nausea/vomiting	6 (15)	6 (17)	1 (4)	5 (n/a)	6 (13)	0 (0)	6 (16)	7.46 (15.8)	1.59 (6.17)	4.09 (10.5)	(n/a) (n/a)	5.7 (n/a)	4.0 (10.4)	0.5 (3)
Pain	15 (21)	23 (31)	20 (25)	32 (n/a)	25 (30)	16.7 (n/a)	19 (24)	18.4 (21.9)	9.13 (21.5)	15.5 (23.7)	(n/a) (n/a)	20 (n/a)	19.0 (24.8)	9.2 (18.1)
Dyspnoea	13 (22)	23 (33)	18 (26)	30 (n/a)	27 (33)	(n/a) (n/a)	9 (15)	14.0 (21.4)	8.33 (19.6)	14 (23.3)	(n/a) (n/a)	11.6 (n/a)	13.1 (24.8)	0 (0)
Insomnia	23.5 (29)	29 (32)	26 (31)	40 (n/a)	35 (35)	(n/a) (n/a)	29 (27)	33.3 (30)	17.5 (21.3)	25.7 (30.8)	(n/a) (n/a)	28.1 (n/a)	23.4 (30)	18.4 (28)
Appetite	10 (19)	13 (22)	10 (23)	13 (n/a)	14 (24)	(n/a) (n/a)	11 (20)	9.7 (23.1)	4.17 (13.5)	8.9 (19.5)	(n/a) (n/a)	10 (n/a)	8.5 (20.8)	5 (12.3)
Constipation	15 (21)	24 (32)	7 (19)	15 (n/a)	22 (28)	(n/a) (n/a)	8 (17)	4.4 (15.8)	7.32 (14)	9.9 (18.8)	18.6 (30)	10.5 (n/a)	11.3 (21.5)	6.2 (13.4)
Diarrhea	28 (36)	27 (32)	28 (40)	35 (n/a)	27 (32)	(n/a) (n/a)	12 (21)	22.8 (27)	14.3 (19.7)	18.2 (22.9)	38.5 (19)	18.1 (n/a)	20.9 (25.8)	9.9 (24.1)
Financial impact	15 (28)	23 (37)	20 (31)	32 (n/a)	14 (27)	(n/a) (n/a)	19 (29)	16.7 (24.2)	8.73 (18.1)	16.3 (23.8)	(n/a) (n/a)	17.1 (n/a)	7.8 (20.8)	11.1 (20.6)

Scores for the late phase of the 12th month are provided.
§ The approximate mean scores were obtained from the presented figure 1 in the study.
† Median scores are provided.
†† 38 patients were treated with IMRT, while 14 were treated with 3D-CRT.
|| Patient number for the late phase of the 12th month are provided.
* Scores range from 0 to 100, with a higher score representing a higher level of functioning or better functioning
** Scores range from 0 to 100, with a higher score representing a greater degree of symptoms or less functioning
The standard deviation is indicated within parentheses.
n/a, not available

Supplementary 2. Comparing long-term QoL outcomes utilizing EORTC QLQ-C30 and CR29 for anal cancer with IMRT in published studies

	Number of patients	Design	Aim	Treatment	Scoring system	Main result
Han (10) (2014)	58	Single-center, longitudinal cohort study	Evaluation of acute and long-term toxicities as well as QoL at baseline, after treatment, and during follow-up	*Primary tumor:* Tumors ≤2 cm: 45 Gy in 25 fractions Tumors 2.1 to 4 cm: 54 Gy in 30 fractions Tumors >4 cm or poorly differentiated: 63 Gy in 35 fractions *Lymph nodes:* Nodes >2 cm: 63 Gy in 35 fractions Nodes ≤2 cm: Initial phase: 36 Gy in 20 fractions Follow-up phase: 22.5 Gy in 15 fractions *Sites of excised involved nodes:* 54 Gy in 30 fractions *Node-negative regions:* T1N0 disease: 27 Gy in 15 fractions	QLQ-C30 QLQ-CR29	QOQ-C30: Global QoL/health status was significantly worse at the end of treatment but returned to baseline levels, remaining stable at 12 months. Social functioning and appetite scores improved significantly at 12 months. QOQ-CR29: Skin and defecation problems worsened significantly at the end of treatment but returned to baseline levels, remaining stable at 12 months. Impotence significantly worsened from a baseline mean score of 30 to 52 at 12 months. Dosimetric parameters correlated with toxicities, showing IMRT's benefits in reducing toxicities without compromising control.

				All other stages: 36 Gy in 20 fractions Fraction size: 1.8 Gy Chemotherapy: 5-FU/MMC		
Joseph (33) (2016)	54	Single-center, longitudinal cohort study	Evaluation of QoL at baseline, after treatment, and during follow-up	*Primary tumor:* 54 Gy delivered to 95% of the volume in 30 fx *Region at risk of disease spread:* 45 Gy delivered to 95% of the volume in 30 fx Fraction size: 1.8 Gy Chemotherapy: 5-FU/MMC	QLQ-C30 QLQ-CR29	QOQ-C30: Functional scales returned to baseline or slightly improved at 12 weeks post-treatment. Symptoms worsened initially, including medium deterioration in diarrhea, which persisted for up to 12 months. QOQ-CR29: Dyspareunia worsened and remained elevated throughout period. Impotence improved at 12 weeks post-treatment. Urinary frequency and dysuria returned to baseline at 12 weeks, but urinary incontinence persisted. The study supported the routine use of IMRT and emphasized the importance of evaluating sexual, urinary, and anorectal functions before starting treatment.

Yeramilli (32) (2020)	42	Single-center, cross-sectional	Evaluation of long-term QoL, patient-reported sexual function, and mood	*T2N0 tumors:* Elective nodal volumes: 42 Gy Primary tumor: 50.4 Gy Fractionation: 28 fx *T3-4, N0-3 tumors*: Elective nodal volumes: 45 Gy Lymph nodes ≤3 cm: 50.4 Gy Lymph nodes >3 cm: 54 Gy Primary tumor: 54 Gy Fractionation: 30 fx Chemotherapy: 5-FU/MMC, 5-FU/cisplatin	QLQ-C30 QLQ-CR29	QOQ-C30: Overall quality of life scores were relatively high, with a mean global quality of life score of 86.5. QOQ-CR29: Both male and female patients reported poor sexual interest, with mean scores of 54.2 (±30.5) and 17.9 (±21.2), respectively. For the 18 symptom scales, patients reported particularly high scores corresponding to worse symptoms for impotence and dyspareunia. Patients undergoing pelvic radiation therapy for anal cancer may experience changes in sexual function, but they typically report mild mood symptoms and display high QOL scores.
Gilbert (34) (2020)	57[l][l]	Multicenter, longitudinal cohort study	Evaluation of QoL at baseline, after treatment, and one-year follow-up	*T1/2 tumors:* Median dose 50.4 Gy in 28 fx (Range 30-54 Gy in 10-30 fx) *T3/ 4 tumors:* Median dose 53.2 Gy in 28 fx (Range 40-54 Gy in 15-30 fx) Chemotherapy: 5-FU/MMC, Capecitabine/MMC	QLQ-C30 QLQ-CR29	QOQ-C30: At one-year follow-up, significant improvements were observed in pain, constipation, appetite loss with moderate improvements in emotional and role functioning. QOQ-CR29: Impotence scores remained relatively poor at one year but did not significantly worsen after treatment. Dyspareunia worsened moderately for women after

						treatment, with an overall one-year mean score indicating mild. At one year, flatulence, impotence, libido (for both genders), and health anxiety had the most severe symptom mean scores, with moderate or small improvements observed for health anxiety and female libido.
Sauter [††] (35) (2022)	52	Single-center, cross-sectional	Evaluation of long-term QoL between healthy people and anal cancer patients	*Minimum dose*: 45 Gy *Boost for advanced tumors and affected lymph nodes:* 9–14 Gy Fraction size: 1.8 Gy Chemotherapy: 5-FU/MMC, Capecitabine/MMC	QLQ-C30 QLQ-ANL27	QLQ-C30: Anal cancer patients showed lower role, emotional, and social functioning, but higher cognitive functioning and overall global health compared to the German reference population. Constipation and diarrhea scores were higher in anal cancer patients. Physical and role functioning strongly impacted global QoL. Fatigue notably impacted QoL negatively. IMRT patients did not differ significantly from 3D-CRT patients.
Hosni (36) (2022)	72	Single-center, longitudinal cohor	Evaluation of QoL at baseline, after treatment, and during follow-up	*Elective targets:* 36 Gy/20 fractions, except for T1N0 cancer which received 27 Gy/15 fractions. *T1N0 disease:* 45 Gy/27 fractions	QLQ-C30 QLQ-CR29	QLQ-C30: Clinically and statistically significant improvements above baseline were observed in role functioning, emotional functioning, appetite loss, pain, social functioning, nausea/vomiting, insomnia, fatigue, and financial problems in long-term.

		t study		*All T1N+ or selected T2 any N with low/intermediate-grade tumor of <4 cm:* 54 Gy/30 fractions *Advanced tumors (T3 and T4) or T2 with high-grade and/or ≥4 cm:* 63 Gy/35 fractions. Chemotherapy: 5-FU/MMC		Baseline QOL did not significantly correlate with long-term QoL, except for specific scales like physical functioning, social functioning, constipation, and financial problems. QOQ-CR29: Anxiety and abdominal/pelvic pain improved significantly above baseline. Body image, bowel embarrassment, fecal incontinence, and hair loss worsened statistically, but not clinically in long-term. Impotence worsened both statistically and clinically. No significant correlation was found between baseline and long-term QoL.
Lefèvre (37) (2022)	232[ll]	Multicenter longitudinal cohort study	Evaluation of QoL at baseline, after treatment, and one-year follow-up	*Elective targets:* 48 to 51.2 Gy *Tumor and pathological lymph nodes:* 60 to 64 Gy Fraction size: 2 Gy Chemotherapy: Induction chemotherapy, concomitant cisplatin, concomitant 5-FU, concomitant cisplatin/5-FU, concomitant capecitabine	QLQ-C30 QLQ-CR29	QLQ-C30: Significant minor score improvements were observed in four items: Global health status/QoL, Emotional functioning, Insomnia, and Appetite. No items showed moderate or major changes, and none worsened from baseline to one year. QOQ-CR29: Of the bowel and bladder items, two worsened significantly from baseline to one year after treatment. These were fecal incontinence, which experienced a minor change, and flatulence, which

						experienced a moderate change. Erectile dysfunction also worsened slightly by 9.4 points. Patients had a low bowel symptom burden and symptom scores one year after treatment, and most patients with high bowel and bladder symptoms before treatment experienced improvement one year after treatment.
Balci Topuz (current study)	27	Single-center, cross-sectional	Evaluation of long-term QoL	*Sequential boost technique:* 45 Gy followed by a 5.4-9 Gy for the high-risk CTV, and additional 5.4-9 Gy boost for the gross disease CTV, reaching a total of 59.4 Gy or 64.8 Gy for stable or progressive cases. Fraction size: 1.8 Gy *Simultaneous Integrated Boost technique:* 45–54 Gy for single CTV, with a range of 54–59.4 Gy for gross disease CTV. Chemotherapy: 5-FU/MMC	QLQ-C30 QLQ-CR29	QOQ-C30: Overall QoL scores were relatively high, with lower scores reported for most symptoms, particularly diarrhea and constipation. QOQ-CR29: Sexual interest decreased for both genders, with urinary frequency [20.7±27.1] being the most prevalent symptom, followed by impotence [37.2±32.9] and dyspareunia [31.3±34].

|| Patient number for the late phase of the 12th month are provided.

†† 38 patients were treated with IMRT, while 14 were treated with 3D-CRT.

CTV, Clinical target volume; IMRT, Intensity-modulated radiation therapy; MMC, Mitomycin C; QoL, Quality of life; 3D-CRT, Three-dimensional conformal radiotherapy; 5-FU, 5-Florourasil.

Supplementary 3. Comparison of mean scores in studies utilizing EORTC QLQ-CR29 for 3D-CRT and IMRT

	3D-CRT		IMRT						
QLQ-CR29	Provencher (28) (2010) n=30	Bentzen (30) (2013) n=128	Han[#] (10) (2014) n=58	Joseph[#] (33) (2016) n=54	Yeramilli (32) (2020) n=42	Gilbert[#] (34) (2020) n=57[‖]	Hosni[#] (36) (2022) n=72	Lefèvre[#] (37) (2022) n=232[‖]	Balci Topuz (current study) n=27
Functional scales*									
Body Image	(n/a) (n/a)	72 (31)	87 (17)	81.0 (22.3)	78.3 (29.2)	76 (28.9)	83.7 (n/a)	80.9 (26.4)	88.4 (15.3)
Anxiety	(n/a) (n/a)	62 (33)	73 (19)	71.3 (25.4)	75.6 (26.9)	60.7 (29.2)	73.8 (n/a)	67.4 (28.8)	76.1 (20.5)
Weight	(n/a) (n/a)	76 (31)	(n/a) (n/a)	81.5 (23.2)	74.6 (27.4)	75.5 (29.4)	(n/a) (n/a)	81.5 (27.9)	86.2 (21.4)
Sexual interest (male)	(n/a) (n/a)	44 (32)	60 (29)	36.4 (31.5)	54.2 (30.5)	28.8 (27.7)	62.6 (n/a)	48.7 (27.9)	24.8 (34.4)
Sexual interest (female)	(n/a) (n/a)	23 (27)	84 (21)	24.2 (23.4)	17.9 (21.2)	18.9 (26.6)	81.8 (n/a)	16.5 (24.3)	10.4 (15.7)
Symptom scales**									
Urinary frequency	(n/a) (n/a)	29 (28)	14[††] (19)	23.6 (22.3)	21.8 (22.2)	32.7 (22)	16[††] (n/a)	20.8 (23.0)	20.7 (27.1)
Blood and mucus in stool	(n/a) (n/a)	13 (17)	18[§] (13)	15.2 (17.3)	9.76 (13.9)	14.6 (17.9)	17.2[§] (n/a)	17.4 (19.2)	6 (14.5)
Stool frequency	(n/a) (n/a)	19 (21)	18[§] (13)	18.1 (17.1)	14 (13.7)	20 (20.9)	17.2[§] (n/a)	16.9 (16.3)	6 (19.6)
Urinary incontinence	(n/a) (n/a)	17 (26)	14[††] (19)	14.8 (21.7)	15.9 26.8)	13.1 (21.7)	16[††] (n/a)	7.6 (19.5)	12.2 (24.6)
Dysuria	(n/a) (n/a)	8 (19)	14[††] (19)	4.6 (11.7)	1.59 (7.18)	2.97 (n/a)	16[††] (n/a)	3.5 (11.9)	1.2 (6.3)
Abdominal pain	(n/a) (n/a)	14 (22)	9 (10)	16.7 (24.6)	3.17 (9.90)	9.52 (18.7)	9.6 (n/a)	13.4 (21.2)	15.9 (26.6)
Buttock pain	(n/a) (n/a)	25 (32)	9 (10)	17.6 (20.3)	13.5 (25.6)	23.3 (25.3)	9.6 (n/a)	20.4 (26.5)	11 (24.3)
Bloating	(n/a) (n/a)	31 (29)	18 (23)	13.9 (20.1)	9.52 (16.9)	(n/a) (n/a)	20.1 (n/a)	26.9 (27.8)	8.5 (21.8)
Dry mouth	(n/a) (n/a)	(n/a) (n/a)	17 (23)	11.1 (17.8)	12.7 (20.8)	23.2 (32.9)	18.6 (n/a)	18.3 (26.3)	0.0 (0.0)
Hair loss	(n/a) (n/a)	(n/a) (n/a)	12 (16)	5.6 (12.6)	20.6 (29.4)	5.3 (13.8)	11.4 (n/a)	7.5 (18.7)	2.4 (8.8)
Taste	(n/a) (n/a)	(n/a) (n/a)	8 (17)	7.4 (18.0)	4.76 (11.8)	10.1 (24.5)	8.3 (n/a)	8.3 (19.8)	1.2 (6.3)
Flatulence	(n/a) (n/a)	47 (32)	18[§] (13)	31.5 (22.5)	28 (27.3)	40.2 (28.3)	17.2[§] (n/a)	34.8 (27.1)	13.4 (22.8)
Faecal incontinence	(n/a) (n/a)	29 (31)	26 (21)	19.4 (23.1)	14 (18.8)	19.3 (27)	29 (n/a)	18.0 (23.4)	8.5 (23.6)

