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TURKISH JOURNAL of ONCOLOGY

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ORIGINAL ARTICLE

Overall Survival and Prognostic Factors in Sarcomas of the Forearm: A Multicenter Retrospective Cohort Study

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OBJECTIVE

To characterize overall survival (OS) and prognostic factors in sarcomas of the forearm and hand after exclusion of carcinoma and other non-sarcoma diagnoses and to explore OS according to index surgical strategy.

METHODS

This multicenter retrospective cohort included 59 unique patients with histologically defined forearm and hand sarcoma treated at four tertiary referral centers between November 2008 and March 2025. Overall survival was analyzed using Kaplan-Meier and log-rank methods. Univariable Cox models evaluated baseline prognostic factors. A parsimonious age-adjusted Cox model assessed baseline regional nodal and/or distant metastatic disease, with Firth-penalized Cox regression performed as a sparse-event sensitivity analysis.

RESULTS

Median age was 48 years; 53 patients had soft-tissue sarcoma and 6 had bone sarcoma. Eleven deaths occurred. Estimated OS was 92.7% at 1 year and 74.8% at both 3 and 5 years. Baseline regional nodal and/or distant metastatic disease was present in 6 of 53 classifiable patients (3 regional nodal only and 3 distant pulmonary metastases) and was associated with poorer OS (5-year OS, 44.4% vs 84.1%; log-rank p=0.024). In the conventional age-adjusted Cox model, the association persisted (HR, 6.85; 95% CI, 1.31-35.79; p=0.023), with a similar Firth-penalized estimate (HR, 7.36; 95% profile-likelihood CI, 1.41-34.58; p=0.020). OS did not differ by limb-sparing surgery versus amputation (p=0.904).

CONCLUSION

Baseline regional nodal and/or distant metastatic disease was associated with substantially poorer OS. Limb-sparing surgery was the predominant definitive strategy. Because outcome events were sparse and treatment selection was retrospective, adjusted and surgical comparisons should be interpreted cautiously.

Keywords: Limb Salvage; metastasis; prognosis; sarcoma; survival analysis; upper extremity.
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INTRODUCTION

Sarcomas of the forearm are rare and present distinctive oncologic and reconstructive challenges. Soft-tissue sarcomas constitute less than 1% of all malignancies, and the dense concentration of tendons, nerves, vessels, and small functional compartments in the forearm can make oncologically adequate resection technically demanding.[1–3] Even relatively limited resections may have substantial functional consequences.

Historically, amputation was frequently used to obtain local control in extremity sarcoma. Improvements in imaging, multidisciplinary treatment, oncologic surgery, radiotherapy (RT), systemic therapy, and reconstruction have enabled limb-sparing surgery to become the preferred approach when adequate margins can be obtained without compromising oncologic principles.[4–9] Nevertheless, amputation remains necessary in selected patients with extensive neurovascular involvement, uncontrolled local disease, or limited reconstructive options.

Prognosis in extremity sarcoma is influenced by tumor biology, metastatic disease, tumor burden, histologic subtype, and treatment selection.[10–13] The roles of chemotherapy and RT vary according to histology, stage, and clinical context. Published forearm-specific series remain small, and their case mix is heterogeneous.[3,7,9,14] Analyses that combine carcinoma with sarcoma may introduce diagnostic heterogeneity that obscures sarcoma-specific prognostic relationships.

The present study therefore evaluated a histologically restricted, patient-level cohort of forearm sarcomas. The primary objectives were to estimate OS, evaluate baseline prognostic factors using time-to-event methods, and explore OS according to index surgical strategy while explicitly addressing sparse events and treatment-selection bias.

MATERIALS AND METHODS

Study Design and Cohort

This retrospective multicenter cohort study was conducted in accordance with the ethical criteria of the 1964 Declaration of Helsinki and was approved by the Ankara Etlik City Hospital Ethics Committee with the Approval No: AEŞH-BADEK1-2025-661 and Approval Date: 24.12.2025.

This retrospective multicenter cohort included patients treated for a primary sarcoma of the forearm between November 2008 and March 2025 at four tertiary oncology referral centers (Ankara Etlik City Hospital, Ankara University Faculty of Medicine, Gazi University Faculty of Medicine, Abdurrahman Yurtaslan Oncology Training and Research Hospital). The source database contained 76 tumor records. For the sarcoma-specific analysis, patients with histologically confirmed carcinoma were excluded: 10 squamous cell carcinoma records, 2 adenocarcinoma records, and 1 clear cell carcinoma record (13 records in total). To maintain a histologically coherent sarcoma cohort, one malignant melanoma and two records coded only as peripheral nerve sheath tumor without a malignant/sarcoma specification were also excluded. Sixty eligible sarcoma records remained. One patient contributed two eligible sarcoma episodes; for patient-level analysis, the earliest index sarcoma was retained and the later record was removed, yielding 59 patients (Fig. 1).

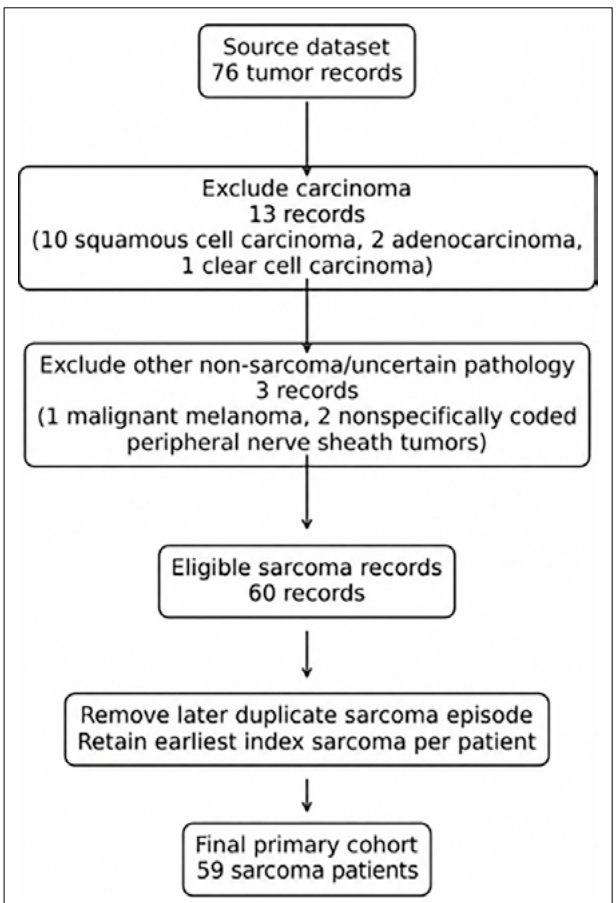

Fig. 1. Study cohort derivation. Carcinoma and other non-sarcoma and uncertain diagnoses were excluded, and one later duplicate eligible sarcoma episode was removed to obtain a unique-patient primary cohort.

Patients referred only for treatment of a metastatic lesion to the forearm or hand, patients previously treated at another institution before referral, and records with benign final pathology were also ineligible. No imputation was performed. Analyses used complete cases for each variable, and denominators are reported when data were missing or non-classifiable.

Variables, Data Definitions, and Outcomes

Demographic variables included age, sex, laterality, and anatomic site. Tumor variables included proximal/middle/distal location, depth, volar/dorsal compartment, histopathologic diagnosis, and maximum tumor dimension. The source field labelled "GRADE" contained stage-like entries rather than reproducible histologic grade; therefore, histologic grade could not be analyzed. Source-recorded stage was not included in primary inferential analyses because a uniform staging system and edition could not be verified retrospectively across the study period.

Baseline regional nodal and/or distant metastatic disease was defined solely from the metastatic-status field recorded at the index treatment assessment, before survival follow-up. "Present" included either documented regional nodal involvement or distant metastasis; the two components were also tabulated separately in the Results. "Absent" required an explicit record of no metastasis. Blank or indeterminate entries were treated as missing. This baseline definition was used for all Kaplan-Meier and Cox analyses and did not incorporate metastases that developed during follow-up.

Index definitive surgery was categorized as limb-sparing resection or amputation when classifiable (Fig. 2). The source database coded surgical margins as negative ("-"), close (<1 cm), or positive ("+"); these neutral categories were retained, and close/positive status was combined only for exploratory prognostic modeling. Because chemotherapy and RT could be delivered in neoadjuvant or adjuvant settings and treatment timing was heterogeneous, these variables were summarized as treatment exposures and were not modeled as baseline causal survival exposures.

Local recurrence was defined as documented recurrence at the primary operative site and was reported descriptively because recurrence timing was incomplete and death represents a competing event. OS time zero was the index operation. Survival time was measured to death from any cause or last documented follow-up using the recorded follow-up interval in months. Follow-up duration was summarized using the reverse Kaplan-Meier method.

Statistical Analysis

Continuous variables are presented as median and interquartile range (IQR), and categorical variables as number and percentage. Baseline characteristics according to index surgical strategy were explored using the Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables because subgroup sizes were small and uneven. No imputation was performed; analyses used complete cases for each variable and denominators are reported when data were missing or non-classifiable.

OS was estimated using the Kaplan-Meier method with 95% confidence intervals (CIs), and survival distributions were compared using the log-rank test. Univariable Cox proportional-hazards models evaluated age, maximum tumor dimension, sex, anatomic site, depth, tumor size >5 cm, baseline regional nodal and/or distant metastatic disease, close/positive margin status, and index surgical strategy. To limit overfitting, the adjusted analysis was restricted to a prespecified Cox model containing age and baseline regional nodal and/or distant metastatic disease. Because only 8 deaths occurred among the 53 complete cases entering the adjusted model, a Firth-penalized Cox regression using the Jeffreys invariant-prior penalty was performed as a sparse-event sensitivity analysis; 95% CIs and p values for the penalized model were obtained from the penalized profile likelihood. Schoenfeld-residual rank-correlation checks were used to assess the proportional-hazards assumption for the conventional Cox model. Sensitivity analyses were performed in the forearm-only subgroup and the soft-tissue-sarcoma-only subgroup. Two-sided p values <0.05 were considered statistically significant. Analyses were performed using the free and open-source software R (version 4.4.1, https://cran.r-project.org), SPSS for Windows Version 23.0 statistical package (Chicago, IL).