Sore skin	(n/a) (n/a)	(n/a) (n/a)	22 (22)	20.4 (21.5)	20.4 (23.8)	22.7 (30.3)	20.5 (n/a)	23.8 (24.6)	3.6 (13.9)
Embarrassment	(n/a) (n/a)	(n/a) (n/a)	13 (24)	15.7 (23.2)	17.8 (25.9)	25.2 (31.9)	17.9 (n/a)	11.8 (23.1)	7.3 (21.3)
Stoma care problems	(n/a) (n/a)	(n/a) (n/a)	(n/a) (n/a)	0.0 (0.0)	8.33 (16.7)	(n/a) (n/a)	33.3 (n/a)	0.0 (0.0)	22 (19)
Impotence	(n/a) (n/a)	69 (37)	52 (43)	39.4 (46.7)	50 (39.8)	46.7 (39.4)	49.5 (n/a)	47.6 (39.1)	37.2 (32.9)
Dyspareunia	(n/a) (n/a)	28 (34)	42 (34)	37.8 (27.8)	48.5 (38.1)	29.5 (38)	30 (n/a)	26.6 (34.8)	31.3 (34)

Scores for the late phase of the 12th month are provided.
§ Defined as defecation problems
†† Defined as micturition problems
|| Patient number for the late phase of the 12th month are provided.
* Scores range from 0 to 100, with a higher score representing a higher level of functioning or better functioning
** Scores range from 0 to 100, with a higher score representing a greater degree of symptoms or less functioning
The standard deviation is indicated within parentheses.
n/a, not available

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REVIEW

Adipokines Reframing the Obesity Paradox in Precision Oncology

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SUMMARY

The increasing coexistence of obesity, insulin resistance, and malignancy has intensified interest in adipokines as mechanistic links between metabolic disease and tumor progression. This review summarizes tumor-specific evidence in breast, colorectal, endometrial, ovarian, and hepatocellular cancers and discusses the biomarker and therapeutic value of circulating adipokines, receptor antagonists, pathway modulators, and metabolism-informed combination strategies. To date, adipokines are bioactive mediators released by adipocytes, stromal cells, and immune cells within adipose depots and tumor-adjacent fat. Rather than acting as isolated biomarkers, they form a dynamic signaling network that regulates proliferation, apoptosis resistance, angiogenesis, epithelial-mesenchymal transition, cancer stem-like behavior, and immune remodeling. Leptin, resistin, visfatin, and chemerin are predominantly associated with pro-tumorigenic effects, whereas adiponectin and omentin are more often linked to anti-inflammatory and anti-proliferative actions. Emerging adipokines such as apelin, vaspin, irisin, and RBP4 (Retinol-binding protein 4) display context-dependent behavior that varies with tumor type, receptor expression, and metabolic state. Mechanistically, adipokines converge on JAK(Janus kinase)/STAT, PI3K (Phosphoinositide 3-kinase)/Akt/mTOR (Mechanistic target of rapamycin), MAPK/ERK (Mitogen-activated protein kinase / Extracellular signal-regulated kinase), AMPK (AMP-activated protein kinase), NF-kB, and insulin/IGF-1 pathways, thereby influencing both tumor cells and the surrounding microenvironment. The data suggest that precision oncology could be improved by integrating adipokine biology into patient stratification strategies, especially for metabolically dysregulated populations in whom tumor behavior and treatment response are shaped by the endocrine and immune state of adipose tissue.

Keywords: Adipokines; adiponectin; biomarkers; metabolic signaling; leptin; obesity-related cancer; precision oncology; therapeutic targeting; tumor microenvironment.

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INTRODUCTION

Obesity-associated malignancies are increasingly recognized as disorders of dysregulated systemic signaling rather than purely cell-autonomous genetic disease. The adipose tissue compartment is now understood as an active endocrine and immune organ capable of shaping tumor initiation, progression, immune escape, and treatment response.[1–3] It should be noted that adipokines are secreted not only by mature adipocytes but also by stromal cells, macrophages, and fibroblasts. Their biological effects extend from energy balance and insulin sensitivity to angiogenesis, extracellular matrix (ECM) remodeling, endocrine cross-talk, and immune-cell metabolism.[4,5] In obesity, adipose tissue hypertrophy, hypoxia, inflammation, and fibrosis shift the secretory profile toward higher concentrations of pro-inflammatory and proliferative mediators and

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lower concentrations of protective molecules. Tumors developing in or near adipose-rich sites are thereby exposed to a complex microenvironment that can favor aggressive behavior. Precision oncology has traditionally focused on tumor genomics, targetable mutations, and histopathology. Two patients with the same tumor subtype may experience different disease trajectories because obesity, insulin resistance, body composition, and adipokine imbalance alter cancer cell signaling and the tumor microenvironment (TME).[6,7] It means that treatment response is also shaped by host metabolic context, and therefore, the adipokine biology offers an important framework for integrating tumor-intrinsic and host-derived determinants of outcome.

The available literature combines clinical, epidemiological, and mechanistic evidence and supports a consistent conceptual finding: Adipokines are neither passive obesity markers nor uniform actors. Instead, they function within a dynamic metabolic-immune signaling network whose consequences depend on receptor expression, tissue specificity, tumor stage, sex, and coexisting metabolic abnormalities.[7,8] This article retains that framework and extends its implications for translational practice. A useful conceptual distinction is to group adipokines as predominantly pro-tumorigenic, predominantly anti-tumorigenic, or context dependent. Leptin, resistin, visfatin, and many chemerin-associated signaling contexts fit the first category; adiponectin and omentin more often occupy the second; and apelin, vaspin, irisin, and RBP4 belong to the third because their biological behavior can vary considerably across tissues and disease states.[9–12] This classification is heuristic rather than absolute, but it remains helpful for organizing translational reasoning.

Another central concept is that adipokines operate across scales. They act systemically through endocrine circulation, locally by paracrine signaling, and within the tumor niche through reciprocal communication between cancer cells, adipocytes, endothelial cells, and immune cells.[2,13] Because of this multilevel action, adipokines can influence both cancer risk and treatment response.

METHODS

Relevant literature was considered across three major evidence domains: Experimental studies describing adipokine-mediated signaling pathways, clinical and epidemiological studies evaluating adipokines as cancer-related biomarkers, and translational reports discussing adipokine-targeted or metabolism-informed therapeutic strategies. Particular attention was given to adipokines with repeated relevance in cancer biology, including leptin, adiponectin, resistin, visfatin, chemerin, omentin, apelin, vaspin, irisin, and retinol-binding protein 4 (RBP4). Tumor types were selected based on their established association with obesity, adipose tissue dysfunction, or metabolic dysregulation. These included breast, colorectal, endometrial, ovarian, and hepatocellular cancers. The analysis aimed to identify recurring mechanistic patterns, areas of consistency, sources of conflicting evidence, and clinically relevant knowledge gaps. The final synthesis was used to propose a precision-oncology framework in which adipokine profiles, metabolic phenotype, receptor expression, and TME features may support improved patient stratification and treatment personalization.

PRO-TUMORIGENIC ADIPOKINES

Leptin is the prototypical adipokine linking excess adiposity to tumor-promoting biology. Originally characterized as a regulator of body weight and energy balance, leptin also signals through OB-R (Leptin receptor) and cytokine-like receptor mechanisms that can activate JAK/STAT3 (Signal transducer and activator of transcription 3), PI3K/Akt, and MAPK/ERK pathways.[14–16] These pathways stimulate cyclin expression, enhance cell-cycle progression, inhibit apoptosis, promote endothelial activation, and reinforce migratory and epithelial-mesenchymal phenotypes.[17–19] Leptin also interacts with estrogen receptor, EGFR (Epidermal growth factor receptor), IGF-1 (Insulin-like growth factor 1), reproductive, and immune signaling, generating amplification loops that may be particularly relevant in breast and gynecological malignancies.[20–24] Resistin and visfatin strengthen the inflammatory-metabolic component of tumor progression. Resistin has been associated with inflammatory signaling, angiogenesis, and VEGF (Vascular endothelial growth factor) -related processes, while visfatin supports proliferative and survival signaling through PI3K/Akt, MAPK/ERK, and STAT3/NF-kB pathways.[6,7] These mediators exemplify how adipokines can connect insulin resistance, chronic inflammation, and oncogenic transcriptional programs. They are especially relevant in metabolically inflamed phenotypes where tumor cells and stromal cells are continuously exposed to pro-survival cytokine-like signals. Chemerin remains more complex. It can promote or restrain tumor progression depending on receptor usage, cellu-

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lar context, and tumor type.[25–27] This duality illustrates an important principle for precision oncology: Adipokines should not be interpreted only by average effect direction. Their clinical meaning may depend on receptor expression patterns, local immune composition, and concurrent metabolic signals. Context dependence does not diminish translational value; it makes biomarker-guided stratification more necessary.

ANTI-TUMORIGENIC AND PROTECTIVE ADIPOKINES

Adiponectin is the best-characterized protective adipokine. Its actions include activation of AMPK, inhibition of PI3K/Akt/mTOR, suppression of NF-kB signaling, promotion of apoptosis, and reduction of angiogenic drive.[8,28] These effects align with a less proliferative, less inflammatory, and more metabolically stable cellular state. In obesity, circulating adiponectin is typically reduced, suggesting that cancer-promoting conditions may arise not only from excess pro-tumor signals but also from loss of endogenous protective regulation. Adiponectin biology also has translational relevance at the receptor level. AdipoR1 (Adiponectin receptor 1), AdipoR2 (Adiponectin receptor 2), and T-cadherin help determine tissue-specific signaling output, and reduced receptor expression or receptor dysfunction in tumors may blunt the anti-proliferative influence of adiponectin even when circulating levels are measurable.[28] This means that future biomarker strategies may need to integrate ligand concentrations with receptor profiling rather than focusing on serum values alone. Omentin appears to share several anti-inflammatory and insulin-sensitizing characteristics, although the evidence base remains smaller and less consistent than for adiponectin. Vascular and metabolic studies indicate that omentin can oppose inflammation and vascular dysfunction, supporting its potential relevance in the broader obesity-cancer interface.[29–31] From a translational viewpoint, adiponectin and omentin represent a therapeutic logic: Restore or mimic protective adipokine signaling to counterbalance obesity-associated tumor promotion.

SIGNALING PATHWAYS AND NETWORK CONVERGENCE

Pathway convergence is one of the strongest mechanistic themes in adipokine research. JAK/STAT3, PI3K/Akt/mTOR, MAPK/ERK, NF-kB, AMPK, and insulin/IGF-1 signaling are the major molecular hubs through which metabolism communicates with growth and survival.[6,32] Leptin prominently activates JAK/STAT3 and PI3K/Akt; resistin and visfatin reinforce NF-kB and MAPK-associated inflammatory proliferation; and adiponectin counterbalances through AMPK activation and downstream suppression of mTOR and inflammatory transcription. This convergence matters because adipokines can modify response to therapies that target the same pathways. For example, PI3K/Akt/mTOR inhibitors may behave differently in tumors embedded in leptin-rich or insulin-resistant environments.[33] Likewise, anti-angiogenic strategies might be influenced by adipokine-driven VEGF and endothelial signaling.[17] Experimental evidence also suggests that leptin-associated mitochondrial and survival signaling may contribute to drug resistance in selected malignancies.[34] Precision medicine that ignores host endocrine context may therefore underestimate one source of variability in response and resistance. The network perspective also helps resolve apparently contradictory findings. A single adipokine may not act identically across all settings because pathway dominance changes with receptor density, co-stimulating cytokines, oxygen tension, hormonal milieu, and metabolic state. Apparent inconsistency in observational studies may therefore reflect biological heterogeneity rather than simple noise.

TUMOR MICROENVIRONMENT (TME), CANCER-ASSOCIATED ADIPOCYTES (CAAS), AND IMMUNE REMODELING

Tumor progression in adipose-rich organs is heavily shaped by stromal ecology. Cancer-associated adipocytes (CAAs) are described as smaller, lipid-depleted, and secretory-active cells with elevated output of adipokines, cytokines, and ECM components.[35] These cells support tumor invasion by increasing matrix remodeling, lipid transfer, inflammatory signaling, and angiogenic potential. Their presence reinforces the idea that adipose tissue adjacent to tumors becomes functionally reprogrammed rather than merely displaced. Experimental and translational studies further show that adipocytes can support tumorigenesis, metastasis, radioresistance, and early mammary tumor progression through local matrix and metabolic effects.[13,36,37] These data link adipokine molecular signaling to tissue-level behavior that can be observed in clinical settings and directed toward experimental goals. Adipokines also regulate immune-cell metabo-

lism and composition within the TME. They can attract immunosuppressive myeloid populations, favor M2-like macrophage polarization, and impair effective cytotoxic T-cell activity, while leptin and adiponectin influence T-cell differentiation and metabolic fitness.[4,23,38] For precision oncology, this means that the biological behavior of obesity-associated cancers cannot be inferred from tumor genomics alone. The adipose compartment is therefore both a biomarker source and a therapeutic target.

TUMOR-SPECIFIC EVIDENCE

Breast cancer remains the most thoroughly studied model of adipokine-tumor interaction. Leptin can promote growth, invasion, angiogenesis, and epithelial-mesenchymal transition (EMT) in both hormone receptor-positive and triple-negative settings, whereas adiponectin is generally associated with lower risk or more favorable metabolic signaling.[18,39,40] Because mammary tissue is embedded in adipose tissue, adipokine effects are likely to be especially relevant in local microenvironmental signaling and endocrine crosstalk. Clinical cohort data have also examined circulating leptin, adiponectin, and resistin in relation to long-term breast cancer prognosis, underscoring the need to interpret biomarkers within patient phenotype and treatment context.[41] Colorectal cancer provides a second important model. Elevated leptin and lower adiponectin have been associated with colorectal adenoma and carcinoma risk in multiple analyses, although the strength of association can change after adjustment for body mass index (BMI) and metabolic covariates.[42,43] This heterogeneity is informative rather than merely contradictory: Adipokines likely participate in early neoplastic and inflammatory transitions, but their net predictive value depends on broader host context. Endometrial, ovarian, and hepatocellular cancers further illustrate the breadth of adipokine relevance. Endometrial cancer is strongly linked to obesity, altered estrogen metabolism, insulin signaling, and adipose inflammation.[44–47] Ovarian tumors interact closely with omental adipose tissue and CAAs.[48] Hepatocellular carcinoma often emerges in the setting of NAFLD (Non-alcoholic fatty liver disease), insulin resistance, fibrosis, and adipokine dysregulation.[49,50] Reproductive-endocrine literature further supports the view that adipokines link metabolic cues to hormonal and gonadal pathways relevant to gynecologic cancer biology.[21,51,52] Together, these examples support the view that adipokines are particularly consequential in cancers embedded in metabolically altered organ ecosystems. Recent regional studies also emphasize that biochemical breast-cancer markers and lymph-node morphology can support recurrence and metastasis prediction, which is consistent with the need to combine circulating biomarkers, tissue features, and metabolic context in precision oncology.[53,54]

BIOMARKERS, CLINICAL HETEROGENEITY, AND THE OBESITY PARADOX

Circulating adipokines have been studied as diagnostic, prognostic, and predictive biomarkers. Repeated interest has focused on leptin, adiponectin, resistin, visfatin, chemerin, and especially the leptin-to-adiponectin ratio, because these markers are biologically plausible and relatively accessible.[6,7,55] A blood-based marker that reflects tumor-promoting metabolic context would be valuable for both risk stratification and treatment planning. Clinical translation remains limited by heterogeneity, and this problem should be treated as a design challenge rather than a reason to abandon the field. Assay differences, population characteristics, timing of measurement, tumor stage, sex, comorbid diabetes, medication use, and body composition all influence results. Two individuals with the same BMI may differ markedly in visceral fat, ectopic fat, muscle mass, NAFLD status, and inflammatory burden.[50] Therefore, future models should combine serum adipokines with imaging-based body composition, metabolic phenotyping, and tissue-level receptor data. Another challenge is that serum adipokines are systemic markers whereas many decisive interactions occur locally within the TME. High circulating leptin may indicate generalized adipose dysfunction, but local receptor density or paracrine signaling at the tumor-fat interface may better predict biological effect. This transition from systemic measurement to local interpretation is essential for aligning adipokine research with precision-oncology standards. Without multidimensional approaches, clinically promising adipokines may continue to appear inconsistent simply because they are being measured too narrowly. The so-called obesity paradox does not necessarily invalidate adipokine biology. Rather, it indicates that cancer outcomes are shaped by body composition, treatment type, immune contexture, metabolic reserve, and possibly treatment tolerance. Leptin, for example, may be pro-tumorigenic in some settings while correlating

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with better immunotherapy outcomes in others. The translational lesson is clear: Biomarker interpretation must be context specific and integrated with clinical phenotype. Because metabolic and inflammatory signals extend beyond classical adipokines, complementary markers such as homocysteine metabolism, MTHFR polymorphism, and oxidative DNA damage may help define high-risk or therapy-sensitive phenotypes in selected cancer contexts.[56–58]

THERAPEUTIC AND PRECISION-ONCOLOGY IMPLICATIONS

Several therapeutic strategies have translational promise. One is direct interference with pro-tumor adipokine signaling, such as leptin receptor antagonists, neutralizing antibodies, or small-molecule pathway inhibitors. Another is restoration of protective signaling through adiponectin receptor agonists, AMPK-activating agents, or metabolic interventions that improve insulin sensitivity.[8,28] A third is reprogramming CAAs to reduce inflammatory output and lipid transfer. These strategies reflect complementary ways of disrupting the metabolic support system of tumors. Combination treatment is likely to be the most realistic path forward. Adipokine-targeted interventions may sensitize tumors to endocrine therapy, chemotherapy, targeted agents, or immunotherapy rather than replacing existing modalities. Precision oncology could use adipokine profiles, receptor expression, pathway activation, and metabolic phenotype to identify patients most likely to benefit from such combinations.[7,59] This would be especially relevant in obesity-associated malignancies or tumors arising in adipose-rich microenvironments.

Lifestyle and metabolic interventions should also be viewed as translational therapies, not merely supportive care. Weight loss, physical activity, improvement of insulin sensitivity, and correction of NAFLD-related metabolic dysfunction can alter adipokine balance and may thereby modify tumor biology.[3,50] Integrating these measures into oncology care could strengthen outcomes, particularly for patients whose disease is strongly shaped by host metabolic state. A practical translational roadmap follows from this evidence. The first step is phenotyping: Patients should be characterized not only by tumor subtype but also by body composition, visceral adiposity, insulin resistance, NAFLD status, and baseline inflammatory-metabolic profile. The second step is biomarker layering, where circulating adipokines and selected receptor or pathway markers are interpreted alongside this phenotype. The third step is intervention matching: Some patients may be candidates for lifestyle-based metabolic correction, some for adipokine-informed combination therapy, and others for exploratory pathway-directed trials. The fourth step is longitudinal monitoring, because adipokine biology is dynamic and may change with treatment, weight loss, sarcopenia, or disease progression. This roadmap is especially relevant for health systems facing parallel increases in obesity, type 2 diabetes, and cancer burden. Multidisciplinary management linking oncology, endocrinology, nutrition, rehabilitation, and laboratory medicine could help operationalize adipokine-informed care. Several research priorities follow directly from this approach: Prospective studies should evaluate whether adipokine panels improve prediction of recurrence, treatment toxicity, or survival when added to standard clinicopathologic models; biomarker studies should distinguish total adipokine abundance from biologically active isoforms; tissue-based investigations should clarify receptor patterns in tumors adjacent to adipose depots; and interventional trials should test whether metabolic optimization changes adipokine profiles in ways that translate into measurable oncologic benefit. Future studies should prioritize standardized biomarker measurement, longitudinal designs, receptor-aware interpretation, and trials that test adipokine-informed intervention strategies. Such work could move the field from associative evidence toward metabolically informed personalized oncology. This broader biomarker-layering approach is particularly relevant for metabolically dysregulated patients, because oxidative stress, folate-cycle variation, and immune-metabolic imbalance may interact with adipokine signaling when tumors develop in inflammatory host environments.[56,57]

CONCLUSION

Adipokines form a mechanistic bridge between metabolic disorders and tumor progression. Their actions extend across angiogenesis, proliferation, apoptosis resistance, extracellular matrix remodeling, immune modulation, and therapeutic response. The central message is that adipokines are actionable components of host-tumor communication and should be incorporated into translational models of cancer biology. Tumor genomics remains indispensable, but metabolic phenotype, adipose tissue quality, and adipokine signaling add a second layer of clinically relevant information.

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REFERENCES

1. Fasshauer M, Bluher M. Adipokines in health and disease. Trends Pharmacol Sci 2015;36:461–70.
2. Park J, Euhus DM, Scherer PE. Paracrine and endocrine effects of adipose tissue on cancer development and progression. Endocr Rev 2011;32:550–70.
3. Tilg H, Moschen AR. Adipocytokines: Mediators linking adipose tissue, inflammation and immunity. Nat Rev Immunol 2006;6:772–83.
4. Ouchi N, Parker J, Lugus J, Walsh K. Adipokines in inflammation and metabolic disease. Nat Rev Immunol 2011;11:85–97.
5. Rondinone CM. Adipocyte-derived hormones, cytokines, and mediators. Endocrine 2006;29:81–90.
6. Kim JW, Kim JH, Lee YJ. The role of adipokines in tumor progression and its association with obesity. Biomedicines 2024;12:97.
7. Kounatidis D, Vallianou NG, Karampela I, Grivakou E, Dalamaga M. The intricate role of adipokines in cancer-related signaling and the tumor microenvironment: Insights for future research. Semin Cancer Biol 2025;113:130–50.
8. Dalamaga M, Diakopoulos KN, Mantzoros CS. The role of adiponectin in cancer: A review of current evidence. Endocr Rev 2012;33:547–94.
9. Boucher J, Masri B, Daviaud D, Gesta S, Guigne C, Mazzucotelli A, et al. Apelin, a newly identified adipokine up-regulated by insulin and obesity. Endocrinology 2005;146:1764–71.
10. Hida K, Wada J, Eguchi J, Zhang H, Baba M, Seida A, et al. Visceral adipose tissue-derived serine protease inhibitor: A unique insulin-sensitizing adipocytokine in obesity. Proc Natl Acad Sci U S A 2005;102:10610–5.
11. Polyzos SA, Kountouras J, Mantzoros CS. Irisin in metabolic diseases. Endocrine 2019;64:1–14.
12. Yang Q, Graham TE, Mody N, Preitner F, Peroni OD, Zabolotny JM, et al. Serum retinol binding protein 4 contributes to insulin resistance in obesity and type 2 diabetes. Nature 2005;436:356–62.
13. Nieman KM, Romero IL, Van Houten B, Lengyel E. Adipose tissue and adipocytes support tumorigenesis and metastasis. Biochim Biophys Acta Mol Cell Biol Lipids 2013;1831:1533–41.
14. Baumann H, Morella KK, White DW, Dembski M, Bailon PS, Kim H, et al. The full-length leptin receptor has signaling capabilities of interleukin 6-type cytokine receptors. Proc Natl Acad Sci U S A 1996;93:8374–8.
15. Friedman JM, Halaas JL. Leptin and the regulation of body weight in mammals. Nature 1998;395:763–70.
16. Tartaglia LA, Dembski M, Weng X, Deng N, Culpepper J, Devos R, et al. Identification and expression cloning of a leptin receptor, OB-R. Cell 1995;83:1263–71.
17. Gonzalez-Perez RR, Xu Y, Guo S, Watters A, Zhou W, Leibovich SJ. Leptin upregulates VEGF in breast cancer via activation of the PI3K/Akt and MAPK signaling pathways. Oncogene 2010;29:254–66.
18. Guo S, Gonzalez-Perez RR, Gomez-Hernandez A. Leptin promotes cell invasion and the epithelial-mesenchymal transition in human breast cancer cells. Cancer Res 2011;71:4650–61.
19. Saxena NK, Vertino PM, Anania FA, Sharma D. Leptin-induced growth stimulation of breast cancer cells involves recruitment of Akt and activation of phosphatidylinositol 3-kinase. Cancer Res 2007;67:2497–505.
20. Caruso A, Gelsomino L, Panza S, Accattatis FM, Naimo GD, Barone I, et al. Leptin: A heavyweight player in obesity-related cancers. Biomolecules 2023;13:1084.
21. Dupont J, Pollet-Villard X, Reverchon M, Mellouk N, Levy R. Adipokines in human reproduction. Horm Mol Biol Clin Investig 2015;24:11–24.
22. Guo S, Liu M, Wang G, Torroella-Kouri M, Gonzalez-Perez RR. Oncogenic role of leptin in breast cancer: Crosstalk between leptin, estrogen and growth factor signaling pathways. J Cell Mol Med 2012;16:2033–44.
23. La Cava A, Matarese G. The weight of leptin in immunity. Nat Rev Immunol 2004;4:371–9.
24. Moschos S, Chan JL, Mantzoros CS. Leptin and reproduction: A review. Fertil Steril 2002;77:433–44.
25. Jiang Y, Wei Y, Li Z, Dong J, Gong W. The biological function and research progress of the adipokine chemerin in tumorigenesis and development. J Cancer 2025;16:3696–702.
26. Rourke JL, Dranse HJ, Sinal CJ. Towards an integrative approach to understanding the role of chemerin in human health and disease. Obes Rev 2013;14:245–62.
27. Wang Z, Wang J, Chen Z. Chemerin in cancer: Mechanistic insights and clinical implications. Cancer Lett 2017;408:13–23.