RESULTS

Fifty-three patients (89.8%) had soft-tissue sarcoma and 6 (10.2%) had bone sarcoma. The most frequent source-recorded diagnoses were pleomorphic sarcoma (n=10), myxofibrosarcoma (n=7), liposarcoma (n=6), synovial sarcoma (n=6, including 1 biphasic), rhabdomyosarcoma (n=4, including 2 alveolar), and leiomyosarcoma (n=3, including 1 pleomorphic); the complete histologic distribution is provided in Table 1. Median age was 48 years (IQR, 38-61 years), 37 patients (62.7%) were male, and 54 tumors (91.5%) were

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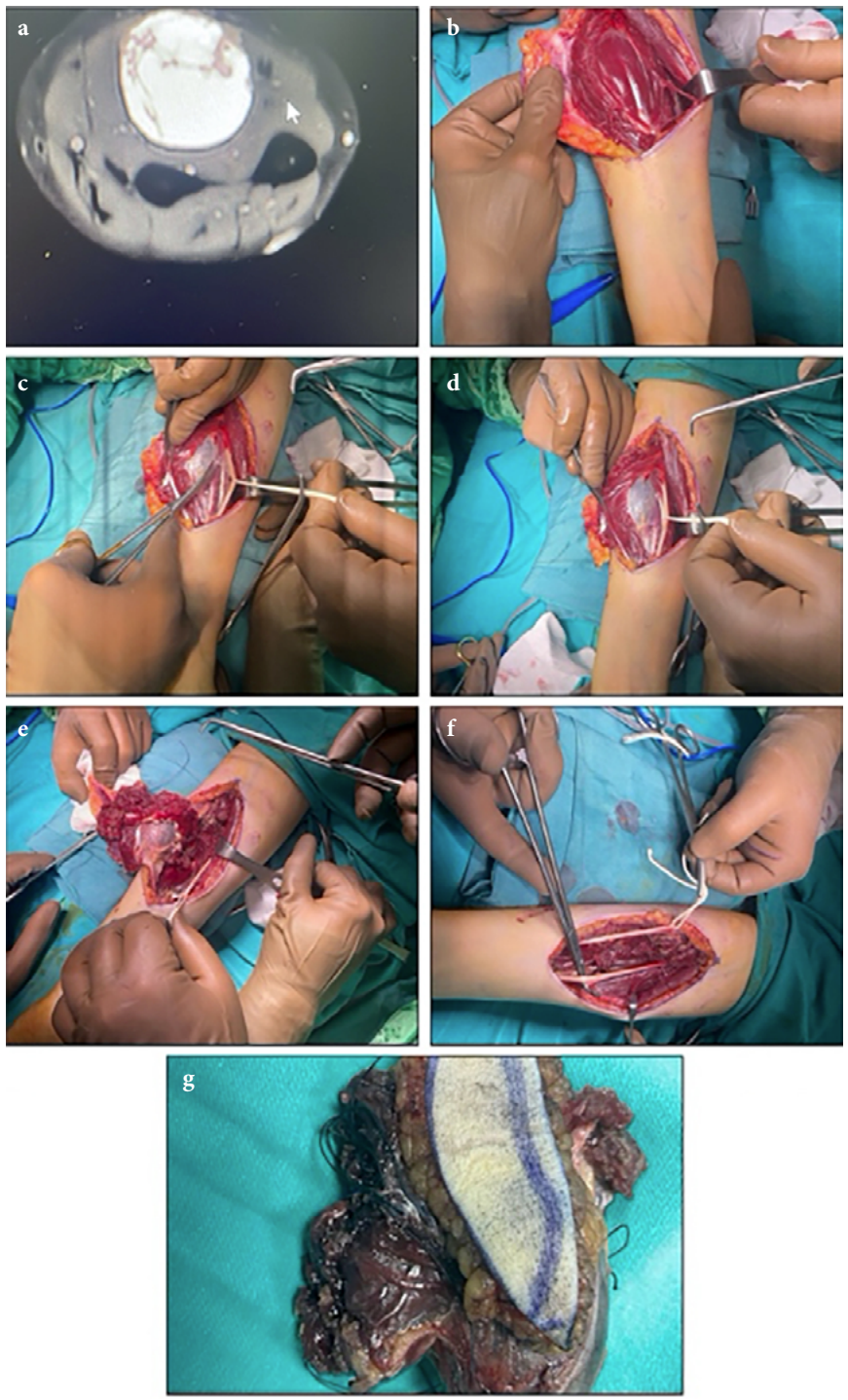

Fig. 2. Representative preoperative imaging and intraoperative sequence of limb-sparing resection of a forearm sarcoma. (a) Preoperative axial magnetic resonance image demonstrating the forearm lesion and its relationship to the surrounding osseous and soft-tissue structures. (b) Initial surgical exposure of the involved compartment. (c) Progressive circumferential dissection with identification and protection of adjacent neurovascular structures. (d) Mobilization of the tumor while preserving uninvolved critical structures. (e) En bloc tumor resection during limb-sparing surgery. (f) Final operative field after tumor removal, demonstrating preservation of the major neurovascular structures and the resulting resection bed. (g) Gross appearance of the resected specimen.

Table 1. Baseline clinical, tumor, treatment, and histopathologic characteristics

Characteristic	Value	
	n	%
Age (years)	48.0 (38.0–61.0)	
Male sex	37	62.7
Deep tumor	40	67.8
Maximum tumor dimension (cm)	12.0 (7.0–17.8)	
Tumor >5 cm	49/58	84.5
Soft-tissue sarcoma	53	89.8
Bone sarcoma	6	10.2
Baseline regional nodal and/or distant metastatic disease	6/53	11.3
Limb-sparing definitive surgery	45/53	84.9
Amputation	8/53	15.1
Chemotherapy exposure	28	47.5
Radiotherapy exposure	26	44.1
Local recurrence	11	18.6
Deaths	11	18.6
Median follow-up (months)	36 (reverse Kaplan–Meier)	
Histopathologic subtype		
Pleomorphic/undifferentiated pleomorphic sarcoma	10	18.6
Myxofibrosarcoma	7	11.9
Liposarcoma	6	10.2
Synovial sarcoma	6	10.2
Malignant peripheral nerve sheath tumor	3	5.1
Clear cell sarcoma	3	5.1
Angiosarcoma	3	5.1
Ewing sarcoma	3	5.1
Osteosarcoma	3	5.1
Leiomyosarcoma	3	5.1
Epithelioid sarcoma	2	3.4
Alveolar rhabdomyosarcoma	2	3.4
Dermatofibrosarcoma protuberans	2	3.4
Rhabdomyosarcoma, other/not otherwise specified	2	3.4
Fibrosarcoma	2	3.4
Malignant mesenchymal tumor, not otherwise specified	1	1.7

Values are n (%) or median (interquartile range), unless otherwise indicated. Denominators vary because complete-case analysis was used for missing or non-classifiable data. Histopathologic labels were standardized from the source pathology terminology for presentation.

located in the forearm. Forty tumors (67.8%) were deep. Median maximum tumor dimension was 12.0 cm (IQR, 7.0–17.8 cm), and 49 of 58 tumors with available measurements (84.5%) exceeded 5 cm.

Baseline regional nodal and/or distant metastatic status was classifiable in 53 patients. Three patients had regional nodal disease only and 3 had distant metastases (all pulmonary); no patient had both regional nodal and distant metastatic disease at baseline. Thus, 6 of 53 classifiable patients (11.3%) met the composite baseline advanced-disease definition. Definitive surgical strategy was classifiable in 53 patients: 45 (84.9%) underwent limb-sparing surgery and 8 (15.1%) underwent amputation. Chemotherapy was recorded in 28 patients (47.5%) and RT in 26 (44.1%). Local recurrence was documented in 11 patients (18.6%). Eleven deaths (18.6%) occurred during follow-up. Median follow-up by reverse Kaplan-Meier analysis was 36 months (Table 1).

In univariable Cox models, baseline regional nodal and/or distant metastatic disease was associated with

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Table 2. Univariable Cox proportional-hazards analyses for overall survival

Variable	n	Deaths	HR	95% CI	p
Age, per year	59	11	1.02	0.98–1.06	0.268
Maximum tumor dimension, per cm	58	11	1.00	0.91–1.10	0.983
Male sex	59	11	1.16	0.34–3.97	0.813
Baseline regional nodal and/or distant metastatic disease	53	8	4.54	1.08–19.06	0.039
Amputation vs limb-sparing surgery	53	11	1.10	0.24–5.09	0.904

HR: Hazard ratio; CI: Confidence interval. Hazard ratios for continuous variables are expressed per one-unit increase. These analyses account for follow-up duration and censoring and replace cross-sectional alive/deceased comparisons.

Table 3. Selected baseline and treatment characteristics according to index surgical strategy

Characteristic	Limb-sparing surgery (n=45)		Amputation (n=8)		p
	n	%	n	%	
Age (years)	51.0 (42.0–63.0)		47.0 (37.0–56.0)		0.510
Maximum tumor dimension (cm)	11.0 (7.0–15.0)		18.0 (14.0–21.8)		0.052
Deep tumor	29/45	64.4	8/8	100	0.088
Baseline regional nodal and/or distant metastatic disease	6/40	15.0	0/7	0	0.571
Close/positive margin	13/44	29.5	0/8	0	0.177
Chemotherapy exposure	17/45	37.8	7/8	87.5	0.017
Radiotherapy exposure	18/45	40.0	4/8	50.0	0.705

Values are median (interquartile range) or n/N (%). Continuous variables were compared using the Mann–Whitney U test and categorical variables using Fisher's exact test. Missing denominators reflect non-classifiable data. The imbalances support substantial confounding by indication in the surgical survival comparison.

poorer OS (HR, 4.54; 95% CI, 1.08–19.06; p=0.039). Age, maximum tumor dimension, sex, tumor depth, tumor size >5 cm, close/positive margin status, and amputation versus limb-sparing surgery were not significantly associated with OS (Table 2).

No deaths occurred among the 6 patients with bone sarcoma, so a stable Cox HR comparing bone with soft-tissue sarcoma was not estimable. Histologic grade was not analyzed because it was not reliably recorded, and source-recorded stage was excluded from primary inference because a uniform staging system and edition could not be verified across the retrospective study period.

Among 53 patients with classifiable definitive surgery, 45 underwent limb-sparing resection and 8 underwent amputation. Tumors in the amputation group were larger (median 18.0 vs 11.0 cm; p=0.052) and all were deep (100% vs 64.4%; p=0.088). Chemotherapy exposure was substantially more frequent after selection for amputation (87.5% vs 37.8%; p=0.017), whereas RT exposure was similar (50.0% vs 40.0%; p=0.705). These imbalances demonstrate clinically important confounding by indication and preclude causal interpretation of the surgical survival comparison (Table 3).

For the entire cohort, estimated OS was 92.7% (95% CI, 81.7–97.2%) at 1 year and 74.8% (95% CI, 58.2–85.6%) at both 3 and 5 years. Median OS was not reached (Fig. 3a; Table 4).

Baseline regional nodal and/or distant metastatic disease was associated with poorer OS. Among 47 patients with explicitly absent baseline regional nodal or distant metastatic disease, 5 deaths occurred and estimated 5-year OS was 84.1% (95% CI, 65.2–93.2%); median OS was not reached. Among 6 patients with baseline regional nodal and/or distant metastatic disease, 3 deaths occurred, estimated 5-year OS was 44.4% (95% CI, 6.6–78.5%), and median OS was 26 months (p=0.024) (Fig. 3b; Table 4).

In the conventional age-adjusted Cox model restricted to 53 patients with classifiable baseline regional nodal and/or distant metastatic status (8 deaths), the composite advanced-disease variable remained associated with mortality (HR, 6.85; 95% CI, 1.31–35.79; p=0.023), whereas age was not significant (HR per year, 0.979; 95% CI, 0.939–1.020; p=0.305). Given the sparse number of events, Firth-penalized Cox regression was performed as a sensitivity analysis and produced a similar estimate for baseline regional nodal and/or distant metastatic disease (HR, 7.36; 95% profile-likelihood

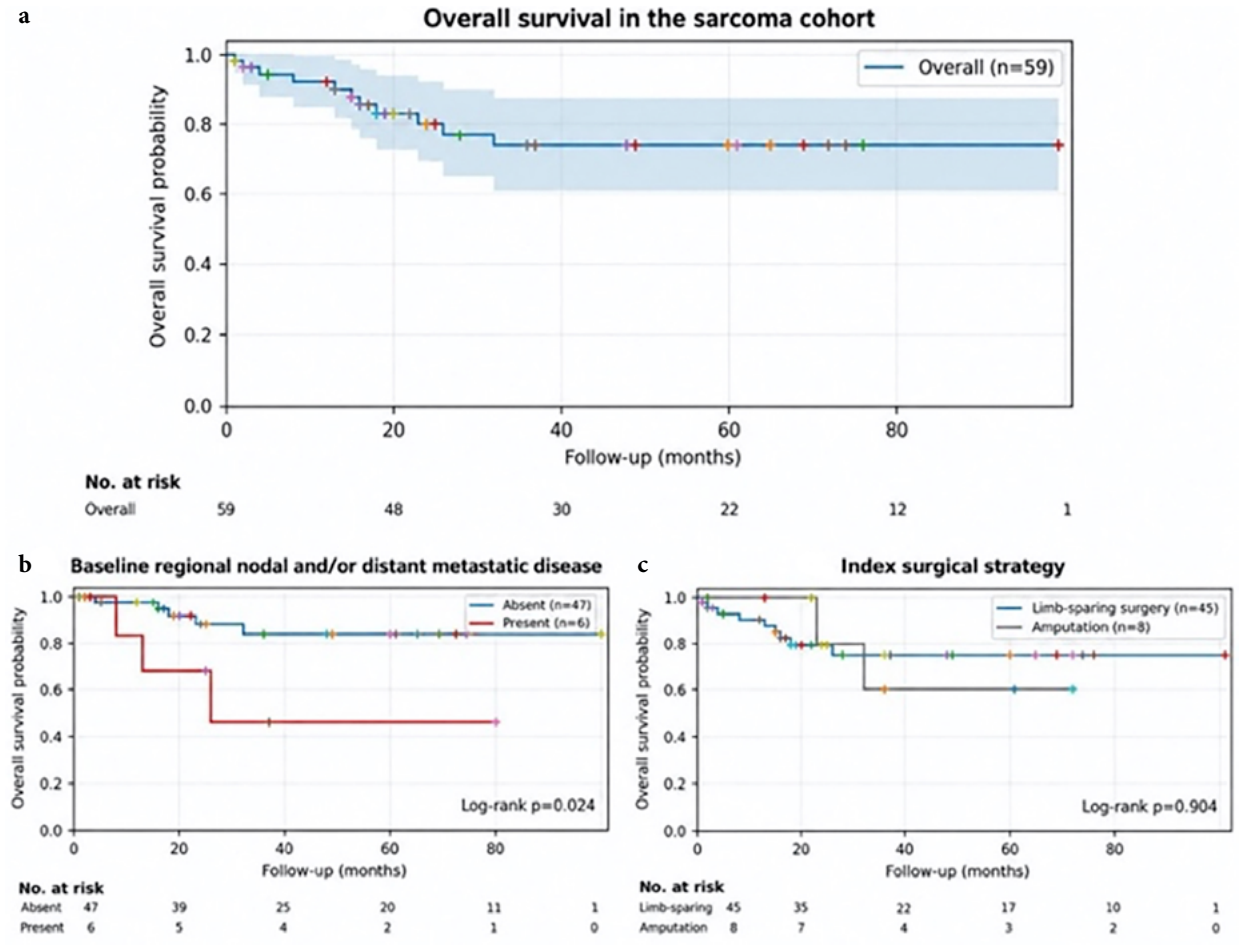

Fig. 3. Kaplan-Meier analyses of overall survival in the sarcoma cohort. (a) Overall survival for the entire cohort (n=59); the shaded area represents the 95% confidence interval, and tick marks indicate censored observations. (b) Overall survival according to baseline regional nodal and/or distant metastatic disease (absent, n=47; present, n=6). Patients with baseline regional nodal and/or distant metastatic disease had significantly poorer overall survival (log-rank p=0.024). (c) Overall survival according to index surgical strategy (limb-sparing surgery, n=45; amputation, n=8). No statistically significant difference in overall survival was observed between the surgical groups (log-rank p=0.904). Numbers at risk are shown below each panel.

Table 4. Kaplan–Meier overall survival estimates

Group	n	Deaths	1-year OS, % (95% CI)	3-year OS, % (95% CI)	5-year OS, % (95% CI)	Median OS, months	Log-rank p
Overall cohort	59	11	92.7 (81.7–97.2)	74.8 (58.2–85.6)	74.8 (58.2–85.6)	Not reached	–
Baseline regional nodal and/or distant metastatic disease absent	47	5	97.6 (83.9–99.7)	84.1 (65.2–93.2)	84.1 (65.2–93.2)	Not reached	
Baseline regional nodal and/or distant metastatic disease present	6	3	83.3 (27.3–97.5)	44.4 (6.6–78.5)	44.4 (6.6–78.5)	26	0.024
Limb-sparing surgery	45	9	90.3 (76.1–96.3)	75.0 (56.8–86.4)	75.0 (56.8–86.4)	Not reached	
Amputation	8	2	100.0	60.0 (12.6–88.2)	60.0 (12.6–88.2)	Not reached	0.904

OS: Overall survival; CI: Confidence interval. Log-rank p values refer to the corresponding two-group comparison; blank cells indicate the companion group in the same comparison.

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Table 5. Parsimonious Cox proportional-hazards model and penalized sensitivity analysis for overall survival

Model	Variable	HR	95% CI	p
Conventional Cox	Age, per year	0.979	0.939–1.020	0.305
Conventional Cox	Baseline regional nodal and/or distant metastatic disease	6.85	1.31–35.79	0.023
Firth-penalized Cox sensitivity analysis	Baseline regional nodal and/or distant metastatic disease	7.36	1.41–34.58	0.020

The conventional model included 53 patients with classifiable baseline disease status and 8 deaths and was adjusted for age. Residual-based proportional-hazards checks were non-significant for age (p=0.651) and baseline regional nodal and/or distant metastatic disease (p=0.693). Because of sparse events, a Firth-penalized Cox model was used as a sensitivity analysis. The penalized estimate is reported for the principal exposure. HR: Hazard ratio; CI: Confidence interval.

CI, 1.41–34.58; p=0.020); age remained non-significant (HR per year, 0.978; 95% profile-likelihood CI, 0.941–1.020; p=0.280). Schoenfeld-residual rank-correlation checks did not indicate violation of the proportional-hazards assumption for age (p=0.651) or the composite advanced-disease variable (p=0.693) (Table 5).

OS did not differ significantly between limb-sparing surgery and amputation (log-rank p=0.904) (Fig. 3c). Five-year OS was estimated at 75.0% (95% CI, 56.8–86.4%) after limb-sparing surgery and 60.0% (95% CI, 12.6–88.2%) after amputation. Given the strong baseline treatment-selection imbalances, this exploratory comparison should not be interpreted as evidence of therapeutic equivalence.

The association between baseline regional nodal and/or distant metastatic disease and poorer OS remained present in the forearm-only subgroup (n=54; log-rank p=0.016) and in the soft-tissue-sarcoma-only subgroup (n=53; p=0.044), consistent with the direction of the primary finding, although precision remained limited by the small number of patients with baseline advanced disease.

DISCUSSION

This multicenter study provides a patient-level analysis of forearm sarcomas after explicit exclusion of carcinoma and other diagnoses that could not be confidently classified as sarcoma. The principal finding was that baseline regional nodal and/or distant metastatic disease was associated with substantially poorer OS in Kaplan-Meier and univariable Cox analyses and remained associated with mortality after age adjustment. A Firth-penalized Cox sensitivity analysis produced a similar effect estimate, although the small number of exposed patients and deaths resulted in wide CIs and limits the precision of the adjusted association.

The adverse association of baseline regional nodal and/or distant metastatic disease with survival is consistent with the broader extremity sarcoma literature, in which systemic disease burden and tumor biology are major determinants of outcome.[10–13] In the present cohort, the composite group comprised 3 patients with regional nodal disease only and 3 with distant pulmonary metastases, with no patient having both at baseline. Regional nodal involvement and distant metastasis are biologically distinct states; they were combined only because each component was too uncommon for stable separate survival modeling. Accordingly, the composite estimate should be interpreted as a marker of baseline advanced disease rather than as a distant-metastasis-specific effect.

Limb-sparing surgery was the predominant definitive procedure, consistent with contemporary management of extremity sarcoma when adequate oncologic resection can be achieved.[4,5] The present study did not demonstrate a survival difference between limb-sparing surgery and amputation. Importantly, the amputation group had larger and uniformly deep tumors and substantially greater chemotherapy exposure, indicating strong confounding by indication. Accordingly, the surgical comparison is descriptive and should not be interpreted as a comparative-effectiveness estimate.

Chemotherapy and RT were intentionally treated as descriptive treatment-pattern variables rather than baseline survival exposures because treatment timing and indications were heterogeneous. This approach avoids attributing post-baseline or selectively administered therapies to baseline prognosis. The lack of a treatment-effect analysis should not be interpreted as evidence for or against benefit from chemotherapy or RT, whose roles depend on histology, stage, grade, resectability, and multidisciplinary treatment strategy.[10,12,13,15–17]

The distal upper extremity contains compact, functionally critical anatomy, and oncologic resection may require sacrifice or reconstruction of tendons, nerves, vessels, or soft tissue.[6–9,18] Although the present study focused on oncologic outcomes, standardized functional outcome measures were not systematically collected. Future prospective multicenter studies should integrate local control, functional out-

comes, patient-reported outcomes, and survival to better characterize the trade-offs between oncologic adequacy and extremity function.

Restricting the cohort to histologically coherent sarcomas and performing patient-level rather than record-level analysis strengthens the internal validity of the current study. The forearm-only and soft-tissue-sarcoma-only sensitivity analyses showed the same direction of association for baseline regional nodal and/or distant metastatic disease, although statistical precision remained limited by the rarity of the disease and the small number of outcome events.

Limitations of the Study

This study has several limitations. First, its retrospective design introduces selection bias, missing-data bias, and residual confounding. Second, only 11 deaths occurred overall and only 8 deaths entered the complete-case adjusted model; although a Firth-penalized Cox sensitivity analysis was used to reduce sparse-data bias, adjusted effect estimates remain imprecise. Third, baseline regional nodal and/or distant metastatic status was missing or indeterminate in six patients, and complete-case analysis was used without imputation. Fourth, regional nodal disease and distant metastasis were combined into a composite baseline advanced-disease variable because only 3 patients had each component; these disease states may have different biologic and prognostic implications. Fifth, histologic grade could not be analyzed, and a uniform stage system/edition could not be verified retrospectively; stage was therefore not used for primary inference. Sixth, chemotherapy and RT timing, dose, and regimen were heterogeneous and were not modeled as causal baseline exposures. Seventh, the 2008–2025 study period spans changes in imaging, systemic therapy, RT planning, pathology classification, and reconstructive practice. Eighth, local recurrence was reported descriptively because complete recurrence-time data and competing-risk modeling were not available. Finally, standardized functional outcome measures were not systematically collected.

CONCLUSION

In this multicenter patient-level cohort of forearm sarcomas assembled after exclusion of carcinoma and other non-sarcoma and uncertain diagnoses, baseline regional nodal and/or distant metastatic disease was associated with substantially poorer OS. The association persisted after age adjustment and in a Firth-penalized sparse-event sensitivity analysis, but the wide CIs require cautious interpretation. Limb-sparing surgery was the predominant definitive strategy. The absence of a survival difference between limb-sparing surgery and amputation should be interpreted cautiously because of pronounced treatment-selection bias. Larger histology-specific collaborative cohorts are needed to refine prognostic estimates and integrate oncologic outcomes with standardized functional measures.

Ethics Committee Approval: The study was approved by the Ankara Etlik City Hospital Ethics Committee (no: AEŞH-BADEK1-2025-661, date: 24/12/2025).

Informed Consent: This is a retrospective, multicenter cohort study.