Turk J Oncol 2026;41(3):240–247
doi: 10.5505/tjo.2026.4949

28. Kadowaki T, Yamauchi T, Kubota N, Hara K, Ueki K, Tobe K. Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. J Clin Invest 2006;116:1784–92.
29. Sena CM. Omentin: A key player in glucose homeostasis, atheroprotection, and anti-inflammatory potential for cardiovascular health in obesity and diabetes. Biomedicines 2024;12:284.
30. Watanabe K, Watanabe R, Konii H, Shirai R, Sato K, Matsuyama TA, et al. Counteractive effects of omentin-1 against atherogenesis. Cardiovasc Res 2016;110:118–28.
31. Yamawaki H. Vascular effects of novel adipocytokines: Focus on omentin. J Cardiovasc Pharmacol 2011;57:409–15.
32. Hu X, Li J, Fu M, Zhao X, Wang W. The JAK/STAT signaling pathway: From bench to clinic. Signal Transduct Target Ther 2021;6:402.
33. Moon HS, Dalamaga M, Kim SY, Polyzos SA, Hamnvik OP, Magkos F, et al. Leptin's role in lipodystrophic and nonlipodystrophic insulin-resistant states. Endocr Rev 2013;34:377–412.
34. Wang WJ, Lai HY, Zhang F, Shen WJ, Chu PY, Liang HY, et al. MCL1 participates in leptin-promoted mitochondrial fusion and contributes to drug resistance in gallbladder cancer. JCI Insight 2021;6:e135438.
35. Dirat B, Bochet L, Dabek M, Daviaud D, Dauvillier S, Majed B, et al. Cancer-associated adipocytes exhibit an activated phenotype and contribute to breast cancer invasion. Cancer Res 2011;71:2455–65.
36. Bochet L, Meulle A, Imbert S, Salles B, Valet P, Muller C. Cancer-associated adipocytes promotes breast tumor radioresistance. Biochem Biophys Res Commun 2013;441:102–6.
37. Iyengar P, Combs TP, Shah SJ, Gouon-Evans V, Pollard JW, Albanese C, et al. Adipocyte-derived collagen VI affects early mammary tumor progression *in vivo*, demonstrating a role for adipocytes in the tumor microenvironment. J Clin Invest 2003;111:1475–83.
38. Liu C, Li X. Role of leptin and adiponectin in immune response and inflammation. Int Immunopharmacol 2025;161:115082.
39. Grossmann ME, Ray A, Dogan S, Mizuno NK, Cleary MP, Litzenburger BC. Obesity and breast cancer: Status of leptin and adiponectin in pathological processes. Cancer Metastasis Rev 2010;29:641–53.
40. Ishikawa M, Kitayama J, Nagawa H. Enhanced expression of leptin and leptin receptor (OB-R) in human breast cancer. Clin Cancer Res 2004;10:4325–31.
41. Obi N, Jung AY, Maurer T, Huebner M, Johnson T, Behrens S, et al. Association of circulating leptin, adiponectin, and resistin concentrations with long-term breast cancer prognosis in a German patient cohort. Sci Rep 2021;11:23526.
42. Kim MH, Kim H. Role of leptin in the digestive system. Front Pharmacol 2021;12:660040.
43. Vahed IE, Moshgelgosha M, Kor A, Pasha MA. The role of adiponectin and leptin in colorectal cancer and adenoma: A systematic review and meta-analysis. BMC Cancer 2025;25:968.
44. Li R, Dong F, Zhang L, Ni X, Lin G. Role of adipocytokines in endometrial cancer progression. Front Pharmacol 2022;13:1090227.
45. Stępień S, Olczyk P, Gola J, Komosińska-Vassev K, Mielczarek-Palacz A. The role of selected adipocytokines in ovarian cancer and endometrial cancer. Cells 2023;12:1118.
46. Strong AL, Strong TA, Rhodes LV, Semon JA, Zhang X, Shi Z, et al. Obesity associated alterations in the biology of adipose stem cells mediate enhanced tumorigenesis by estrogen receptor positive breast cancer cells. Breast Cancer Res 2013;15:R102.
47. Tewari S, Vargas R, Reizes O. The impact of obesity and adipokines on breast and gynecologic malignancies. Ann N Y Acad Sci 2022;1518:131–50.
48. Cai Q, Yang J, Shen H, Xu W. Cancer-associated adipocytes in the ovarian cancer microenvironment. Am J Cancer Res 2024;14:3259–79.
49. Ke Y, Pan Y, Huang X, Bai X, Liu X, Zhang M, et al. Correlations between circulating adipokines and hepatocellular carcinoma: A systematic review and meta-analysis. Front Endocrinol 2025;16:1548924.
50. Polyzos SA, Kountouras J, Mantzoros CS. Adipokines in nonalcoholic fatty liver disease. Metabolism 2019;92:82–97.
51. Roa J, Tena-Sempere M. Connecting metabolism and reproduction: Roles of central energy sensors and key metabolic hormones. Mol Cell Endocrinol 2014;397:4–14.
52. Tena-Sempere M. Roles of ghrelin and adipokines in the control of reproduction: Metabolic cues and gonadal function. Endocrinology 2013;154:2139–48.
53. Akhundova JN, Amirova MF. Lymph nodes morphological changes and breast cancer subtypes in prediction of metastases. World Med Biol 2024;4:15–9.
54. Akhundova JN, Amirova MF, Gasimov NV, Sultanova MJ. Which lymph nodes should be exactly removed during breast cancer surgery to prevent metastasis? Health 2024;16:1013–26.
55. Ghadge AA, Khaire AA. Leptin as a predictive marker for metabolic syndrome. Cytokine 2019;121:154735.
56. Dadashova A, Amirova M, Mammadova F. Impact of methylenetetrahydrofolate reductase gene polymorphism on cancer and thalassemia incidence. Zaporozhye Med J 2025;27:320–4.
57. Dadashova A, Aliyeva G, Mamedov M, Melikova L. Homocysteine-driven oxidative stress in pediatric

lymphoma: A cross-sectional study of metabolic and genetic modulators. Leuk Lymphoma 2026;67:332–41.
58. Dadashova AR, Bagirova SA, Hasan-Zade NCh. 8-oxoguanosine as a marker of oxidative DNA damage in oncohematological diseases: Pathogenetic and prognostic significance (review of literature). Klin Lab Diagn 2026;71:395–9.
59. Ma X, Yang S, Li D. New insights into adipokines and the tumor microenvironment in breast cancer. Cancer Control 2025;32:10732748251347917.

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REVIEW

Communication Problems Between Oncology Patients' Families and Oncology Physicians: A Narrative Review

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SUMMARY

Cancer is a leading cause of premature death worldwide. A cancer diagnosis can cause psychological distress in patients, such as anxiety, fear of the future, and depression. Given the increasing life expectancy and home confinement periods for oncology patients, communication between family members and physicians is clearly critical. This study aims to gather information on the importance of communication between the families of oncology patients and oncology physicians, the causes of problems in this area, and their solutions. A multifactorial approach is appropriate when addressing communication problems between physicians and patient relatives. Communication improvement programs should be widespread, and physician participation in these programs should be increased. Physicians should be open to communication and patient in answering questions from patient relatives. They should remember that the most important expectation of patient relatives from physicians is trust and information. Family members should be educated to have realistic expectations regarding the process. They should be warned to be cautious about information of unknown origin obtained from the internet and media outlets. It is crucial for family members to share their doubts regarding the accuracy of this information with the treating physician, and for the physician to address these concerns with patience. In addition to factors related to the physician and the patient's family member, restructuring the healthcare system to better accommodate the needs of the patient's family member is also a key factor to consider in resolving communication issues between the physician and the patient's family member.

Keywords: Communication; oncology physician; patient, patient relatives.
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INTRODUCTION

According to global cancer data, it has been found that approximately one in five men or women is diagnosed with cancer, and one in nine men and one in twelve women die from cancer.[1] Cancer, along with cardiovascular causes, is one of the leading causes of premature death worldwide.[2] Cancer is a global health issue that causes mortality and morbidity and, as such, can have a profound impact on patients and their families. A cancer diagnosis can lead to psychological distress in patients, including anxiety, fear of the future, and depression.[3–5] The challenging process of chemotherapy and radiation therapy following a cancer diagnosis can also reduce patients' quality of life and exacerbate psychological problems associated with the disease. In addition, anxiety about the possibility of the disease recurring after treatment is completed is one of the

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causes of psychological disorders observed in oncology patients.[4] Open communication between the patient and the treating oncologist is crucial throughout all stages of the patient's journey following a cancer diagnosis; in fact, studies have shown that effective communication between the patient and the physician can have a positive impact on the patient's health outcomes.[6–8] Although it is clear how important patient-physician communication is in the disease management process, relatives of oncology patients may request that the treating physician not share the patient's oncological diagnosis and treatment plan with the patient.[9,10] This situation, which oncology physicians frequently encounter in Turkey, makes managing the process quite challenging from the physician's perspective and, at the same time, renders communication between the physician and the patient's family members far more critical. Unfortunately, there are very few studies in the literature that examine communication between patients' relatives and physicians, compared to those that investigate patient-physician communication. The aim of our study is to compile information regarding the importance of communication between the relatives of oncology patients and oncology physicians, as well as the causes of and solutions to the problems in this area.

COMMUNICATION PROBLEMS BETWEEN ONCOLOGY PATIENTS' FAMILIES AND ONCOLOGY PHYSICIANS

The Importance of Communication with The Physician and Its Contribution to the Treatment Process

It is well known how important a healthy and trustworthy patient-physician relationship is during the patient's treatment process.[11] It has been observed that studies examining communication between patients' relatives and physicians are significantly fewer in number compared to those examining the patient-physician relationship. A review aimed to identify the psychosocial needs of breast cancer patients and their relatives.[12] The study found that relatives wanted to be informed about the prognosis and the course of the disease; however, they were unable to obtain sufficient information on these topics. A study highlighted the importance of the patient-physician relationship and supported this claim by providing examples of cases in which family members could influence patient-physician communication in either a negative or positive direction.[13] The study concluded that establishing healthy communication among the physician, the patient, and the patient's family plays a vital role in selecting the appropriate treatment for the patient and ensuring its proper implementation. In the meta-synthesis conducted by Hoeck et al.,[14] it was emphasized that a cancer diagnosis not only affects the patient but also has a negative impact on the patient's family members, and that cancer is a family disease. It has been demonstrated that the psychosocial interactions established by patients and their families have a significant impact on the patient's acceptance of their diagnosis, their ability to adapt to the process, and their psychological well-being. A review has found that, as the duration of home care for cancer patients increases, the supportive roles played by their relatives are becoming increasingly important.[15] In a Finnish study conducted by Eriksson et al.,[16] researchers investigated what relatives of cancer patients thought about the actions of healthcare professionals in providing information and emotional support. A survey was conducted among the relatives of patients in 168 cancer wards across Finland. It was found that informing relatives about the patient's cancer diagnosis is critically important; however, unfortunately, fewer than one-third of the relatives received sufficient information about the patient's diagnosis. It has been noted that physicians should communicate more frequently with patients' relatives regarding the patient's cancer diagnosis. In a Norwegian study conducted by Ekstedt et al.,[17] it was stated that the relatives of cancer patients are the patient's most important source of social and emotional support. Furthermore, it has been noted that as diagnostic and treatment options improve and, consequently, cancer-related survival rates increase the responsibility of family members to support the patient in every way grows; and that when family members receive support, this has a positive impact on the patient's well being. In the study, a 24 member multidisciplinary team consisting of social workers, doctors, and nurses held a group discussion on the topics under consideration, after which the discussion was subjected to hermeneutic analysis. According to the analysis, it was concluded that the healthcare system needs to be revised to focus more on patients' families and provide them with greater support. A Brazilian study aimed to examine the perspectives of nurses working in a palliative cancer care unit regarding family involvement in the palliative cancer care process.[18] The results of this study, conducted through interviews with 17 nurses, emphasized the importance of adapting and integrating family members into the process, and it was determined that this would improve the patient's quality of life and comfort.

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The Causes of Communication Problems with Physicians

In a systematic review conducted by Ilıc et al.,[19] the information needs of relatives of pediatric cancer patients and the factors that facilitate or hinder the fulfillment of these needs were examined. The study revealed that patients' relatives sought different information throughout the entire process from diagnosis and treatment to follow up and rehabilitation and that patients' siblings tended to ask different questions than their parents. It was observed that patients' siblings were more likely to ask questions regarding the cause of the disease and their own risk of developing it. The study found that the most important factor determining whether patients' relatives receive adequate information is the competence of the healthcare professional. Among these competencies, the ability to communicate effectively with patients' relatives, encourage them to ask questions, provide accurate and clear explanations, and demonstrate patience, sensitivity, honesty, and empathy stood out as particularly significant factors. It has been found that when a healthcare professional explains the relevant situation in an understandable way without using medical jargon, it is important for the patient's family members to receive the information they need. Healthcare professionals should be aware that patients' families may request different types of information; they should encourage patients' families to ask questions freely and create a calm and peaceful environment in which this communication can take place. An Iranian study based on interviews with 14 patients and 11 physicians addressed issues in patient-physician communication.[20] The study categorized communication problems into five main categories: Misperceptions regarding the physician's identity, the physician's unprofessional attitude, the physician's sense of superiority, the patient's cultural differences, and the lack of patient-supportive units within the healthcare system. It has been noted that the media plays a role in creating a misperception of the physician's identity and in leading patients to develop irrational expectations. A doctor's failure to take the patient's question seriously, lack of empathy, and failure to use nonverbal communication are among the factors listed under the heading of unprofessional conduct. Failing to give the patient's complaints sufficient attention stands out as the most significant factor listed under the heading of the doctor viewing themselves as superior. It has been suggested that the patient's cultural differences play a role in leading them to develop unrealistic expectations regarding the diagnosis and treatment process. The large number of patients; the resulting inability to devote sufficient time to each patient; and the lack of an environment conducive to effective communication have been identified as factors contributing to problems in patient-physician communication. It has been established that communication problems within the healthcare system cannot be resolved simply by training healthcare professionals in communication; rather, it is necessary to educate patients' families on this matter as well and to structure healthcare systems in a way that supports them. Çetin et al.,[21] evaluated the results of a survey administered to the relatives of 168 cancer patients undergoing treatment in radiation oncology. Patients were asked questions under the headings of empathy, information, and trust. It has been observed that an increase in the time a physician spends with a patient and their family member has a significant impact on all three areas: Trust, information sharing, and empathy. Additionally, it has been found that an increase in the family member's educational level positively influences communication between the family member and the physician.

Today, most patients and their families use the internet and media outlets to learn about health issues.[22–24] A Korean study examining the impact of internet use on the patient-physician relationship from the perspective of physicians found that while internet use can increase patients' and their families' knowledge about health issues, it can also negatively affect patient-physician communication.[22] Patients and their families may form incorrect conclusions about the illness based on information they find online and may become unnecessarily anxious. Doctors have emphasized their concern that all of these factors could hinder effective doctor-patient communication. In a study conducted by Iverson et al.,[23] while concerns were raised that internet use could disrupt the patient-physician relationship, the authors emphasized its potential to improve patient adherence to treatment. A review examined the impact of internet use on the patient-physician relationship.[24] The study found that internet use can have both positive and negative effects on the patient-physician relationship. The information obtained can help patients adhere to their treatment regimen; however, inaccurate information from unverified sources can undermine a patient's trust in their physician and harm the patient-physician relationship. It has been noted that the quality of online information sources is crucial for fostering a positive patient-physician relationship. Programs broadcast on media outlets also have the potential to influence communi-

cation between physicians, patients, and their relatives.[20,25] In a study conducted by Dönmez et al.,[25] the communication challenges faced by physicians in their interactions with patients, patients' relatives, and other healthcare workers were evaluated through two TV series aired in Turkey that focus on fictional scenarios experienced by hospital staff. It is noteworthy that the physicians playing the lead roles in these series are also portrayed as characters with social communication difficulties who struggle to communicate effectively with patients and their relatives. It has been observed that in TV series, this communication gap is overcome thanks to the professional competence of the doctors. The portrayal in these series carries the risk of further exacerbating communication problems between doctors, patients, and their families. While professional success is crucial in a physician's medical career, it cannot be viewed as a substitute for addressing communication gaps. In today's world, where social media and media outlets significantly influence communication between physicians, patients, and their families, it is essential for physicians to be knowledgeable and sensitive in this regard in order to foster healthy communication.