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ORIGINAL ARTICLE

The Effect of Foot Bath and Massage on Chemotherapy-Induced Nausea and Vomiting in Pediatric Hematology-Oncology Patients: A Randomized Controlled Study

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OBJECTIVE

This study aimed to evaluate the effect of foot bath and massage on chemotherapy-induced nausea and vomiting in pediatric hematology-oncology patients.

METHODS

This research was designed as a randomized controlled study. The population consisted of children aged 8–18 years who were receiving chemotherapy and being followed in the pediatric hematology and oncology clinic and outpatient clinic of the University Faculty of Medicine Children's Hospital between December 2022 and December 2023. Using a computer-generated randomization scheme created by Randomization.com, the children were assigned to either the intervention or control group. The sample size was calculated using a power analysis program, which determined that 15 children per group, for a total of 30 participants, were required. Data were collected using the Child Information Form and the Baxter Retching Faces Scale (BARF). Children in the intervention group received a 20-min foot bath that began 5 min before the initiation of chemotherapy following premedication and continued during the first 15 min of chemotherapy. The control group did not receive a foot bath. The BARF scale was administered to both groups before chemotherapy and at the 15th min of chemotherapy.

RESULTS

No statistically significant difference was found between the intervention and control groups in the mean BARF scores at the 15th min of chemotherapy ($p>0.05$).

CONCLUSION

Although the difference between the intervention and control groups in mean BARF scores at the 15th min of chemotherapy was not statistically significant, the intervention group demonstrated lower BARF scores compared to the control group.

Keywords: Chemotherapy; foot bath; foot massage; nausea; pediatrics; vomiting.
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INTRODUCTION

Cancer is one of the leading causes of death among children and adolescents. It is estimated that each year, 400.000 children and adolescents aged 0–19 years are diagnosed with cancer. The most common types of childhood cancers include leukemias, brain tumors, lymphomas, neuroblastoma, and Wilms tumor. At the same time, more than 80% of children with cancer in high-income countries receive treatment due to access to comprehensive healthcare services, < 30% of children in low- and middle-income countries are treated. Standard cancer treatments include chemotherapy, surgery, and radiotherapy.[1]

Children with cancer experience numerous symptoms related to diagnosis and treatment, which significantly affect their daily lives.[2] These symptoms include fatigue, hair loss, nausea, vomiting, loss of appetite, anxiety, pain, insomnia, restlessness, diarrhea, constipation, weight loss, exhaustion, taste changes, mucositis, numbness in the hands and feet, and dry mouth.[3] Chemotherapy-induced nausea and vomiting (CINV) are among the most common acute morbidities observed in children undergoing cancer treatment and have a considerable impact on their quality of life.[4] One study reported that 60.9% of hospitalized children receiving chemotherapy experienced nausea and 41.3% experienced vomiting.[3] Another study found that nausea and vomiting were more prevalent among children aged 10–12 years (nausea: 14%, vomiting: 56%) compared to those aged 13–15 years (nausea: 10%, vomiting: 39%) and 16–18 years (nausea: 10%, vomiting: 19%).[2]

Symptoms such as nausea and vomiting impair children's physical, mental, and social functioning, negatively affect prognosis, lead to delays or limitations in treatment, and cause emotional distress.[2] Although CINV is among the two most frequently reported symptoms by children with cancer, pharmacological management alone is not sufficient.[5] More than 40% of children continue to experience nausea and vomiting despite receiving antiemetic treatment.[5] Although progress has been made in antiemetic prophylaxis over the last two decades, only a limited number of pediatric chemotherapy agents have well-established emetogenic risk profiles.[4] Consequently, the increasing preference of families for complementary and alternative therapies (CAT) highlights the need for further research in this area.[4] When properly applied, CAT can enhance the effectiveness of antiemetic medications, reduce symptom burden during cancer treatment, and improve overall well-being and quality of life in children.[5]

Several studies have evaluated the effectiveness of different CAT modalities in controlling nausea and vomiting during cancer treatment.[5] Among children with cancer, commonly used CAT approaches include acupuncture, hypnotherapy,[5,6] acupressure, creative arts therapy,[5] aromatherapy,[5,7] foot massage, and reflexology.[7] However, uncertainty remains regarding which CAT method is most effective in preventing or reducing nausea and vomiting during and after cancer treatment.[5] Some studies have shown that both foot massage and foot reflexology are effective in reducing CINV, yet evidence on how children can specifically benefit from these interventions remains limited.[7]

Therefore, the aim of this study was to evaluate the effect of foot bath and massage on CINV in pediatric hematology-oncology patients.

Hypothesis

H1: Foot bath and massage reduce CINV in pediatric hematology-oncology patients.

MATERIALS AND METHODS

Study Design

This study was conducted as a randomized controlled trial.

Study Setting

The research was carried out in the pediatric hematology and oncology inpatient and outpatient clinic of the University Children's Hospital.

Measures and Tools

Data were collected using the Child Information Form and the Baxter Retching Faces Scale (BARF).

Child Information Form

The Child Information Form was developed by the researchers based on a review of the literature.[8–19] The form consists of two sections: Sociodemographic characteristics (two items) and disease-related characteristics (six items).

BARF

The BARF scale was developed by Baxter et al.[20] to evaluate nausea and vomiting among children aged 7–18 years presenting to pediatric day-surgery and emergency departments with vomiting complaints. The Turkish validity and reliability study was conducted by Şişman et al.[21] among children aged 7–18 years to assess post-operative nausea and vomiting.

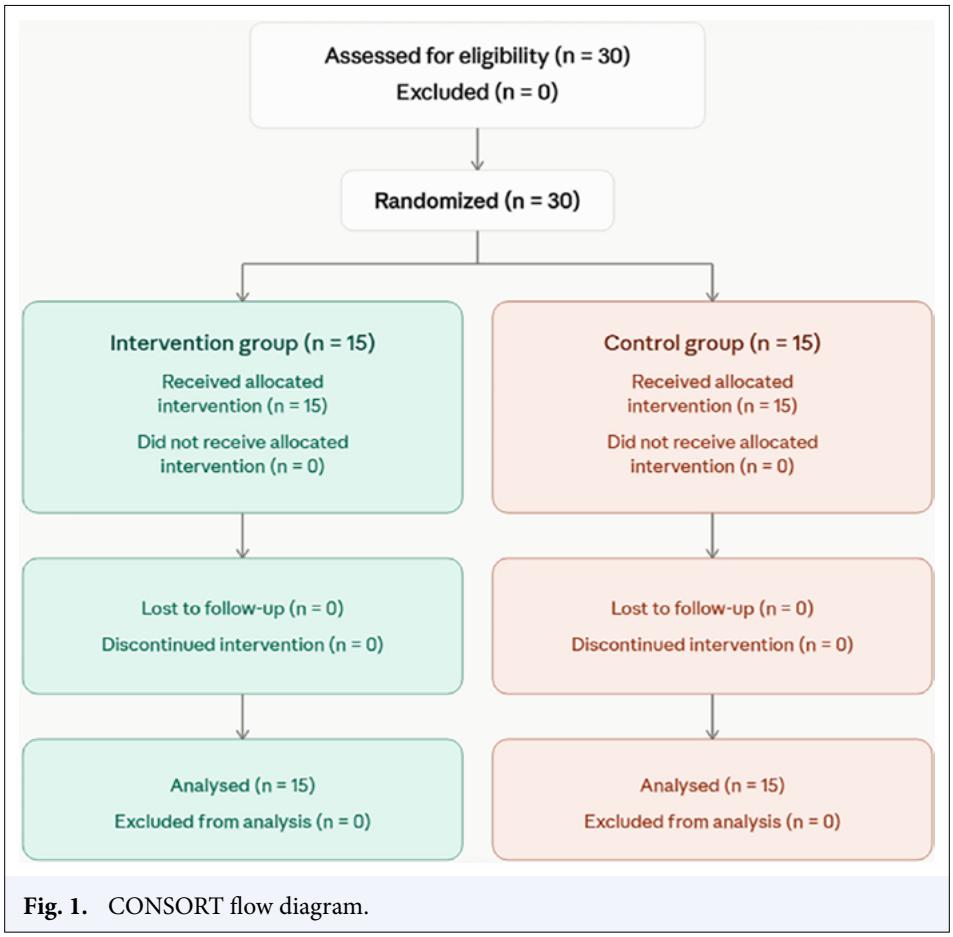

Fig. 1. CONSORT flow diagram.

The original scale demonstrated strong reliability (Spearman correlation coefficient=0.93; BARF score p=0.20), and the Turkish version was also found to be valid and reliable (Cochran's Q=9; p=0.437). The scale consists of six faces illustrating expressions ranging from "no nausea" to "vomiting," scored between 0 and 10. The leftmost face represents "no nausea" (0 points), whereas the rightmost face represents "the most severe nausea/vomiting imaginable" (10 points).[20,21]

Study Procedure

Randomization and Data Collection Process

Children who met the eligibility criteria and whose parents provided verbal consent were consecutively enrolled in the study. Children were allocated to the intervention and control groups in a 1:1 ratio using a computer-generated randomization scheme created through Randomization.com.[22] As each eligible participant was enrolled, the researcher assigned the participant to the corresponding group according to the predetermined randomization sequence. Before the foot bath procedure, the Child Information Form was completed for children in both the intervention and control groups through face-to-face interviews conducted by the researcher. Because of the nature of the intervention and the single-researcher study design, allocation concealment was not implemented.

Children in the intervention group received a 20-min foot bath, beginning 5 min before the initiation of chemotherapy following premedication and continuing during the first 15 min of chemotherapy. Children in the control group received no intervention. The BARF scale was administered to both groups before chemotherapy and again at the 15th min of chemotherapy. All randomized participants received the allocated intervention, completed the study, and were included in the final analysis. No participants were lost to follow-up or excluded from the analysis (Fig. 1).[23]

Foot Bath Intervention

Foot baths were administered in the patients' hospital rooms. Each child was positioned lying in bed, and

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Fig. 2. Foot bath device.[23]

their feet and ankles were placed into the warm water. The Beurer FB 35 Foot Bath and Massage Device was used for the intervention (Fig. 2).

During the foot bath, vibration and bubble massage were applied simultaneously to stimulate foot reflexology zones. The water temperature was set at 40°C using the device's built-in heating system, which maintained a constant temperature throughout the session. Each foot bath session lasted a total of 20 min, beginning 5 min before the initiation of chemotherapy and continuing during the first 15 min of chemotherapy.

The Beurer FB 35 device is an electric foot bath system suitable for use in children aged 8 years and older. It can heat water up to 40°C and maintain the temperature. The device provides foot reflex zone massage, vibrational massage, and bubble massage and includes a foot spa feature.

After each session, the device was cleaned using an appropriate disinfectant.

Foot Bath Temperature and Duration

A review of studies involving foot bath interventions showed that the water temperature ranged between 38–45°C and the duration of the bath varied between 10–30 min.[8–19] Based on this evidence, the water temperature in the present study was set at 40°C, and the foot bath intervention was standardized to a total duration of 20 min (5 min before chemotherapy and 15 min during chemotherapy).

Sample of the Study

Population and Sample

The population of the study consisted of children aged 8–18 years who were receiving chemotherapy and being followed between December 2022 and December 2023 in the pediatric hematology and oncology inpatient and outpatient clinics of the University Faculty of Medicine Children's Hospital.

Before starting the study, the required sample size for the intervention and control groups was determined using power analysis (G*Power software). The power analysis was performed using the BARF score means reported in the study by Yurdakul et al.[24] for the experimental group (1.43±1.45) and control group (4.80±2.07). The analysis indicated that 15 children per group, for a total of 30 participants, were required (comparison of two independent means; Type I error: 0.01, Type II error: 0.10, power: 0.90).

Inclusion and Exclusion Criteria

Inclusion Criteria

- Child and family voluntarily agreed to participate in the study,
- Child was between 8 and 18 years of age,
- Child had received chemotherapy at least once,
- Child had experienced chemotherapy-induced nausea and/or vomiting at least once,
- No impairment in skin integrity or sensory loss in the feet.

Exclusion Criteria

- Lack of voluntary participation by the child or family,
- Child had mental retardation, hearing impairment, or speech difficulties.

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences 24.0.

The BARF scores did not follow a normal distribution ($p>0.05$). Therefore, descriptive analyses and the Mann–Whitney U test were used. A significance level of $p<0.05$ was considered statistically significant.

Ethical Considerations

Written approval was obtained from the University Faculty of Medicine Children's Hospital and the Gaziantep University Clinical Research Ethics Committee (Date: November 24, 2022, and No: 2022/339). Before data collection, parents were informed about the study, and verbal consent was obtained from them. The research followed the ethical guidelines specified in the World Medical Association's Declaration of Helsinki.

RESULTS

It was found that 66.7% of the children in the intervention group were male and 46.7% were aged 8–10 years, whereas 60% of those in the control group were male and 66.7% were aged 8–10 years; additionally, 73.3% of the intervention group had leukemia, 46.7% had been diagnosed for 13 weeks or longer, 73.3% were in the consolidation phase, 46.7% were in week 13 or later of chemotherapy, 73.3% received Kytril and 26.7% received Avil as premedication, and 53.3% were treated with alkylating agents, whereas in the control group 66.7% had leukemia, 66.7% had been diagnosed for 13 weeks or longer, 73.3% were in the consolidation phase, 60.1% were in week 13 or later of chemotherapy, 80% received Kytril and 40% received Avil as premedication, and 26.7% received alkylating agents and antitumor antibiotics (Table 1).

When the mean BARF scores of the children in the intervention and control groups were compared, a statistically significant difference was found between the groups 5 min before the initiation of chemotherapy ($p<0.05$). However, there was no statistically significant difference between the intervention and control groups in the mean BARF scores at the 15th min of chemotherapy ($p>0.05$). Although the difference between the groups at the 15th min was not statistically significant, the intervention group had a lower mean BARF score compared to the control group. To account for the baseline difference in BARF scores, change scores (baseline BARF score minus the BARF score at the 15th min of chemotherapy) were calculated and compared between the groups. The intervention group demonstrated a significantly greater improvement in BARF scores than the control group (Mann–Whitney U=44.000, Z=-3.308, p=0.001) (Table 2).

Table 1 Distribution of sociodemographic and disease-related characteristics of children in the intervention and control groups

Sociodemographic and disease-related characteristics	Intervention group		Control group	
	n	%	n	%
Gender				
Female	5	33.3	6	40.0
Male	10	66.7	9	60.0
Age (years)				
8–10	7	46.7	10	66.7
11–14	5	33.3	3	20.0
15–18	3	20.0	2	13.3
Cancer type				
Leukemia	11	73.3	10	66.7
Lymphoma	3	20.0	1	6.7
Other	1	6.7	4	26.6
Time since diagnosis (weeks)				
1–6	4	26.7	1	6.7
7–12	4	26.7	4	26.7
≥13	7	46.7	10	66.7
Chemotherapy phase				
Induction	4	26.7	4	26.7
Consolidation	11	73.3	11	73.3
Chemotherapy week				
1–4	3	20	2	13.3
5–8	3	20	2	13.3
9–12	2	13.3	2	13.3
≥13	7	46.7	9	60.1
Premedication used				
Kytril (Granisetron hydrochloride)	11	73.3	12	80
Avil (Pheniramine hydrogen maleate)	4	26.7	6	40.0
Type of chemotherapy used				
Antimetabolites	3	20.0	3	20.0
Alkylating agents	5	53.3	4	26.7
Vinca alkaloids	2	13.3	2	13.3
Antitumor antibiotics	2	13.3	4	26.7
Enzymes	2	13.3	3	20.0
Platinum	0	0.0	2	13.3
Other (Etoposide)	1	6.7	2	13.3

DISCUSSION

A review of the literature revealed that no study has directly examined the effect of foot baths on CINV. Therefore, the findings of the present study were interpreted primarily in the context of research investigating the physiological and psychological effects of foot baths and massage. Studies evaluating the effect of foot massage on nausea and vomiting are also limited, and the available evidence is restricted to adult populations.[25]

Warm foot baths are widely used as a complementary and alternative therapy for managing various symptoms. Foot baths and foot massage have been applied across several health conditions. Previous research has shown that foot baths significantly increase salivary immunoglobulin A levels reduce cortisol levels, decrease sympathetic activity, and increase parasympathetic activity in both healthy and cancer patients – effects associated with analgesic and relaxing outcomes.[26,27] In healthy women, mechanically

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Table 2 Comparison of BARF scores before chemotherapy, at the 15th min of chemotherapy, and change in BARF scores between the intervention and control groups

Mean BARF scores in the intervention and control groups	Mean±SD	Min–max	Statistical analysis
Intervention group, 5 min before the initiation of chemotherapy	1.60±1.88	0–6	U=70.500; p=0.041*
Control group, 5 min before the initiation of chemotherapy	0.40±0.82	0–2	
Intervention group, 15th min of chemotherapy	0.53±1.18	0–4	U=95.500; p=0.392
Control group, 15th min of chemotherapy	1.33±2.69	0–10	
Intervention group, change in BARF score (baseline–15th min)	1.07±1.28	0–4	U=44.000; p=0.001*
	-0.93±2.12	-8–0	

*: p<0.05. BARF: Baxter retching faces scale; SD: Standard deviation.

stimulated warm foot baths have been shown to enhance parasympathetic activity, reduce sympathetic activity, and increase leukocyte and natural killer (NK) cell counts.[18] Other studies have demonstrated that foot baths improve blood flow and enhance parasympathetic nervous system activity.[17]

Among adults with chemotherapy-induced peripheral neuropathy, foot baths were found to be more effective than foot massage in increasing skin temperature, reducing neurotoxicity, and improving quality of life.[15] Foot massage has also been reported to reduce CINV in adult patients.[25] In addition, foot baths have been shown to rapidly improve pulmonary function in patients with bronchial asthma,[14] improve sleep quality in adults with insomnia,[9,10,12,13] relieve pain in diabetic peripheral neuropathy,[19] and improve quality of life related to chemotherapy-induced fatigue in cancer patients.[8] Studies in children have shown that foot baths reduce body temperature in febrile children,[11,16,28] and that foot massage reduces chemotherapy-related pain in pediatric cancer patients.[29] For these reasons, the use of foot baths in nursing practice has been recommended due to their physiological benefits.[18]

Based on these studies, foot baths have been reported to induce vasodilation, facilitate heat distribution, increase toxin oxidation, support thermoregulation by maintaining balance within the hypothalamic temperature-regulating center, and enhance blood circulation, thereby increasing the capacity of phagocytes to destroy microorganisms and detoxify the blood.[11] In addition, foot baths increase immunoglobulin A levels, reduce cortisol,[26,27] enhance parasympathetic activity while reducing sympathetic activation,[17,18,26,27] and elevate leukocyte and NK cell levels.[18] These physiological effects contribute to reducing pain, eliminating bacteria, relieving fatigue, promoting muscle relaxation, and supporting oxygen and nutrient delivery to the brain.[11] Massage has similarly been reported to reduce anxiety and pain, improve blood circulation, increase serotonin and dopamine levels, decrease cortisol, and suppress pain mechanisms.[30]

Despite the positive physiological mechanisms reported in the literature, no statistically significant difference was observed between the intervention and control groups in BARF scores at the 15th min of chemotherapy. However, when baseline differences were taken into account by comparing change scores, the intervention group demonstrated a significantly greater improvement in BARF scores than the control group. These findings suggest that although post-treatment scores alone did not differ significantly between groups, the intervention was associated with a greater reduction in nausea and vomiting over time.

These findings indicate that the intervention may contribute to reducing CINV, although the absence of a significant difference in post-treatment scores suggests that its effectiveness should be interpreted with caution. The significant improvement observed in the change-score analysis supports the potential benefit of the intervention; however, larger randomized controlled studies are needed to confirm these findings.

Limitations and Strengths

This study has several limitations. First, the small sample size may have prevented the clinically observed improvements from achieving statistical significance. In addition, a statistically significant difference in baseline BARF scores was observed between the intervention and control groups before chemotherapy, despite random allocation. This baseline imbalance may have influenced the post-intervention comparisons and should be considered when interpreting the findings. Furthermore, limiting the nausea and vomiting assessment to the 15th min of chemotherapy restricted the ability to evaluate the intervention's effects over a broader time frame.

The single-session design and intervention duration may also have limited the potential impact of warm foot baths and massage. Variations in cancer types and chemotherapy protocols among participants likely contributed to differences in nausea and vomiting responses, making homogeneous evaluation more difficult.

Furthermore, the effects of foot baths and massage may be influenced by psychological status, anxiety, and environmental stimuli – factors that are difficult to control and may have impacted the results. Since the intervention was evaluated only in the short term, its long-term effects could not be assessed.

Moreover, because nausea and vomiting were assessed only during the acute phase of chemotherapy, the findings are limited to the acute phase and should not be interpreted as reflecting the intervention's effects on delayed CINV. Future studies should evaluate both acute and delayed phases to provide a more comprehensive assessment of the intervention.

CONCLUSION

Although previous studies have shown that foot baths and massage exert positive physiological effects – such as increasing parasympathetic activity, reducing stress response, improving circulation, and promoting relaxation – the present study found no statistically significant difference between the intervention and control groups in post-treatment BARF scores. However, when changes from baseline were analyzed, the intervention group demonstrated significantly greater improvement in BARF scores than the control group. These findings suggest that warm foot bath and massage may contribute to reducing CINV; however, larger randomized controlled trials with more homogeneous patient populations, longer intervention periods, and multiple assessment time points are required before routine clinical implementation can be recommended.

Finally, the lack of previous studies examining the effects of foot baths and massage on CINV in pediatric populations limited the ability to compare findings with the existing literature. Because the few available studies were conducted only in adults, this further restricted the strength of the comparative analysis.

Although warm foot bath and massage showed a clinically favorable trend toward reducing nausea and vomiting, the current evidence is insufficient to recommend their routine use in clinical practice. These findings suggest that foot bath and massage may have potential as complementary supportive interventions; however, their effectiveness should be confirmed in larger randomized controlled trials with more homogeneous patient populations, longer intervention periods, and multiple assessment time points before clinical implementation can be recommended.

Ethics Committee Approval: The study was approved by the Gaziantep University Faculty of Medicine Children's Hospital and the Gaziantep University Clinical Research Ethics Committee (no: 2022/339, date: 24/11/2022).

Informed Consent: Before data collection, parents were informed about the study, and verbal consent was obtained from them.

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ORIGINAL ARTICLE

Is External Pelvic Radiotherapy Really Needed in Grade 3 Deeply Invasive Endometrial Cancer?

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OBJECTIVE

The aim of this study was to compare vaginal cuff brachytherapy (VBT) and external pelvic radiotherapy (EPRT) regarding oncologic outcomes and toxicity in surgically staged stage IB (International Federation of Gynecology and Obstetrics 2009) grade 3 endometrioid endometrial cancer (EC) patients.