Suggestions for Resolving Communication Problems

A study evaluated the effectiveness of communication enhancement programs administered to healthcare professionals working in oncology.[26] A total of 21 studies were reviewed, and in most of these studies, the programs were administered to experienced clinicians. Of the 21 studies evaluated, 19 found that these programs were effective in improving communication and building trust. In a randomized study conducted by Delvaux et al.,[27] the impact of workshop programs administered to physicians on their communication with patients and their families was investigated. In the study, physicians participated in six workshops, each lasting three hours. The analysis revealed that these training programs had a positive impact on communication between physicians and their patients and their families. In a randomized controlled trial conducted by Fujimori et al.,[28] the effectiveness of communication skills training programs for oncologists was evaluated. Of the 30 oncologists who agreed to participate in the study, 15 were enrolled in the program. The results of the study showed that communication enhancement programs have a positive impact on patient-oncologist communication in the areas of emotional support, information-sharing skills, and creating a supportive environment. Additionally, the self-confidence scores of physicians who participated in the program were found to be higher than those of physicians who did not participate. It has been recommended that oncologists take advantage of these programs to improve their communication skills. Today, various training programs including those involving patient participation or simulation-based approaches are being implemented in medical schools to strengthen communication between physicians and patients and their families.[29,30] When the studies are evaluated, it is noteworthy that many of the training programs are applied to experienced clinicians. It is clear that communication improvement programs benefit physicians regardless of their experience level. It should not be forgotten that communication is a skill that can be improved through training.

In today's world, where the survival rates and duration of home care for cancer patients are increasing, it is clear that communication between patients' relatives and physicians is of critical importance. In our country, the fact that many patients' relatives request that the cancer diagnosis not be shared with the patient is another factor that underscores this importance. Communication problems between a physician and a patient's family member may stem from the physician, but they can also be caused by the family member's level of education and unrealistic expectations, as well as media and online content, or the healthcare system itself. From this perspective, it is appropriate to view communication issues between physicians and patients' relatives as multifactorial. Communication training programs should be expanded, and physician participation in these programs should be increased. Physicians should be open to communication, patient-centered, patient-centered, and patient-centered, and should be patient when responding to questions from patients' families, recognizing that different family members may have different questions. In this era, when the internet is used as a source of information by a very large segment of society, healthcare providers should be prepared to address questions from patients' families regarding information they have obtained online. It is important to remember that the most important expectations patients' families have of their doctors are trust and knowledge. Patients' families should be educated to have realistic expectations regarding the treatment process. They should be warned to be cautious about information of unknown origin that they may come across on the internet and in the media. It is very important for family members to share their concerns about the accuracy of this information with the treating physician and for the physician to address these

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concerns with patience; knowing that they can ask the physician any questions that come to mind is a factor that strengthens communication. In addition to factors related to the physician and the patient's family member, structuring the healthcare system and hospital conditions to be more patient-family-centered is also a key consideration in addressing communication issues between physicians and patients' family members.

CONCLUSION

With the increasing survival rates and home confinement periods for oncology patients, it is clear that communication between patient relatives and physicians is crucial. Communication problems between physicians and patient relatives need to be addressed from a multifactorial perspective. In addition to training programs for physicians, awareness programs for patient relatives and improvements in the healthcare system can be effective in resolving these communication issues.

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REFERENCES

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2024;74(3):229–63.
2. Bray F, Laversanne M, Weiderpass E, Soerjomataram I. The ever-increasing importance of cancer as a leading cause of premature death worldwide. Cancer 2021;127(16):3029–30.
3. Fereidouni Z, Dehghan Abnavi S, Ghanbari Z, Gashmard R, Zarepour F, Khalili Samani N, et al. The impact of cancer on mental health and the importance of supportive services. Galen Med J 2024;13:e3327.
4. Maheu C, Singh M, Tock WL, Eyrenci A, Galica J, Hébert M, et al. Fear of cancer recurrence, health anxiety, worry, and uncertainty: A scoping review about their conceptualization and measurement within breast cancer survivorship research. Front Psychol 2021;12:644932.
5. Ye M, Du K, Zhou J, Zhou Q, Shou M, Hu B, et al. A meta-analysis of the efficacy of cognitive behavior therapy on quality of life and psychological health of breast cancer survivors and patients. Psychooncology 2018;27(7):1695–703.
6. Stewart MA. Effective physician-patient communication and health outcomes: A review. CMAJ 1995;152(9):1423–33.
7. Hagerty RG, Butow PN, Ellis PM, Dimitry S, Tattersall MH. Communicating prognosis in cancer care: A systematic review of the literature. Ann Oncol 2005;16(7):1005–53.
8. Griffin SJ, Kinmonth AL, Veltman MW, Gillard S, Grant J, Stewart M. Effect on health-related outcomes of interventions to alter the interaction between patients and practitioners: A systematic review of trials. Ann Fam Med 2004;2(6):595–608.
9. Oksüzoğlu B, Abali H, Bakar M, Yildirim N, Zengin N. Disclosure of cancer diagnosis to patients and their relatives in Turkey: Views of accompanying persons and influential factors in reaching those views. Tumori 2006;92(1):62–6.
10. Yalçin A, Silay K, Büyükçelik A, Işikdoğan A, Türk HM, Coşkun HŞ, et al. Opinions of the Turkish population on cancer and being informed of the diagnosis of cancer. Turk J Med Sci 2015;45(2):387–92.
11. Ifrim RA, Klugarová J, Măguriță D, Zazu M, Mazilu DC, Klugar M, et al. Communication, an important link between healthcare providers: A best practice implementation project. JBI Evid Implement 2022;20(S1):S41–8.
12. Schmid-Büchi S, Halfens RJ, Dassen T, van den Borne B. A review of psychosocial needs of breast-cancer patients and their relatives. J Clin Nurs 2008;17(21):2895–909.
13. Hahn SR, Feiner JS, Bellin EH. The doctor-patient-family relationship: A compensatory alliance. Ann Intern Med 1988;109(11):884–9.
14. Hoeck B, Ledderer L, Hansen HP. Dealing with cancer: A meta-synthesis of patients' and relatives' experiences of participating in psychosocial interventions. Eur J Cancer Care 2017;26(6):e12652.
15. Partanen E, Lemetti T, Haavisto E. Participation of relatives in the care of cancer patients in hospital: A scoping review. Eur J Cancer Care 2018;27(2):e12821.
16. Eriksson E, Lauri S. Informational and emotional support for cancer patients' relatives. Eur J Cancer Care 2000;9(1):8–15.

17. Ekstedt M, Stenberg U, Olsson M, Ruland CM. Health care professionals' perspectives of the experiences of family caregivers during in-patient cancer care. J Fam Nurs 2014;20(4):462–86.
18. da Silva MM, Lima LS. Participation of the family in hospital-based palliative cancer care: Perspective of nurses. Rev Gaucha Enferm 2014;35(4):14–9. Article in Portuguese.
19. Ilic A, Sievers Y, Roser K, Scheinemann K, Michel G. The information needs of relatives of childhood cancer patients and survivors: A systematic review of qualitative evidence. Patient Educ Couns 2023;114:107840.
20. Keshavarzi MH, Safaie S, Faghihi SAA, Zare S. Barriers of physician-patient relationships in professionalism: A qualitative study. J Adv Med Educ Prof 2022;10(3):199–206.
21. Çetin İA, Akay SU, Uçum MF, Nohut AR, Kaya MI, Kara I. Communication skills between the relatives and the doctors of patients with cancer treated in radiation oncology: A cross-sectional questionnaire study. Turk J Oncol 2021;36(1):1–7.
22. Kim J, Kim S. Physicians' perception of the effects of internet health information on the doctor-patient relationship. Inform Health Soc Care 2009;34(3):136–48.
23. Iverson SA, Howard KB, Penney BK. Impact of internet use on health-related behaviors and the patient-physician relationship: A survey-based study and review. J Am Osteopath Assoc 2008;108(12):699–711.
24. Luo A, Qin L, Yuan Y, Yang Z, Liu F, Huang P, et al. The effect of online health information seeking on physician-patient relationships: Systematic review. J Med Internet Res 2022;24(2):e23354.
25. Dönmez İH, Göze FE. Problematisation of the interpersonal communication in the hospital themed TV series: The example of Hekimoğlu and Mucize Doktor. Gümüşhane Univ Fac Commun Electron J 2020;8(2):829–62. [Article in Turkish]
26. Sheldon LK. Communication in oncology care: The effectiveness of skills training workshops for healthcare providers. Clin J Oncol Nurs 2005;9(3):305–12.
27. Delvaux N, Merckaert I, Marchal S, Libert Y, Conradt S, Boniver J, et al. Physicians' communication with a cancer patient and a relative: A randomized study assessing the efficacy of consolidation workshops. Cancer 2005;103(11):2397–411.
28. Fujimori M, Shirai Y, Asai M, Kubota K, Katsumata N, Uchitomi Y. Effect of communication skills training program for oncologists based on patient preferences for communication when receiving bad news: A randomized controlled trial. J Clin Oncol 2014;32(20):2166–72.
29. Gilligan C, Powell M, Lynagh MC, Ward BM, Lonsdale C, Harvey P, et al. Interventions for improving medical students' interpersonal communication in medical consultations. Cochrane Database Syst Rev 2021 Feb 9;2021(2):CD012418.
30. The Medical School Objectives Writing Group. Learning objectives for medical student education--guidelines for medical schools: Report I of the Medical School Objectives Project. Acad Med 1999;74(1):13–8.

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REVIEW

Tumor Treating Fields for Glioblastoma Multiforme: Effectiveness and Safety

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SUMMARY

Glioblastoma multifome (GBM) is the most common and most lethal primary brain tumor in adults. The standard treatment for GBM with good performance is maximal surgical resection followed by adjuvant chemoradiotherapy and adjuvant temozolomide therapy. In addition to this treatment, alternating electric fields or tumor treating fields (TTFields) are also recommended at category 1 level in the NCCN guidelines. In this review, the mechanism of action of alternating electric fields therapy in GBM, its efficacy in GBM and expected side effects will be discussed. TTFields is a treatment modality that acts on dividing cells by generating therapeutic levels of electric fields. Causing DNA damage and inhibiting DNA repair, activating apoptosis, autophagy and immunogenic death pathways, causing destruction of the cytoskeleton network, causing the formation of pores in the membrane and causing cellular destruction by disrupting cellular ion balance are the effects of alternating electric field therapy on cells. TTFields, which has also been tested in tumors such as lung cancer, pancreatic cancer and malignant mesothelioma, has proven to be a survival-enhancing treatment in primary and recurrent GBM patients. The risk of serious toxicity was found to be very low and the most common side effects were mild and moderate dermatologic toxicities. Having proven its efficacy and safety in GBM patients, TTFields is likely to benefit many more patients if cost issues can be overcome.

Keywords: GBM; toxicity; tumor treating fields.
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INTRODUCTION

Glioblastoma multifome (GBM) is the most common and most lethal primary brain tumor in adults. It has a highly aggressive course with a 5-year survival rate of 5–7%.[1,2] The disease, which is most commonly seen in the brain, can also be observed in the brain stem, cerebellum and spinal cord more rarely. The median age of onset is 64 years.[3] GBM can occur without a known precursor lesion (primary) or with the transformation of a low-grade tumor over time (secondary). Primary GBM is much more common than secondary GBM. Primary GBM, which has a worse prognosis, tends to occur at older ages than secondary GBM.[3–5] There are different genetic alterations that can be seen in GBM patients: Epidermal growth factor receptor (EGFR) overexpression, PTEN mutation and loss of chromosome 10 are especially typical for primary GBM, whereas isocitrate dehydrogenase-1 (IDH1) mutation, TP53 mutation and loss of 19q are seen especially in secondary GBM.[5,6] Especially the identification of IDH1 mutation status stands out as a reliable marker in the molecular differentiation of primary-secondary GBM. The standard treatment in GBM with

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good performance is adjuvant chemoradiotherapy and adjuvant temozolomide treatment after maximal surgical resection.[5,7,8] The agent of choice in chemoradiotherapy is temozolomide, as in adjuvant treatment. In addition to this treatment, alternating electric fields or tumor treating fields (TTFields) are also recommended at category 1 level in the NCCN guideline.[9] TTFields is a treatment modality that acts on dividing cells by generating electric fields at therapeutic levels.[10,11] Although alternating electric fields therapy is recommended at category 1 level by the NCCN for the treatment of GBM, many oncology physicians have questions about the efficacy of this treatment and may have difficulties in accessing this costly treatment. In this review, the mechanism of action of alternating electric fields therapy in GBM, its efficacy in GBM and expected side effects will be discussed.

TUMOR TREATING FIELDS THERAPY FOR GLIOBLASTOMA MULTIFORME: EFFECTIVENESS AND SAFETY

The effect of electric field on living cells was demonstrated for the first time in 1922 with a study showing the migration of bacteria in an electric field.[12] Alternating electric field can be used in medicine for nerve-muscle stimulation, acceleration of wound healing and treatment of various muscle and joint diseases.[13,14] Causing DNA damage and inhibiting DNA repair, activating apoptosis, autophagy and immunogenic death pathways, causing destruction of the cytoskeleton network, causing the formation of pores in the membrane and causing cellular destruction by disrupting cellular ion balance are the effects of alternating electric field treatment on cells; mitotic arrest and cell death occur in cells with the help of these mechanisms.[10,11] Giladi et al.[15] showed that TTFields inhibited the repair of radiotherapy-induced DNA damage in glioma cells. In the study conducted by Kirson et al.,[16] it was shown that alternating electric field application had an inhibitory effect on the growth of human and rat tumor cell groups. Analyses have shown that the cytotoxic effect of the electric field on dividing cells is maximum in the range of 150–200 kHz.[17] The treatment was found to have this effect on selectively dividing cells. These findings suggest that electric field therapy may also have a therapeutic role in malignant tumors. In GBM patients, TTFields is administered via a noninvasive and portable device that transmits alternating electric current to the brain via arrays placed on the scalp.