METHODS

Records of 85 patients treated between 1994 and 2018 at two tertiary cancer centers were retrospectively reviewed. Pelvic lymph node dissection (LND) was performed in 14% of patients, pelvic+para-aortic LND in 85%, and sentinel LND in one patient. Patients receiving EPRT±VBT were classified as group 1 and those receiving VBT alone as group 2. The primary endpoint was locoregional recurrence (LRR).

RESULTS

Median dissected lymph node count was 37 (range, 12–110). Lymphovascular space invasion (LVSI) was present in 49% of patients. VBT alone, EPRT alone, and EPRT+VBT were delivered in 65%, 7%, and 28% of patients, respectively. After a median follow-up of 92 months, LRR and distant metastasis (DM) occurred in 3 and 7 patients. LVSI was associated with numerically higher LRR (8% vs. 0%) and DM (15% vs. 0%), although neither reached statistical significance. Among patients with LVSI, EPRT±VBT did not reduce LRR compared with VBT alone, and outcomes were not associated with age. Five-year overall, disease-free, LRR-free, and DM-free survival rates were 84%, 82%, 83%, and 82%, respectively, with no significant difference between treatment groups, including LVSI-positive patients. Acute genitourinary toxicity was significantly higher in the EPRT±VBT group.

CONCLUSION

VBT alone provides adequate disease control with lower toxicity in surgically staged stage IB grade 3 EC, particularly in patients with absent or focal LVSI.

Keywords: Brachytherapy; deep myometrial invasion; endometrial cancer; external radiotherapy; grade 3.
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INTRODUCTION

With an estimated 420,242 new cases and 97,704 associated deaths in 2022, endometrial cancer (EC) is the second most common gynecologic cancer worldwide.[1] The standard treatment of EC consists of surgical staging with hysterectomy and bilateral salpingo-oophorectomy (BSO), followed by adjuvant chemotherapy and/or radiotherapy (RT) based on clinicopathological risk factors. Patients with International Federation of Gynecology and Obstetrics (FIGO) 2009 stage IB, grade 3 EC are considered as the high-intermediate risk (HIR) group regardless of lymphovascular space invasion (LVSI) according to the European Society for Gynecologic Oncology (ESGO)/European Society for Radiotherapy and Oncology (ESTRO)/European Society for Pathology (ESP) 2025 guideline and this group of patients is being upstaged as stage IIC in the latest FIGO 2023 staging system.[2,3] The ESGO-ESTRO-ESP guideline recommends adjuvant external pelvic RT (EPRT) for patients in the HIR group, particularly for ones with a substantial LVSI.[3] However, the role of EPRT after complete surgical staging with lymph node dissection (LND) is still controversial.[3] On the other hand, the recent American Society for Radiation Oncology (ASTRO) guideline strongly recommends EPRT for patients with >50% myometrial invasion and grade 3 disease, regardless of LVSI and type of LN assessment.[4]

Studies have revealed that adjuvant RT increased the locoregional control in patients with early-stage HIR disease, but studies comparing vaginal brachytherapy (VBT) alone and EPRT for patients with grade 3 deeply invasive endometrioid type EC are limited.[5] Trials comparing VBT alone and EPRT in patients with an HIR disease showed no difference in terms of survival but the rate of pelvic recurrence was more common in the VBT alone group than the EPRT group.[6,7] However, early-stage HIR EC is a heterogeneous population and trials comparing VBT alone and EPRT in the HIR group also included patients with stage II disease, in which EPRT is strongly recommended according to the ESGO/ESTRO/ESP 2021 guideline.[6–8] To the best of our knowledge, there is no evidence for the superiority of EPRT to VBT in patients with grade 3 deeply invasive endometrioid type EC after complete surgical staging. Thus, we aimed to compare the impact of VBT alone and EPRT on locoregional control, distant metastasis (DM), and survival in these patients that underwent comprehensive surgical staging.

MATERIALS AND METHODS

Patient Population and Treatment

Medical records of 121 patients who received adjuvant RT after comprehensive surgical staging between 1994 and 2018 for FIGO 2009 stage IB grade 3 disease in two tertiary cancer centers were retrospectively evaluated. Thirty-six patients were excluded from the study due to inadequate nodal evaluation, histopathology other than endometrioid type, and inadequate follow-up; thus, 85 patients were analyzed in this study (Fig. 1). A magnetic resonance imaging and/or transvaginal ultrasonography with clinical examination was performed to evaluate myometrial invasion before surgery for all patients. Eighty-four (99%) patients were treated with total abdominal hysterectomy (TAH) and BSO, and 1 (1%) patient had undergone a type 2 hysterectomy and BSO. Pelvic LND was performed in 14% of patients, pelvic+para-aortic LND in 85%, and sentinel LND in one patient. The decision of adjuvant treatment after surgery was given in multidisciplinary tumor board consisting of gynecologic oncologists, medical oncologists, radiation oncologists, pathologists, and radiologists who were experienced in gynecologic oncology for every patient. Patients were treated with VBT alone, EPRT with or without VBT based on the clinicopathological risk factors after surgery. Since the number of patients that received EPRT alone is low, EPRT alone and EPRT+VBT groups were combined as EPRT±VBT group while performing statistical analyses.

EPRT was performed through two-dimensional (2D) RT, 3D conformal RT (3D-CRT), intensity-modulated RT (IMRT), or volumetric-modulated arc therapy (VMAT). The EPRT dose was prescribed to the pelvic area encompassing the surgical bed and pelvic lymphatics. The VBT dose was prescribed to the vaginal mucosa or to a 5-mm depth from the vaginal surface both in the VBT alone and EPRT+VBT groups.

This retrospective study was conducted in compliance with version of the 1975 Declaration of Helsinki, as revised in 2000, and an informed consent was obtained from each patient before treatment. The ethical approval was obtained from Hacettepe University Institutional Review Board (Date: 21.11.2023, Decision no: 2023/07/12).

Follow-up

Gynecologic examinations were performed in all patients every 3 months for the first 2 years, every 6 months for years 3-5, and annually thereafter. Imaging was performed when there was a suspicion of local/regional or distant recurrence. The acute toxicity includ-

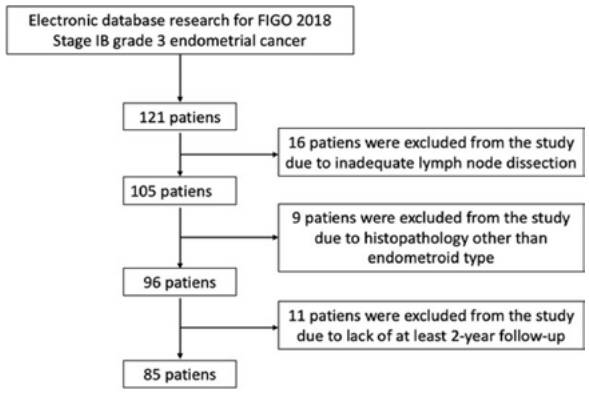

Fig. 1. Flowchart for inclusion and exclusion of patients.

ed any events occurred during RT and the following 90 days after RT while the late toxicity included complaints of more than 3 months after RT. All toxicities were assessed according to the Radiation Therapy Oncology Group/European Organization for the Treatment of Cancer toxicity criteria.[9]

Statistical Analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences version 24.0. The primary endpoint of this study was locoregional recurrence (LRR) which includes a vaginal cuff and/or pelvic LN recurrence. The secondary endpoints were DM, overall survival (OS), disease-free survival (DFS), LRR-free survival (LRRFS), and DM-free survival (DMFS). All time-related events were calculated from the last day of RT to the last follow-up, death, or recurrence, whichever came first. Survival estimates were calculated using the Kaplan–Meier test and survival was compared between the groups with the log-rank test. The univariate analysis was performed using the log-rank test to evaluate the impact of clinical parameters on survival outcomes. The multivariate analysis was not performed due to the small number of significant predictors in the univariate analysis for survival. The comparison of the clinical parameters between the groups was made by a Chi-square test. P<0.05 was considered statistically significant.

RESULTS

Patient and Tumor Characteristics

The median age of all patients was 62 years (range: 37–81 years). The median number of dissected LNs was 37 (range: 12–110). The median tumor size was 4 cm (range: 1.3–13 cm). All patients had an endometrioid type EC. Forty-two (49%) patients had LVSI. Substantial and focal LVSI was present in 7 (17%) and 6 (14%) of these 42 patients, respectively, but the extent of LVSI was unknown in 29 (69%) patients. Six of seven patients with substantial LVSI received EPRT ±VBT, while one received VBT alone. Median number of dissected LNs were 21 (range, 15–35) and 35 (range, 12–95) in patients with substantial LVSI and no/focal LVSI, respectively.

Table 1 Patient, tumor, and treatment characteristics

Parameters	VBT alone (n=55) (%)	EPRT±VBT (n=30) (%)	p
Age (years)			
≥60	35 (64)	18 (60)	0.741
<60	20 (36)	12 (40)	
Type of surgery			
TAH+BSO	54 (98)	30 (100)	1.000
Type 2 Hysterectomy	1 (2)	0	
Type of LND			
Pelvic	4 (7)	9 (30)	**0.010**
Pelvic and para-aortic	51 (93)	21 (70)	
Tumor size (cm)			
≥4	24 (44)	20 (67)	0.083
<4	23 (42)	8 (27)	
Unknown	8 (14)	2 (6)	
LVSI			
Present	26 (47)	15 (50)	0.600
Absent	16 (29)	12 (40)	
Unknown	13 (24)	3 (10)	
Chemotherapy administration			
Yes	2 (4)	11 (37)	<0.001
No	53 (96)	19 (63)	

VBT: Vaginal brachytherapy; EPRT: External pelvic radiotherapy; LND: Lymph node dissection; LVSI: Lymphovascular space invasion, TAH: Total abdominal hysterectomy; BSO: Bilateral salpingo-oophorectomy.

VBT alone, EPRT alone, and EPRT+VBT were performed in 55 (65%), 6 (7%), and 24 (28%) patients, respectively. EPRT was utilized through 2D-RT, 3D-CRT, IMRT, and VMAT in 2 (7%), 5 (17%), 8 (27%), and 15 (50%) patients, respectively. The median dose of EPRT and VBT was 45.5 Gy (range: 45–50.4 Gy) in median 25 fractions (range: 23–28 fractions) and 27.5 Gy (range: 12–35 Gy) in 5 fractions (range: 2–5 fractions), respectively.

Thirteen (15%) patients received systemic chemotherapy in addition to RT either given before or after RT or with sandwich approach. Age, type of surgery, tumor size, and presence of LVSI were similar between the groups, but pelvic and para-aortic LND and chemotherapy administration were significantly more frequent in the VBT alone group (Table 1).

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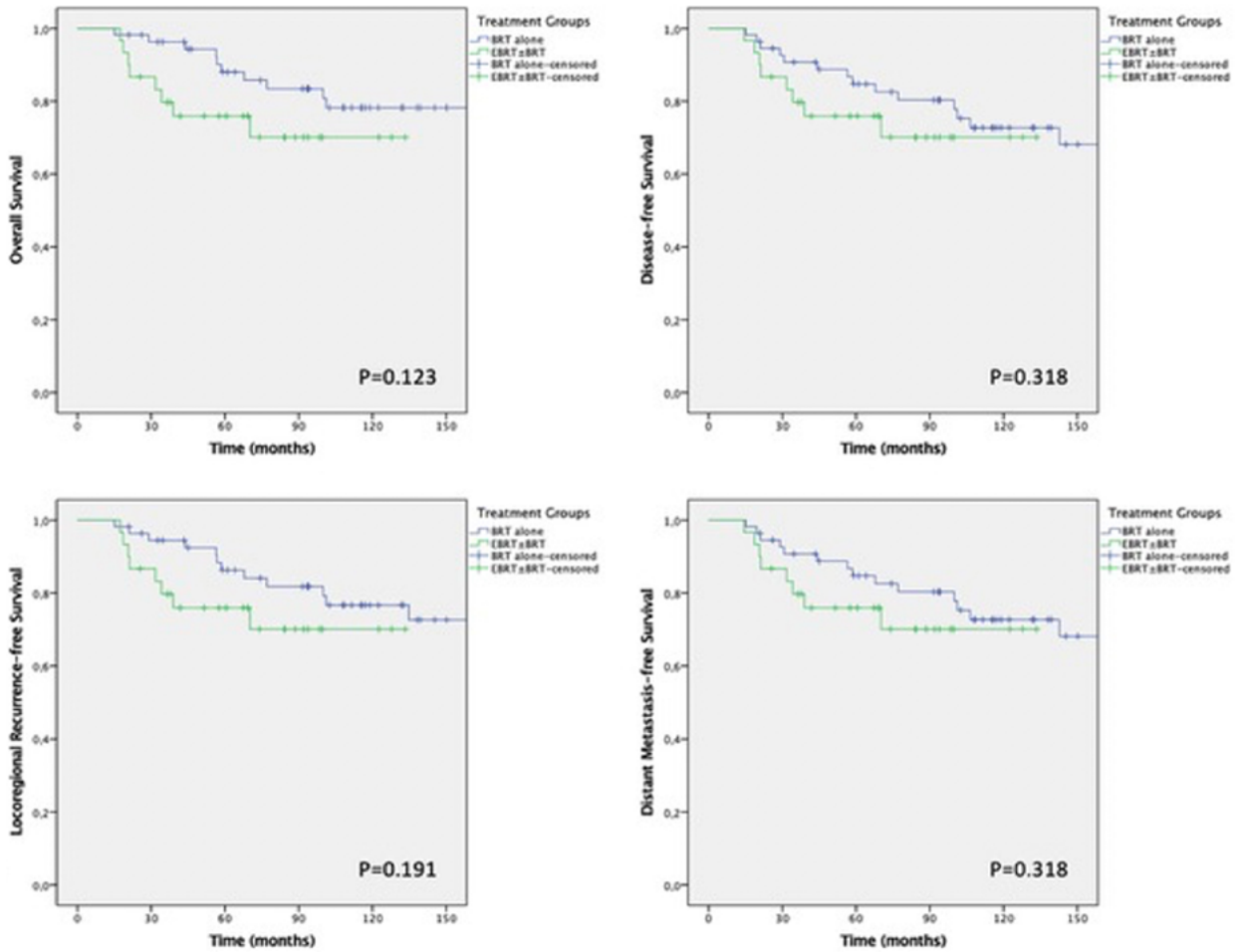

Fig. 2. Comparison of OS, DFS, LRRFS, and DMFS between treatment groups in whole cohort.

OS: Overall survival; DFS: Disease-free survival; LRRFS: Locoregional recurrence-free survival; and DMFS: Distant metastasis-free survival.

Treatment Outcomes

The median follow-up was 92 months (range: 15–336 months). At the last follow-up, three (4%) patients died due to disease progression and 17 (20%) patients due to other causes, respectively. LRR and DM were observed in 3 (4%) and 7(9%) patients, respectively. LRR developed in the vaginal cuff in 2, and pelvic LNs in 1 patient, respectively, all who received VBT alone. The most common site of DM was the intraperitoneal metastases above pelvic periton (43%), followed by lung (29%), inguinal lymph nodes (14%), and bone (14%).

The LRR rate was 5% in patients with VBT and 0% in patients treated with EPRT either with VBT or alone, but the difference was not significant (p=0.286). The median time to LRR was 92 months (range: 15–336 months). LRR rates were higher in patients with LVSI than in those without LVSI; however, the difference was not statistically significant (8% vs. 0%, p=0.275). When the 42 patients with LVSI were analyzed separately, LRR rates remained similar between the treatment groups (EPRT±VBT vs. VBT alone) (0% vs. 13%, p=0.283). LRR occurred in 6% of patients aged ≥60 years, whereas no LRR was observed among patients aged <60 years (p=0.297). DM rates were also higher in patients with LVSI than in those without LVSI, although the difference did not reach statistical significance (15% vs. 0%, p=0.074). DM rates were comparable between patients aged ≥60 and <60 years (10% vs. 7%, p=1.000).

The 5- and 10-year OS, DFS, LRRFS, and DMFS rates were 84% and 74%, 82% and 70%, 83% and 70%, and 82% and 70%, respectively. All survival rates were similar between the treatment groups in the whole cohort and also among patients with positive LVSI (Figs. 2, 3). The seven patients with known substantial LVSI

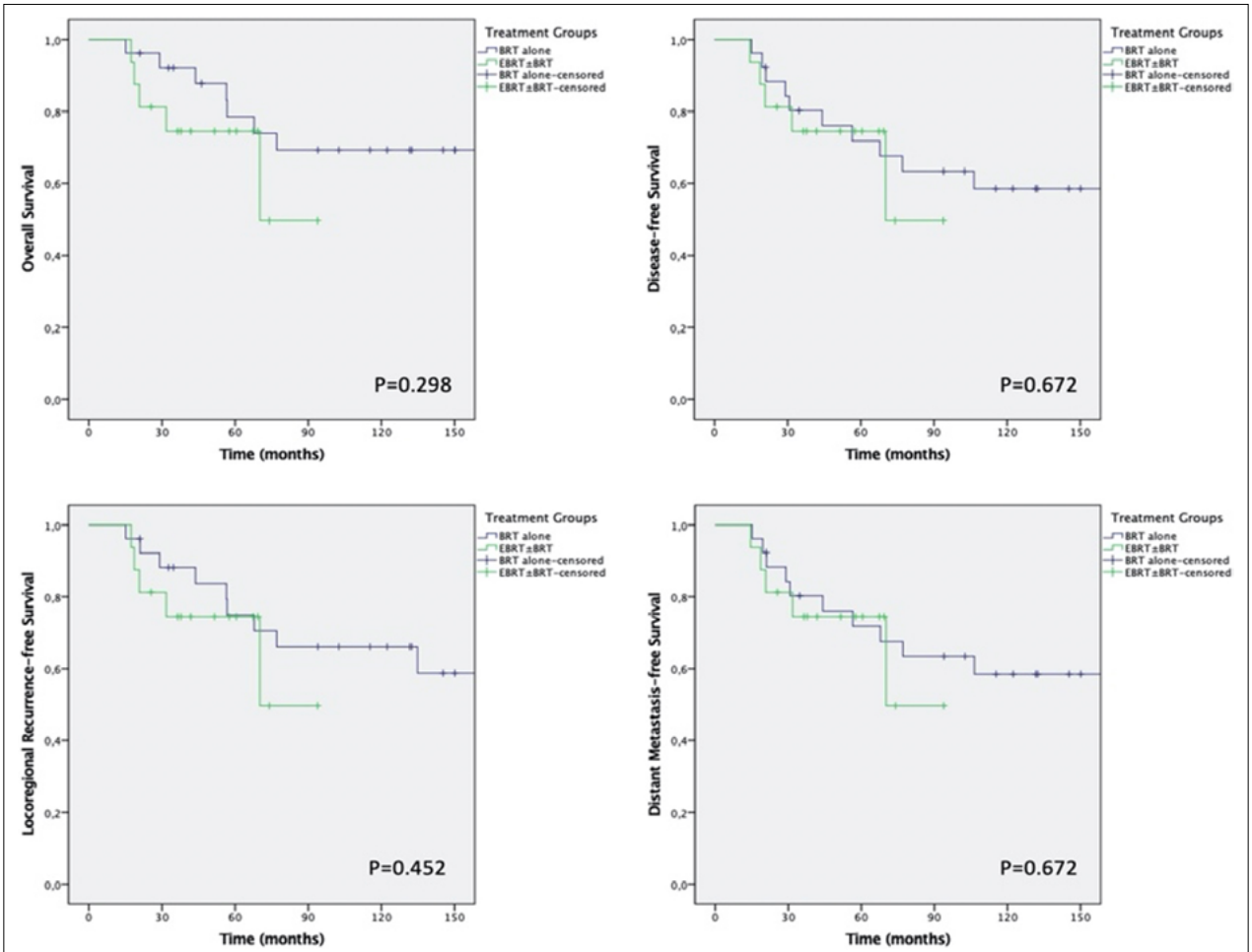

Fig. 3. Comparison of OS, DFS, LRRFS, and DMFS between treatment groups in patients with LVSI.

OS: Overall survival; DFS: Disease-free survival; LRRFS: Locoregional recurrence-free survival; DMFS: Distant metastasis-free survival; and LVSI: Lymphovascular space invasion.

when compared to the patients with known no LVSI or focal LVSI showed statistically significantly worse OS, DFS, LRRFS, and DMFS rates (Fig. 4).

The univariate analysis revealed that age (≥60 vs. <60) and LVSI were significant prognostic factors for both DFS and DMFS. In addition, LVSI was a significant and marginally significant predictor for LRRFS and OS, respectively. Age was also a marginally significant predictor for OS (Table 2).

Toxicity

No grade ≥3 acute toxicity was observed while acute grade 1–2 genitourinary (GU) and gastrointestinal (GI) toxicity was observed in 9 (11%) and 2 (2%) patients, respectively. The rate of acute GU toxicity was higher in the EPRT±VBT group than the VBT alone group (27% vs. 2%, p=0.001). Two (2%) patients developed acute grade 2 dermatitis. Although acute vaginal toxicity was not observed, late vaginal toxicity developed in 5 (6%) patients. The rate of late vaginal toxicity and acute GI toxicity rate was moderately higher in patients treated with EPRT±VBT than those treated with VBT alone (10% vs. 4%, p=0.340 and 7% vs. 0%, p=0.122), though it did not reach a statistical significance. Chronic cystitis and ileus were observed together as late GU and GI toxicities in one patient who received EPRT+VBT. Acute and late GI and GU toxicities were similar in patient's w/wo chemotherapy.