In the pilot study conducted by Kirson et al.[18] 200 kHz TTFields were applied to recurrent GBM patients. In a study of 10 patients, the median time to progression was 26 weeks and median overall survival was 62 weeks. These durations were reported to be approximately 2 times the reported durations for this patient group. The only instrument-related side effect was mild contact dermatitis and no serious side effects were observed. The study concluded that TTFields therapy is an effective and safe treatment modality for human cancers. In a pilot study by Salzberg et al.,[19] 100–200 kHz TTFields was applied to patients with locally advanced and/or metastatic solid tumors. The study included 6 patients who underwent multiple-line treatment. In 1 patient, partial response was observed, and in 3 patients tumor growth stopped during treatment. Disease progression was observed in 1 of the remaining 2 patients, and in the other patient with mesothelioma, regression was observed in the lesion near TTFields, while progression was observed in the lesion in the distant region. No serious treatment-related toxicity was detected. It was emphasized that TTFields is a safe and effective treatment modality that deserves further research. TTFields has also been tested in tumors such as lung cancer, pancreatic cancer and malignant mesothelioma and has been shown to be an effective and safe treatment modality.[20–23] In another study by Kirson et al.,[24] TTFields was administered in combination with temozolomide in newly diagnosed GBM patients. At the end of the study, progression-free survival was 155 weeks and overall survival was +39 months. TTFields treatment did not cause systemic toxicity and did not increase temozolomide-related side effects. It was concluded that TTFields added to chemotherapy increased chemotherapy sensitivity without increasing treatment-related toxicity. In a phase 3 study by Stupp et al.,[25] 200 kHz TTFields were compared with chemotherapy in patients with recurrent GBM. Although there was no significant difference between the groups in terms of overall survival, TTFields was found to be superior in terms of toxicity and quality of life. In a randomized study by Stupp et al.,[26,27] GBM patients were divided into temozolomide or temozolomide + TTFields arms after chemoradiotherapy. TTFields was applied at 200 kHz. As a result of the analysis, progression-free survival and overall survival were significantly higher in the TTFields group in both preliminary and final analysis. In a subgroup analysis of the EF-14 study, increased adherence to TTFields treatment was found to be an independent prognostic factor that increased survival in GBM.[28] In a secondary analysis

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of the EF-14 study, it was found that there was no decrease in quality of life in the group that added TTFields to temozolomide compared to the other group, but the side effect of skin itching was observed more in the group that received TTFields.[29] Fallah et al.[30] investigated the efficacy of bevacizumab + TTFields treatment in recurrent GBMs in a phase 2 study. In the study of 23 patients, median progression-free survival was 4.1 months and overall survival was 10.5 months. Grade 3–4 side effects thought to be treatment-related were observed in 2 patients. It was concluded that TTFields treatment is a safe and effective treatment. In a subgroup analysis study on Korean patients included in the EF-14 study, median overall survival and 1 and 2-year survival rates were significantly higher in the group that received TTFields treatment.[31] No serious toxicity was detected and skin irritation was observed in 30% of patients. The results demonstrate once again that TTFields is a safe and effective treatment.

Studies have shown that TTFields is a treatment approach with a low risk of serious toxicity. The most common treatment-related side effect is dermatologic toxicities.[26–33] Allergic dermatitis, irritant dermatitis, ulcers and mechanical lesions are side effects that can occur as dermatologic toxicity. Although topical corticosteroids may be sufficient in the management of dermatologic toxicities, topical-oral antibiotics may also be used in appropriate patients. Scalp cleansing, appropriate shaving and relocation of the instrument are recommended measures to reduce the risk of toxicity.[33]

TTFields is a very expensive treatment and its utilization rate can vary significantly from country to country due to the cost it brings to the healthcare system.[34] While the SEOM-GEINO and ASCO-SNO guidelines state that TTFields can be considered in newly diagnosed GBMs, it is recommended at category 1 level in the NCCN guideline.[9,35,36] Although there is no clear recommended treatment scheme for recurrent GBM, TTFields is one of the treatment options that can be preferred by current guidelines. TTFields, which has proven its efficacy and safety in GBM patients, is likely to benefit many more patients if cost issues are overcome.

CONCLUSION

TTFields is a treatment modality that has proven its efficacy and safety in newly diagnosed and recurrent GBM with its antimitotic and apoptotic effects.

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REFERENCES

1. Wirsching HG, Galanis E, Weller M. Glioblastoma. Handb Clin Neurol 2016;134:381–97.
2. Wu W, Klockow JL, Zhang M, Lafortune F, Chang E, Jin L, et al. Glioblastoma multiforme (GBM): An overview of current therapies and mechanisms of resistance. Pharmacol Res 2021;171:105780.
3. Davis ME. Glioblastoma: Overview of disease and treatment. Clin J Oncol Nurs 2016;20:2–8.
4. Ohgaki H, Kleihues P. The definition of primary and secondary glioblastoma. Clin Cancer Res 2013;19:764–72.
5. Wilson TA, Karajannis MA, Harter DH. Glioblastoma multiforme: State of the art and future therapeutics. Surg Neurol Int 2014;5:64.
6. Ohgaki H, Kleihues P. Genetic pathways to primary and secondary glioblastoma. Am J Pathol 2007;170:1445–53.
7. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, et al; European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups; National Cancer Institute of Canada Clinical Trials Group. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352:987–96.
8. Clarke J, Butowski N, Chang S. Recent advances in therapy for glioblastoma. Arch Neurol 2010;67:279–83.
9. Nabors LB, Portnow J, Baehring J, Bhatia A, Bloch O, Brem S, et al. NCCN guidelines central nervous system cancers. Version 2.2025-8.28.2025. Available at: https://virtualtrials.org/pdf2025/cns.pdf. Accessed Aug 5, 2026.
10. Shams S, Patel CB. Anti-cancer mechanisms of action of therapeutic alternating electric fields (tumor treating fields [TTFields]). J Mol Cell Biol 2022;14:mjac047

11. Mun EJ, Babiker HM, Weinberg U, Kirson ED, Von Hoff DD, et al. Tumor-treating fields: A fourth modality in cancer treatment. Clin Cancer Res 2018;24:266–75.
12. Northrop JH. The stability of bacterial suspensions: I. A convenient cell for microscopic cataphoresis experiments. J Gen Physiol 1922;4:629–33.
13. Sanseverino ER, Vannini A, Castellacci P. Therapeutic effects of pulsed magnetic fields on joint diseases. Panminerva Med 1992;34:187–96.
14. Palti Y. Stimulation of internal organs by means of externally applied electrodes. J Appl Physiol 1966;21:1619–23.
15. Giladi M, Munster M, Schneiderman RS, Voloshin T, Porat Y, Blat R, et al. Tumor treating fields (TTFields) delay DNA damage repair following radiation treatment of glioma cells. Radiat Oncol 2017;12:206.
16. Kirson ED, Gurvich Z, Schneiderman R, Dekel E, Itzhaki A, Wasserman Y, et al. Disruption of cancer cell replication by alternating electric fields. Cancer Res 2004;64:3288–95.
17. Swanson KD, Lok E, Wong ET. An overview of alternating electric fields therapy (NovoTTF therapy) for the treatment of malignant glioma. Curr Neurol Neurosci Rep 2016;16:8.
18. Kirson ED, Dbalý V, Tovarys F, Vymazal J, Soustiel JF, Itzhaki A, et al. Alternating electric fields arrest cell proliferation in animal tumor models and human brain tumors. Proc Natl Acad Sci U S A 2007;104:10152–7.
19. Salzberg M, Kirson E, Palti Y, Rochlitz C. A pilot study with very low-intensity, intermediate-frequency electric fields in patients with locally advanced and/or metastatic solid tumors. Onkologie 2008;31:362–5.
20. Pless M, Droege C, von Moos R, Salzberg M, Betticher D. A phase I/II trial of tumor treating fields (TTFields) therapy in combination with pemetrexed for advanced non-small cell lung cancer. Lung Cancer 2013;81:445–50.
21. Giladi M, Weinberg U, Schneiderman RS, Porat Y, Munster M, Voloshin T, et al. Alternating electric fields (tumor-treating fields therapy) can improve chemotherapy treatment efficacy in non-small cell lung cancer both *in vitro* and *in vivo*. Semin Oncol 2014;41:S35–41.
22. Babiker HM, Picozzi V, Chandana SR, Melichar B, Kasi A, Gang J, et al. Tumor treating fields with gemcitabine and nab-paclitaxel for locally advanced pancreatic adenocarcinoma: Randomized, open-label, pivotal phase III PANOVA-3 study. J Clin Oncol 2025;43:2350–60.
23. Ceresoli GL, Aerts JG, Dziadziuszko R, Ramlau R, Cedres S, van Meerbeeck JP, et al. Tumour treating fields in combination with pemetrexed and cisplatin or carboplatin as first-line treatment for unresectable malignant pleural mesothelioma (STELLAR): A multicentre, single-arm phase 2 trial. Lancet Oncol 2019;20:1702–9.
24. Kirson ED, Schneiderman RS, Dbalý V, Tovarys F, Vymazal J, Itzhaki A, et al. Chemotherapeutic treatment efficacy and sensitivity are increased by adjuvant alternating electric fields (TTFields). BMC Med Phys 2009;9:1.
25. Stupp R, Wong ET, Kanner AA, Steinberg D, Engelhard H, Heidecke V, et al. NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: A randomised phase III trial of a novel treatment modality. Eur J Cancer 2012;48:2192–202.
26. Stupp R, Taillibert S, Kanner AA, Kesari S, Steinberg DM, Toms SA, et al. Maintenance therapy with tumor-treating fields plus temozolomide vs temozolomide alone for glioblastoma: A randomized clinical trial. JAMA 2015;314:2535–43.
27. Stupp R, Taillibert S, Kanner A, Read W, Steinberg D, Lhermitte B, et al. Effect of tumor-treating fields plus maintenance temozolomide vs maintenance temozolomide alone on survival in patients with glioblastoma: A randomized clinical trial. JAMA 2017;318:2306–16.
28. Toms SA, Kim CY, Nicholas G, Ram Z. Increased compliance with tumor treating fields therapy is prognostic for improved survival in the treatment of glioblastoma: A subgroup analysis of the EF-14 phase III trial. J Neurooncol 2019;141:467–73.
29. Taphoorn MJB, Dirven L, Kanner AA, Lavy-Shahaf G, Weinberg U, Taillibert S, et al. Influence of treatment with tumor-treating fields on health-related quality of life of patients with newly diagnosed glioblastoma: A secondary analysis of a randomized clinical trial. JAMA Oncol 2018;4:495–504.
30. Fallah J, Chaudhary RT, Rogers LR, Wei W, Brewer CJ, Peereboom DM, et al. Clinical outcomes of the combination of bevacizumab and TTFields in patients with recurrent glioblastoma: Results of a phase II clinical trial. J Clin Oncol 2020;38:2537–7.
31. Kim CY, Paek SH, Nam DH, Chang JH, Hong YK, Kim JH, et al. Tumor treating fields plus temozolomide for newly diagnosed glioblastoma: A subgroup analysis of Korean patients in the EF-14 phase 3 trial. J Neurooncol 2020;146:399–406.
32. Bokstein F, Blumenthal D, Limon D, Harosh CB, Ram Z, Grossman R. Concurrent tumor treating fields (TTFields) and radiation therapy for newly diagnosed glioblastoma: A prospective safety and feasibility study. Front Oncol 2020;10:411.
33. Lacouture ME, Davis ME, Elzinga G, Butowski N, Tran D, Villano JL, et al. Characterization and management of dermatologic adverse events with the NovoTTF-100A system, a novel anti-mitotic electric field device for the treatment of recurrent glioblastoma. Semin Oncol 2014;41:1–14.

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doi: 10.5505/tjo.2026.4720

34. Khagi S, Kotecha R, Gatson NTN, Jeyapalan S, Abdullah HI, Avgeropoulos NG, et al. Recent advances in tumor treating fields (TTFields) therapy for glioblastoma. Oncologist 2025;30:oyae227.
35. Segura PP, Quintela NV, García MM, Berrón SDB, Sarrió RG, Gómez JG, et al. SEOM-GEINO clinical guidelines for high-grade gliomas of adulthood (2022). Clin Transl Oncol 2023;25:2634–46.
36. Mohile NA, Messersmith H, Gatson NT, Hottinger AF, Lassman A, Morton J, et al. Therapy for diffuse astrocytic and oligodendroglial tumors in adults: ASCO-SNO guideline. J Clin Oncol 2022;40:403–26.

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REVIEW

Biological Selection in Liver Transplant Oncology: Current Indications and Limits for Hepatocellular Carcinoma, Cholangiocarcinoma and Colorectal Liver Metastases

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SUMMARY

Liver transplant oncology has moved beyond the blunt expansion of size-based criteria. The central question now is whether tumour behaviour during treatment can identify the uncommon patient whose disease remains transplantable. This review examines hepatocellular carcinoma, perihilar and intrahepatic cholangiocarcinoma, and colorectal liver metastases, with emphasis on the evidence and policy shifts most relevant to current practice. In hepatocellular carcinoma, downstaging is best understood as a biological stress test rather than a technical bridge, and alpha-fetoprotein trend, radiological response, and time under observation now refine morphology-based thresholds. In perihilar cholangiocarcinoma, the lesson is different but equally clear: Transplantation succeeds when diagnosis, neoadjuvant therapy, staging, and operative discipline are delivered as a protocol. In intrahepatic cholangiocarcinoma, transplantation has become credible in very early cirrhotic tumours and in exceptionally selected liver-limited disease with durable treatment response, although the evidence remains centre-specific. Colorectal liver metastases mark the sharpest frontier, where comparative data have made transplantation intellectually defensible but not routine. Across these indications, the common denominator is biological selection, transparent reporting of the denominator, and careful stewardship of a scarce graft. The field will advance less by indiscriminately broadening criteria than by more precisely defining which cancers, in which biological states, genuinely justify transplantation.

Keywords: Cholangiocarcinoma; colorectal carcinoma; hepatocellular carcinoma; liver transplantation; metastasis; organ transplantation.

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INTRODUCTION

The old language of 'expanded criteria' no longer describes where transplant oncology actually stands. It suggests that progress comes mainly from relaxing limits that were once regarded as fixed. In reality, the field has advanced by becoming more selective, not less. Size and number still matter, but they now sit

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beside alpha-fetoprotein, radiological response, interval observation, molecular profile and the broader tempo of disease.[1–6]

It is useful to separate mature indications from emerging ones. Hepatocellular carcinoma remains the benchmark indication and the reference point against which all newer oncological indications are judged. Perihilar cholangiocarcinoma has moved into the category of an established but protocol-dependent indication. Intrahepatic cholangiocarcinoma and colorectal liver metastases sit further forward on the curve: Both are now clinically real, neither can be dismissed as experimental in the old sense, but both still demand tighter selection and more transparent reporting than hepatocellular carcinoma (Table 1).[5–23]

Policy has started to reflect this change. In the United States, the 2025 guidance that brought hepatocellular carcinoma, intrahepatic cholangiocarcinoma and colorectal liver metastases together under adult transplant-oncology review did more than tidy up administration. It acknowledged that transplant oncology can no longer be governed by hepatocellular carcinoma rules alone. The practical question is no longer whether liver transplantation can cure selected hepatic malignancy. It plainly can. The harder question is which tumours justify a scarce graft, under what evidential threshold, and with what obligation to report denominator data as carefully as headline survival.[5,6,10,16,17,23]

SEARCH STRATEGY AND SCOPE

This narrative review was designed to answer a practical transplant question: What now makes a liver cancer biologically transplantable? PubMed/MEDLINE, contemporary consensus statements, and current allocation guidance were reviewed, with an emphasis on prospective series, multicentre cohorts, policy documents, and higher-quality reviews that directly inform listing practice. The aim was not exhaustive historical coverage, but a clinically useful synthesis of the evidence most likely to change selection decisions today.

HEPATOCELLULAR CARCINOMA: THE BENCHMARK FOR BIOLOGICAL SELECTION

Hepatocellular carcinoma remains the model through which the field learned to think about curative transplantation in cirrhosis. Milan criteria remain foundational, not because they capture tumour biology perfectly, but because they created a reproducible oncological threshold.[1] UCSF criteria showed that modest expansion beyond Milan could preserve acceptable post-transplant outcomes,[2] while later models such as Metroticket 2.0 and the alpha-fetoprotein model made it clear that morphology alone was too blunt an instrument.[3,4] The 2024 ILTS-ILCA consensus captures the contemporary position well: Size and number still matter, but they should now be

Table 1 Current position of liver transplantation across the major transplant-oncology indications

Disease	Current position	Selection essentials	Representative clinical message
Hepatocellular carcinoma	Mature and established indication	Milan/T2 disease or protocol-based downstaging; alpha-fetoprotein trend; radiological response; interval observation; no extrahepatic spread or macrovascular invasion	Successful downstaging can yield 5-year post-transplant survival in the mid-70% range, but recurrence rises when tumour burden extends well beyond standard limits.
Perihilar cholangiocarcinoma	Established, but only in protocol-driven programmes	Unresectable hilar disease; approved neoadjuvant chemoradiation pathway; operative staging; no transperitoneal biopsy; strict exclusion of metastatic spread	In expert centres, 5-year survival of around 65%- 82% is achievable. Results deteriorate sharply when the protocol is diluted.
Intrahepatic cholangiocarcinoma	Emerging and deliberately constrained	Very early cirrhotic tumours or exceptionally selected liver-limited unresectable disease with durable response; prolonged stability on therapy; no extrahepatic disease	Very early disease can achieve 5-year survival around 65%-73%; selected locally advanced disease has shown promising 5-year survival, but evidence remains limited and centre-specific.
Colorectal liver metastases	Emerging indication in highly selected patients	Liver-only disease; resected primary; sustained response to first-line chemotherapy; favourable molecular profile; low carcinoembryonic antigen; adequate interval from diagnosis; no progression or extrahepatic spread	SECA-II and TransMet show survival that is difficult to match with non-transplant therapy alone, but recurrence is common, and selection must remain ruthless.

T2, OPTN stage T2 hepatocellular carcinoma.

interpreted alongside alpha-fetoprotein, treatment response and time under observation.[5]

In practice, downstaging is best understood as a biological stress test rather than a technical manoeuvre. Locoregional therapy does not simply shrink tumours; it reveals which tumours continue to behave in a transplantable manner when exposed to treatment and time. Long-term UCSF data, the prospective MERITS-LT experience and subsequent multicentre series all point in the same direction. When entry criteria, response thresholds, and observation intervals are met, successful downstaging can achieve post-transplant survival close to that observed in patients who began treatment according to conventional criteria.[24–28]

The same literature also clarifies the limits of expansion. Xu et al.[27] reported in a 2025 national multicentre prospective cohort that successful downstaging reached 82% within UNOS downstaging criteria but only 66% in all-comers beyond those limits. Once transplantation occurred, post-transplant survival was similar, but recurrence and intention-to-treat survival worsened as pre-treatment burden moved further beyond standard boundaries. Downstaging can therefore extend access responsibly, but only up to a point.[25–28]

Several practical conclusions follow. Alpha-fetoprotein trend is more informative than a single value. Waiting time is not merely an administrative burden; it is an opportunity to reveal aggressive biology. Choice of locoregional therapy matters, but the larger point is that response history matters more than the device used. Programmes that treat downstaging as a technical gateway rather than a biological filter risk selecting the very tumours most likely to recur.[24–28]

The next pressure point concerns systemic therapy, particularly immune checkpoint inhibition. Modern hepatocellular carcinoma management increasingly involves programmed death-1 or programmed death-ligand 1 blockade before referral, which means transplant teams now encounter candidates previously exposed to agents capable of provoking allograft rejection. The available evidence remains heterogeneous and retrospective. Some patients have proceeded safely to transplantation after washout, but acute rejection and graft loss are well documented, and no universally accepted safe interval can yet be defended.[5,29]

PERIHILAR CHOLANGIOCARCINOMA: SUCCESS DEPENDS ON THE WHOLE PROTOCOL

Perihilar cholangiocarcinoma is the clearest example of transplantation succeeding because an entire protocol works, not because a single operation does. Historic results were poor when patients were taken directly to transplantation without rigorous diagnosis, neoadjuvant therapy, operative staging or exclusion of occult spread. The Mayo experience changed that narrative. Heimbach et al.[7] first reported excellent survival in unresectable perihilar cholangiocarcinoma managed with neoadjuvant chemoradiation followed by transplantation. Rea et al.[8] then showed that protocol-based transplantation could outperform resection in selected patients, with 5-year survival around 82%. In the multicentre United States series reported by Murad et al.,[9] 5-year recurrence-free survival reached 65%, despite dropout during neoadjuvant treatment.

These data explain why perihilar cholangiocarcinoma should now be regarded as an established indication in expert centres. They also explain why casual enthusiasm is dangerous. Good results depend on the whole pathway: Accurate diagnosis, careful biliary management, disciplined neoadjuvant therapy, operative staging and strict exclusion of metastatic disease. Put bluntly, the protocol is part of the treatment.[7–12]

Current policy captures that reality. Under OPTN policy, standardised exception access for perihilar cholangiocarcinoma depends on management under an approved written protocol incorporating neoadjuvant therapy and operative staging. Diagnostic support may come from a malignant-appearing hilar stricture together with positive cytology or biopsy, a CA19-9 concentration above 100 U/mL in the absence of cholangitis, aneuploidy, or a hilar mass smaller than 3 cm. Transperitoneal biopsy should be avoided because of the recognised risk of tumour seeding.[10]

What matters in practice is not merely that transplantation works for perihilar cholangiocarcinoma, but why it works. The ideal candidate is not discovered on the day of transplantation; the ideal candidate is shaped by months of disease control, protocol adherence and repeated failure of the tumour to declare systemic behaviour. Centres that bypass one or more of these steps tend to recreate the disappointing results of the pre-protocol era.[7–12]

INTRAHEPATIC CHOLANGIOCARCINOMA: CREDIBLE, BUT STILL DELIBERATELY CONSTRAINED

If perihilar cholangiocarcinoma is now established, intrahepatic cholangiocarcinoma remains the field's most interesting unsettled indication. The older lit-

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erature was difficult to interpret because it mixed tiny incidental tumours found in explants with large, biologically aggressive cancers transplanted without a coherent selection strategy. That mixture obscured the fact that intrahepatic cholangiocarcinoma is not one transplant population.[11,12]

Two routes to transplantation have now emerged. The first concerns very early intrahepatic cholangiocarcinoma in cirrhotic patients, usually solitary lesions no larger than 2 cm. In this setting, Sapisochin et al.[30,31] showed that survival could be substantially better than the historical literature suggested, with 5-year survival ranging from 65% to 73%. Those studies mattered not because they proved that all intrahepatic cholangiocarcinoma should be transplanted, but because they showed how profoundly tumour burden and host context shape outcome.

The second route is more provocative and more clinically relevant: Liver-limited, unresectable intrahepatic cholangiocarcinoma with durable control on therapy. In the prospective series reported by Lunsford et al.[32] and subsequently updated by McMillan et al.,[33] selected patients treated with neoadjuvant systemic therapy and then transplanted achieved encouraging medium-term and 5-year survival. Early TESLA data now support the same principle, namely that biological stability over time is central and that transplantation only becomes credible once the tumour has already behaved well.[34]

Policy has moved, but carefully. Current OPTN guidance allows consideration of biopsy-proven, unresectable, solitary intrahepatic cholangiocarcinoma or mixed hepatocellular-cholangiocarcinoma no larger than 3 cm in cirrhotic patients, provided there has been locoregional or systemic treatment, at least 6 months of radiological stability, and no extrahepatic disease.[6] That conservatism is appropriate. It acknowledges that intrahepatic cholangiocarcinoma has earned a place in transplant oncology while also recognising that the evidence base remains small, centre-specific and vulnerable to selection bias.[33–35]

The practical conclusion is straightforward. Intrahepatic cholangiocarcinoma should no longer be dismissed as a blanket contraindication. Equally, it should not be normalised too quickly. At present, the strongest indications are very early cirrhotic intrahepatic cholangiocarcinoma and exceptionally selected liver-limited disease with durable response to therapy. Outside those circumstances, the burden of proof remains high.[30–35]

COLORECTAL LIVER METASTASES: THE METASTATIC FRONTIER

No development in contemporary liver transplantation has generated more interest, scepticism and ethical scrutiny than transplantation for colorectal liver metastases. For years the idea seemed closed: Recurrence appeared inevitable and the use of a deceased-donor graft for metastatic colorectal cancer difficult to justify. The Oslo group reopened the question by showing that inevitability of recurrence did not necessarily translate into futility of treatment.[13–15]

Hagness et al.[13] first reported 5-year overall survival of about 60% after transplantation for carefully selected non-resectable colorectal liver metastases. SECA-II tightened selection further and raised 5-year survival to 83%, with disease-free survival still modest but with a recurrence pattern that was often slow-growing, pulmonary and potentially amenable to local therapy.[15] This was an important conceptual shift. It suggested that the meaningful end point in colorectal liver metastases may not be recurrence-free survival alone, but prolonged overall survival with salvageable relapse.[13–16]

TransMet moved the field a step further by providing comparative evidence rather than single-centre optimism. In patients with permanently unresectable, liver-only colorectal liver metastases responding to chemotherapy, transplantation plus chemotherapy produced 5-year overall survival of 73%, compared with 9% for chemotherapy alone.[17] For transplant oncology, that trial matters enormously. It does not make colorectal liver metastases a routine indication, but it does make the old reflex dismissal intellectually untenable.[16,17]

The current challenge is ruthless selection. Contemporary United States guidance expects histologically proven colon or rectal adenocarcinoma, liver-only disease, a resected primary with negative margins, at least 12 months from diagnosis of liver metastases, response to first-line systemic therapy, no lesion larger than 10 cm before treatment, carcinoembryonic antigen no higher than 80 ng/mL, no extrahepatic disease on cross-sectional imaging and positron emission tomography, microsatellite-stable disease, and BRAF wild-type biology.[6] These are not bureaucratic hurdles. They are an attempt to translate outcome data into fair national practice.

The logic becomes clearer when the Oslo studies are read alongside the IHPBA consensus. High carcinoembryonic antigen levels, large lesions, progression on chemotherapy, a short interval from primary tumour treatment to transplantation, and unfavourable biology all indicate that the disease will outrun the graft.

Table 2 Practical selection variables and red flags in contemporary transplant-oncology assessment

Disease	Features that support listing	Red flags / likely contraindications	Practical message
Hepatocellular carcinoma	Falling or low alpha-fetoprotein; response to locoregional therapy; prolonged stability; tumour burden within accepted downstaging limits	Rising alpha-fetoprotein despite therapy; rapid progression; macrovascular invasion; extrahepatic spread; inability to downstage	Downstaging is a biological filter, not a technical gateway.
Perihilar cholangiocarcinoma	Clear protocol eligibility; completion of neoadjuvant pathway; negative staging for metastases; disease confined to the hilum	Transperitoneal biopsy; metastatic disease; protocol deviation; inability to complete staging or neoadjuvant treatment	In perihilar cholangiocarcinoma, the protocol itself is part of the treatment.
Intrahepatic cholangiocarcinoma	Solitary small tumour in cirrhosis or liver-limited disease with durable response; prolonged radiological stability; no nodal or extrahepatic disease	Multifocal or bulky disease; progression on systemic therapy; extrahepatic spread; biologically aggressive relapse pattern	Best considered within trial-like governance or prospective audit.
Colorectal liver metastases	Liver-only disease; resected primary; response to first-line chemotherapy; low carcinoembryonic antigen; favourable biology such as BRAF wild-type and microsatellite stability	Progression on chemotherapy; high carcinoembryonic antigen; large dominant lesion; short interval from primary treatment; extrahepatic disease; unfavourable molecular profile	The realistic goal is prolonged survival with manageable recurrence, not zero recurrence.

[15,16,18,19] Colorectal liver metastases are not an indication to be rescued by surgical bravado. It is an indication in which the operation makes sense only once the biology has already behaved well.

Living donor liver transplantation has become central in this space. Recent North American experience, including the Rochester programme, shows that highly structured living-donor pathways can provide transplantation to selected patients with colorectal liver metastases without directly competing for scarce deceased-donor grafts.[18,20,21] That does not abolish the ethical question; it changes its shape. The discussion is no longer only about justice between candidates on the waiting list, but also about the acceptability of exposing a healthy donor to risk for metastatic disease. Recurrence remains common and should be discussed plainly, but pulmonary relapse may be slow-growing and treatable. The realistic aim is not zero recurrence. It is a substantial prolongation of life, ideally with preserved function and access to salvage therapy.[15,16,18–22]

CROSS-CUTTING LESSONS

Across all four disease groups, the same principles recur. Morphology has become necessary but insufficient. Tumour size, number and distribution still matter, but they are now only the entry point. Alpha-fetoprotein trajectory in hepatocellular carcinoma, protocol completion in perihilar cholangiocarcinoma, radiological stability in intrahepatic cholangiocarcinoma, and molecular profile plus chemotherapy response in colorectal liver metastases all reflect the same deeper idea: Behaviour under treatment is a better proxy for transplantability than anatomy alone (Table 2).[4,5,10,16,19,21–23,34]

Pre-transplant therapy should therefore be understood as part of the selection process rather than as a delay before the 'real' treatment. Downstaging, chemoradiation and systemic therapy all function as biological filters. That is why time on treatment is valuable information rather than wasted time. The same is true after transplantation: Surveillance intensity, willingness to treat limited recurrence, and immunosuppression strategy all influence the real benefit obtained from a graft.[9,15–17,23,29,33]

Centre effect remains real. The best results in transplant oncology do not come from isolated technical excellence in the operating theatre. They come from integrated programmes in which radiology, interventional oncology, hepatology, medical oncology, pathology, anaesthesia, surgery and structured surveillance are aligned. This matters most for uncommon indications, where seemingly small lapses in staging or protocol discipline can completely alter outcome.[9,12,16,19,23,33]

Allocation ethics remain central. New indications should not be advanced simply because transplantation can technically be performed. They should advance when alternative therapies have been honestly compared, when denominator data are transparent, and when the magnitude of benefit is strong enough to justify the use of a scarce graft. That threshold will dif-

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fer among hepatocellular carcinoma, perihilar cholangiocarcinoma, intrahepatic cholangiocarcinoma, and colorectal liver metastases because the maturity of the evidence varies.[6,10,16,17,19,21–23]

FUTURE DIRECTIONS

The next phase of transplant oncology is unlikely to be driven by crude expansion of size-based criteria. The bigger gains will probably come from finer biological discrimination, including better integration of molecular profiling, radiomics, circulating biomarkers and response-adapted selection models.[5,11,12,21,23,34]

Just as important will be a better study design. Future reports need to describe referral volume, exclusions before listing, dropout during therapy, reasons for non-transplantation, recurrence pattern and salvage treatment, because post-transplant survival curves alone tell only part of the story.[16,17,19,21–23] The same priorities now recur across recent consensus statements, narrative reviews and programme reports: Dynamic biomarkers in hepatocellular carcinoma, protocol fidelity in cholangiocarcinoma, and denominator-based governance in colorectal liver metastases.[36–50]

CONCLUSIONS

Liver transplantation for cancer has moved well beyond a debate about whether malignancy should ever be an indication. The more useful question is which cancers, in which biological states, under which protocols, justify a graft. Hepatocellular carcinoma remains the benchmark and the most mature model of biological selection beyond anatomy. Perihilar cholangiocarcinoma is now an established indication when managed within a rigorous neoadjuvant and staging pathway. Intrahepatic cholangiocarcinoma has entered legitimate transplant practice, but only in carefully circumscribed settings. Colorectal liver metastases have crossed from bold experiment to serious clinical option in expert programmes, although they remain the most ethically and scientifically demanding indication.

The central lesson is shared across the whole field. Good transplant oncology does not come from stretching criteria until they break. It comes from using morphology, biology, treatment response and time to identify the uncommon patient whose cancer remains transplantable. The future of the field will depend less on how far criteria can be widened and more on how carefully candidates are chosen, and outcomes are audited.

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REFERENCES

1. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334:693–9.
2. Yao FY, Ferrell L, Bass NM, Watson JJ, Bacchetti P, Venook A, et al. Liver transplantation for hepatocellular carcinoma: Expansion of the tumour size limits does not adversely impact survival. Hepatology 2001;33:1394–403.
3. Mazzaferro V, Sposito C, Zhou J, Pinna AD, De Carlis L, Fan J, et al. Metroticket 2.0 model for analysis of competing risks of death after liver transplantation for hepatocellular carcinoma. Gastroenterology 2018;154:128–39.
4. Duvoux C, Roudot-Thoraval F, Decaens T, Pessione F, Badran H, Piardi T, et al. Liver transplantation for hepatocellular carcinoma: A model including alpha-fetoprotein improves the performance of Milan criteria. Gastroenterology 2012;143:986–94.e3.
5. Kodali S, Roberts JP, Pomfret EA, Heimbach JK, Shah SA, Clavien PA, et al. The 2024 ILTS-ILCA consensus recommendations for liver transplantation for hepatocellular carcinoma and intrahepatic cholangiocarcinoma. Liver Transpl 2025;31:815–31.
6. Organ Procurement and Transplantation Network. Liver updates to NLRB guidance and further alignment with LI-RADS. Notice of OPTN policy and guidance changes. Available at: https://www.hrsa.gov/sites/default/files/hrsa/optn/lic_updates-alignment-nlr-band-li-rads_pnjune2025.pdf. Accessed May 9,2026.
7. Heimbach JK, Haddock MG, Alberts SR, Gores GJ, Rosen CB. Liver transplantation for unresectable perihilar cholangiocarcinoma. Liver Transpl 2004;10:S65–8.

8. Rea DJ, Heimbach JK, Rosen CB, Haddock MG, Alberts SR, Kremers WK, et al. Liver transplantation with neoadjuvant chemoradiation is more effective than resection for hilar cholangiocarcinoma. Ann Surg 2005;242:451–8.
9. Murad SD, Kim WR, Harnois DM, Douglas DD, Burton J, Kulik LM, et al. Efficacy of neoadjuvant chemoradiation, followed by liver transplantation, for perihilar cholangiocarcinoma at 12 US centres. Gastroenterology 2012;143:88–98.e3.
10. Organ Procurement and Transplantation Network. OPTN policies effective as of 10 December 2025. Policy 9.5.A: Requirements for cholangiocarcinoma MELD or PELD score exceptions. Available at: https://www.hrsa.gov/sites/default/files/hrsa/optn/optn_policies.pdf 2025. Accessed May 9, 2026.
11. Goldaracena N, Gorgen A, Sapisochin G. Current status of liver transplantation for cholangiocarcinoma. Liver Transpl 2018;24:294–303.
12. Twohig P, Ghabril M, Hanje AJ, Lacerda M, Lee BP, Black SM, et al. Current status of liver transplantation for cholangiocarcinoma. World J Gastrointest Surg 2022;14:1–11.
13. Hagness M, Foss A, Line PD, Scholz T, Jørgensen PF, Fosby B, et al. Liver transplantation for nonresectable liver metastases from colorectal cancer. Ann Surg 2013;257:800–6.
14. Dueland S, Guren TK, Hagness M, Glimelius B, Line PD, Pfeiffer P, et al. Chemotherapy or liver transplantation for nonresectable liver metastases from colorectal cancer? Ann Surg 2015;261:956–60.
15. Dueland S, Syversveen T, Solheim JM, Solberg S, Grut H, Bjørnbeth BA, et al. Survival following liver transplantation for patients with nonresectable liver-only colorectal metastases. Ann Surg 2020;271:212–8.
16. Bonney GK, Chew CA, Lodge P, Hubbard J, Halazun KJ, Trunečka P, et al. Liver transplantation for non-resectable colorectal liver metastases: The International Hepato-Pancreato-Biliary Association consensus guidelines. Lancet Gastroenterol Hepatol 2021;6:933–46.
17. Adam R, de Gramont A, Figueras J, Kokudo N, Kunstlinger F, Masi A, et al. Liver transplantation plus chemotherapy versus chemotherapy alone in patients with permanently unresectable colorectal liver metastases (TransMet): Results from a multicentre, open-label, prospective, randomised controlled trial. Lancet 2024;404:1107–18.
18. Hernandez-Alejandro R, Ruffolo LI, Sasaki K, Kim MH, Aucejo FN, Cattral MS, et al. Recipient and donor outcomes after living-donor liver transplantation for unresectable colorectal liver metastases. JAMA Surg 2022;157:524–30.
19. Sasaki K, Ruffolo LI, Kim MH, Aucejo FN, Chun YS, Hernandez-Alejandro R, et al. The current state of liver transplantation for colorectal liver metastases in the United States: A call for standardized reporting. Ann Surg Oncol 2023;30:2769–77.
20. Byrne MM, Chávez-Villa M, Ruffolo LI, Loria A, Endo Y, Niewiemski A, et al. The Rochester protocol for living donor liver transplantation of unresectable colorectal liver metastasis: A 5-year report on selection, approval, and outcomes. Am J Transplant 2025;25:780–92.
21. Byrne MM, Bekki Y, Chavez-Villa M, Hernandez-Alejandro R. Recipient prioritization and graft choice in liver transplantation for colorectal liver metastasis. Curr Opin Organ Transplant 2025;30:179–85.
22. Varley R, Tarazi M, Davé M, Mobarak S, Stott MC, Baltatzis M, et al. Liver transplantation for non-resectable liver metastases from colorectal cancer: A systematic review and meta-analysis. World J Surg 2021;45:3404–13.
23. Elzein SM, Ruff SM, Line PD, Kodali S, Pomfret EA, Hernandez-Alejandro R, et al. Liver transplantation for cancer: Current challenges and future directions. J Clin Med 2025;14:5365.
24. Yao FY, Mehta N, Flemming J, Dodge J, Hameed B, Fix O, et al. Downstaging of hepatocellular cancer before liver transplant: Long-term outcome compared with tumours within Milan criteria. Hepatology 2015;61:1968–77.
25. Mehta N, Guy J, Frenette CT, Dodge JL, Osorio RW, Minteer WB, et al. Down-staging outcomes for hepatocellular carcinoma: Results from the MERITS-LT Consortium. Gastroenterology 2021;161:1502–12.
26. Tabrizian P, Florman SS, Schwartz ME, Roayaie S, Hemming A, Miller C, et al. Ten-year outcomes of liver transplantation for hepatocellular carcinoma after downstaging. JAMA Surg 2022;157:779–88.
27. Xu E, Tabrizian P, Gutierrez J, Hoteit M, Yao FY, Parikh ND, et al. Downstaging of hepatocellular carcinoma before liver transplantation: Results from a national multicentre prospective cohort study. Hepatology 2025;82:612–25.
28. Natarajan B, Tabrizian P, Hoteit M, Frenette C, Parikh N, Ghaziani T, et al. Downstaging hepatocellular carcinoma before liver transplantation: A multicentre analysis of the all-comers protocol in the MERITS-LT Consortium. Am J Transplant 2023;23:1771–80.
29. Rezaee-Zavareh MS, Ghabril M, Lai JC, Saab S, Mehta N, Kodali S. Immune checkpoint inhibitors and liver transplantation: A systematic review and meta-analysis. J Hepatol 2025;82:107–19.
30. Sapisochin G, de Lope CR, Gastaca M, de Urbina JO, Suarez MA, Santoyo J, et al. Very early intrahepatic cholangiocarcinoma in cirrhotic patients: Should liver transplantation be reconsidered? Am J Transplant 2014;14:660–7.

Turk J Oncol 2026;41(3):259–266
doi: 10.5505/tjo.2026.4995

31. Sapisochin G, Facciuto M, Rubbia-Brandt L, Marti J, Mehta N, Yao FY, et al. Liver transplantation for very early intrahepatic cholangiocarcinoma or combined hepatocellular-cholangiocarcinoma in cirrhotic patients: An international retrospective study. Hepatology 2016;64:1178–88.
32. Lunsford KE, Javle M, Heyne K, Shroff RT, Abdel-Wahab R, Gupta N, et al. Liver transplantation for locally advanced intrahepatic cholangiocarcinoma treated with neoadjuvant therapy: A prospective case-series. Lancet Gastroenterol Hepatol 2018;3:337–48.
33. McMillan RR, Javle M, Kodali S, Saharia A, Mobley C, Heyne K, et al. Survival following liver transplantation for locally advanced, unresectable intrahepatic cholangiocarcinoma. Am J Transplant 2022;22:823–32.
34. Yaqub S, Busund S, Smedman TM, Syversveen T, Khan A, Solheim JM, et al. Liver transplantation for locally advanced non-resectable intrahepatic cholangiocarcinoma treated with neoadjuvant therapy: Early results from the TESLA trial. Br J Surg 2025;112:znaf054.
35. Endo Y, Sasaki K, Munir MM, Woldesenbet S, Resende V, Rawicz-Pruszyński K, et al. Survival benefit relative to treatment modalities among patients with very early intrahepatic cholangiocarcinoma: An analysis of the National Cancer Database. J Gastrointest Surg 2023;27:2103–13.
36. Halazun KJ, Rosenblatt RE, Mehta N, Lai Q, Hajifathalian K, Gorgen A, et al. Dynamic alpha-fetoprotein response and outcomes after liver transplant for hepatocellular carcinoma. JAMA Surg 2021;156:559–67.
37. Cucchetti A, Serenari M, Sposito C, Di Sandro S, Mosconi C, Vicentin I, et al. Including mRECIST in the Metroticket 2.0 criteria improves prediction of hepatocellular carcinoma-related death after liver transplant. J Hepatol 2020;73:342–8.
38. Mehta N, Bhangui P, Yao FY, Mazzaferro V, Toso C, Akamatsu N, et al. Liver transplantation for hepatocellular carcinoma. Working Group Report from the ILTS Transplant Oncology Consensus Conference. Transplantation 2020;104:1136–42.
39. Berenguer M, Burra P, Ghobrial M, Hibi T, Metselaar H, Sapisochin G, et al. Posttransplant management of recipients undergoing liver transplantation for hepatocellular carcinoma. Working Group Report from the ILTS Transplant Oncology Consensus Conference. Transplantation 2020;104:1143–9.
40. Sapisochin G, Javle M, Lerut J, Ohtsuka M, Ghobrial M, Hibi T, et al. Liver transplantation for cholangiocarcinoma and mixed hepatocellular cholangiocarcinoma. Working Group Report from the ILTS Transplant Oncology Consensus Conference. Transplantation 2020;104:1125–30.
41. Sapisochin G, Fernandez de Sevilla E, Echeverri J, Charco R. Liver transplantation for cholangiocarcinoma: Current status and new insights. World J Hepatol 2015;7:2396–403.
42. Sapisochin G, Ivanics T, Heimbach J. Liver transplantation for intrahepatic cholangiocarcinoma: Ready for prime time? Hepatology 2022;75:455–72.
43. Sun D, Lv G, Dong J. Liver transplantation for intrahepatic cholangiocarcinoma: What are new insights and what should we follow? Front Oncol 2022;11:841694.
44. Achurra P, Fernandes E, O'Kane GM, Gurakar A, Sapisochin G. Liver transplantation for intrahepatic cholangiocarcinoma: Who, when and how. Curr Opin Organ Transplant 2024;29:161–71.
45. Maspero M, Sposito C, Bongini MA, Cascella T, Flores M, Maccauro M, et al. Liver transplantation for intrahepatic cholangiocarcinoma after chemotherapy and radioembolization: An intention-to-treat study. Transpl Int 2024;37:13641.
46. Line PD, Ruffolo LI, Toso C, Dueland S, Nadalin S, Hernandez-Alejandro R. Liver transplantation for colorectal liver metastases: What do we need to know? Int J Surg 2020;82S:87–92.
47. Maspero M, Sposito C, Virdis M, Citterio D, Pietrantonio F, Bhoori S, et al. Liver transplantation for hepatic metastases from colorectal cancer: Current knowledge and open issues. Cancers (Basel) 2023;15:345.
48. Tsilimigras DI, Schizas D, Bakopoulos A, Pawlik TM. Liver transplantation for colorectal liver metastasis: The exception, not the rule. Hepatobiliary Surg Nutr 2024;13:857–60.
49. Dawood ZS, Brown ZJ, Munir MM, Waqar U, Rawicz-Pruszynski K, Endo Y, et al. Outcomes of liver transplant for colorectal liver metastasis: A systematic review and meta-analysis. J Gastrointest Surg 2024;28:1943–50.
50. Dueland S, Grut H, Syversveen T, Hagness M, Line PD. Selection criteria related to long-term survival following liver transplantation for colorectal liver metastasis. Am J Transplant 2020;20:530–7.