DISCUSSION

In this retrospective study, we observed that the LRR, DM, and survival rates were similar in patients with grade 3 deeply invasive endometrioid type EC treated

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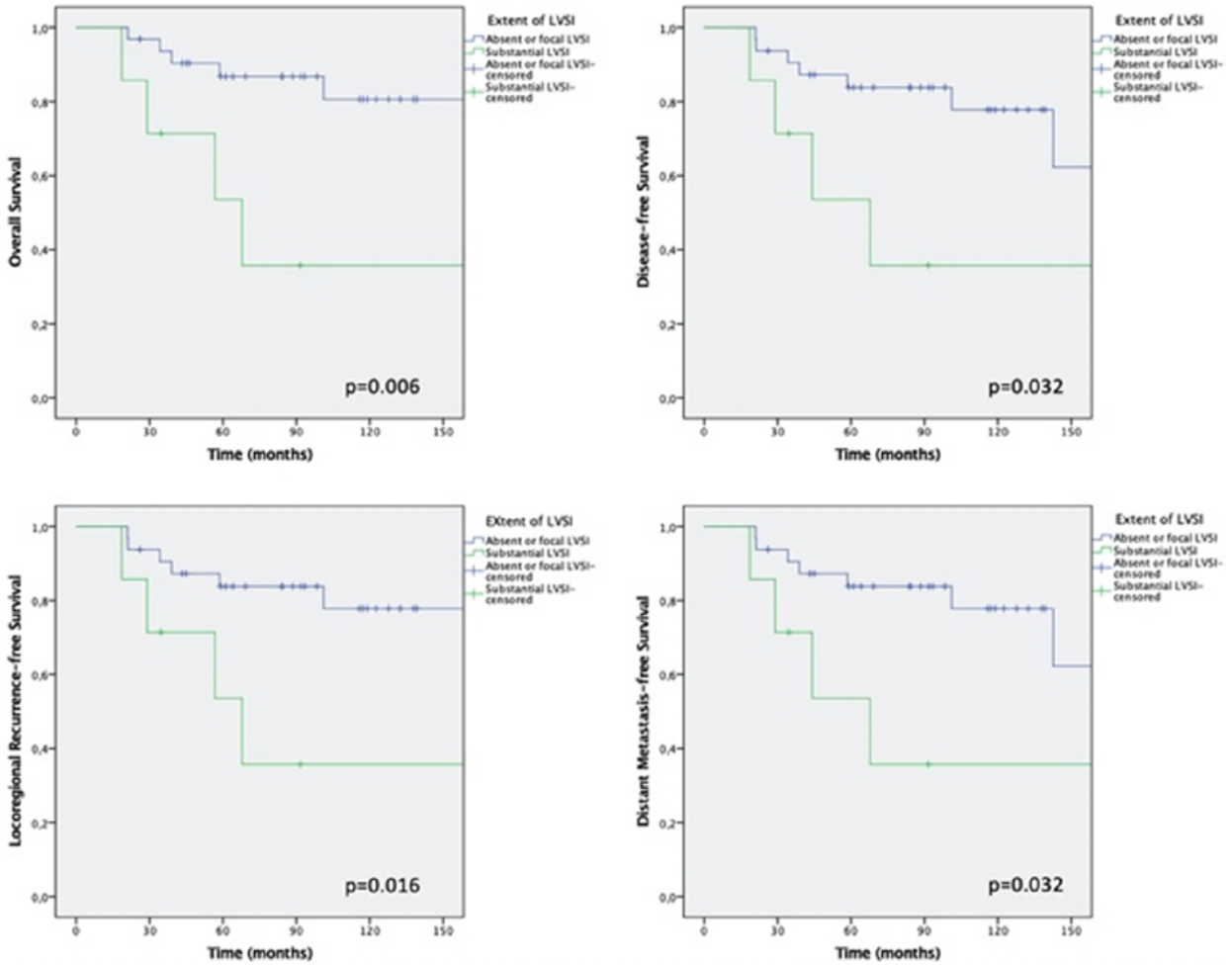

Fig. 4. Comparison of OS, DFS, LRRFS, and DMFS between patients with no/focal LVSI and those with substantial LVSI.

OS: Overall survival; DFS: Disease-free survival; LRRFS: Locoregional recurrence-free survival; DMFS: Distant metastasis-free survival; and LVSI: Lymphovascular space invasion.

with either VBT or EPRT with or without VBT after comprehensive surgical staging with a median follow-up of 92 months. In addition, patients aged ≥60 years had significantly worse DFS and DMFS than younger patients, suggesting that advanced age may represent an adverse prognostic factor in this population. Sixty-five percent of patients in our retrospective study were treated with VBT alone and the remaining with EPRT either alone or combined with VBT. Three (5%) patients who received VBT alone developed an LRR, in whom two experienced vaginal and one experienced pelvic LN recurrence. There was no intrapelvic recurrence among patients treated with EPRT. All treatments were well-tolerated, with acute GU, GI, and late vaginal toxicities moderately higher in the EPRT±VBT group than the VBT alone group. Since the rate of pelvic LN recurrence was very low in our patients with VBT alone, we think that VBT alone seems to be effective and safe in patients with grade 3 deeply invasive endometrioid type EC after comprehensive surgical staging.

According to the ESGO/ESTRO/ESP 2021 guideline, HIR EC is a heterogeneous group, including stage I endometrioid-type disease with a substantial LVSI and stage II disease, as well as stage IB grade 3 endometrioid-type EC regardless of the LVSI status in patients with an unknown molecular classification.[8] Within the HIR group, grade 3 EC is associated with a poorer prognosis which led to the most recent FIGO staging system having them put in the same stage together with aggressive histological subtypes.[2,10] According to the new FIGO 2023 staging, grade 3 disease with any myometrial involvement is considered as stage IIC and non-

Table 2 Univariate analyses for predictors of 5-y OS, DFS, LRRFS, and DMFS

Variables	OS	p	DFS	p	LRRFS	p	DMFS	p
Age (years)								
≥60	78	0.082	75	**0.021**	79	0.209	75	**0.021**
<60	93		93		86		93	
Type of surgery								
TAH+BSO	83	0.584	81	0.269	82	0.282	81	0.269
Type 2 Hysterectomy	100		0		0		0	
Type of LND								
Pelvic	83	0.549	83	0.804	83	0.660	83	0.804
Pelvic and para-aortic	84		81		82		81	
Tumor size (cm)								
≥4	79	0.165	79	0.543	79	0.209	79	0.543
<4	88		83		86		83	
LVSI								
Present	76	0.084	72	**0.027**	74	**0.043**	72	**0.027**
Absent	84		84		84		84	
Chemotherapy administration								
Yes	85	0.525	85	0.738	85	0.626	85	0.738
No	84		81		82		81	
Type of RT								
VBT alone	88	0.123	85	0.318	86	0.191	85	0.318
EBRT±VBT	76		76		76		76	

OS: Overall survival; DFS: Disease-free survival; LRRFS: Locoregional recurrence-free survival; DMFS: Distant metastasis-free survival; RT: Radiotherapy; VBT: Vaginal brachytherapy; EPRT: External pelvic radiotherapy; LND: Lymph node dissection; LVSI: Lymphovascular space invasion; TAH: Total abdominal hysterectomy; BSO: Bilateral salpingo-oophorectomy.

aggressive histology with a substantial LVSI as stage IIB, respectively.[2] However, it is not clear in what stage a patient with aggressive histology and substantial LVSI would be. According to the newest staging system, all patients with HIR and HR criteria should be treated with surgical LN staging either with systematic LND or sentinel LND. However, the cornerstone studies related to adjuvant treatment recommendations of EC patients with risk factors after surgery were based on the former staging system and the majority of these studies were either with TAH/BSO only or with selective lymph node sampling. It is still unclear to treat patients with HIR with always EPRT after comprehensive surgical staging.

Randomized studies have shown that EPRT improved locoregional control in patients with early-stage EC compared with no adjuvant treatment.[11,12] The PORTEC-1 and Gynecologic Oncology Group (GOG)-99 trials revealed that the greatest risk reduction in LRR with adjuvant EPRT was present in the HIR subset.[11,12] The pooled analysis of MRC-ASTEC and NCIC-CT-EN5 trials comparing EPRT with no adjuvant therapy in patients with intermediate- to high-risk early-stage EC showed that the isolated local recurrence rate was low (6.1%) in the observation arm, in which VBT was used in approximately 50% of these patients.[13] Although EPRT reduced the LRR rate, the authors concluded that EPRT cannot be recommended as a standard treatment in these patients considering the lack of OS benefit and increased toxicity.[13]

Besides tumor control, toxicity is of utmost importance in early-stage EC when deciding for adjuvant on treatment. The major disadvantage of EPRT is that it may increase the rates of GI and GU toxicity. The PORTEC-2 trial comparing VBT with EPRT after TAH-BSO in HIR patients showed that there was no significant difference in LRR, DM, or survival rates between patients treated with VBT or EPRT but the quality of life was improved with VBT.[7,14] Another randomized study comparing VBT alone with EPRT+VBT in stage I EC patients of all grades showed the superiority of EPRT+VBT to VBT alone for LRR, but no survival benefit was demonstrated.[15] In that study, late GI toxicity and vaginal tissue reactions were more frequent in EPRT+VBT group than VBT alone group.[15] Considering the lack of survival benefit and a higher toxicity profile, the conclusion of that partic-

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ular study was that combined EPRT+VBT should be reserved for those with high-risk disease only.[15] The other study by GOG, the GOG-249 trial, compared VBT+chemotherapy to EPRT alone in patients with HIR and high-risk stage I-II disease after TAH/BSO and bilateral pelvic and para-aortic LND and within a follow-up time of 53 months VBT+chemotherapy was not shown to be superior EPRT alone in terms of recurrence-free survival and OS with a higher rates of acute toxicity and slightly higher pelvic and para-aortic recurrence.[6] Acute adverse events were more frequent and severe in the VBT and chemotherapy arm in that trial while there was little difference between the arms when evaluating distribution of late toxicity. In our study, we found that the acute toxicity was higher in patients treated with EPRT consistent with the literature. Again, the rate of late vaginal toxicity was higher when EPRT with or without VBT was applied. Only a minority of our patients received systemic treatment, contribution of chemotherapy to the toxicity in our patients was very limited.

Several retrospective studies have demonstrated that both EPRT and VBT alone improved locoregional control, but a number of studies also reported that EPRT prolonged survival, particularly in patients with high-risk features.[16–18] On the contrary, a study based on the Surveillance, Epidemiology, and End Results (SEER) database revealed that VBT alone had a local control and survival benefit in patients with stage IB grade 3 disease.[18] In total, 1,095 patients in whom the majority were treated with LND were included in that particular SEER database analysis and 52% received VBT, 56% received EPRT, 16% received chemotherapy, and 29% received no adjuvant treatment. Survival outcomes were reported to be significantly worse for stage IB grade 3 and stage II grade 3 relative to stage II grades 1–2 in that study and VBT had a local control benefit across all patients that translated into a survival benefit in stage IB grade 3. Atahan et al.,[19] on the other hand, demonstrated that VBT alone after complete surgical staging was effective with minimal toxicity in patients with intermediate- to high-risk stage I disease, but only 13% of all patients had stage IB grade 3 disease in that study. Similarly, a recent Turkish retrospective study also agreed with the supported effectiveness and low toxicity profile of VBT alone in the early-stage HIR or high-risk patients after complete surgical staging.[20] The only retrospective study dedicated to patients with grade 3 deeply invasive endometrioid type EC concluded that adjuvant RT delayed the time to relapse and improved survival, but without any difference between VBT and EPRT in terms of oncologic outcomes.[21] In consistent with the SEER database analysis and similar studies in literature, there was no statistically significant difference in terms of LRR, DM, and survival rates in our patients with FIGO 2009 stage IB grade 3 disease when compared VBT with EPRT. VBT alone in our study was effective with minimal toxicity. However, the number of patients in our study was quite low that may mask the difference between the groups and to keep in mind that the rate of LRR in our patients with VBT alone was 5% compared to 0% in patients with EPRT.

Our study also revealed that LVSI was a significant prognostic factor for survival. The pooled analyses of PORTEC-1 and 2 trials reporting substantial LVSI as the most important prognostic factor for oncologic outcomes suggested the use of 3-tiered LVSI scoring and recommended EPRT±chemotherapy for patients with stage I EC with substantial LVSI.[22] However, it should be noted that routine LND was not required in these studies, and the majority of patients did not undergo pathologic LN evaluation.[7,12] The significance of substantial LVSI in patients with surgical staging of LNs remains still controversial. A few studies reported no significant difference in outcomes among patients with no, focal, or substantial LVSI that underwent a complete LN staging.[23,24] The practice patterns for LN staging and adjuvant treatment recommendations differ between Europe and the USA. While only bulky or suspicious LNs are dissected in the European practice, surgical evaluation of the LNs (i.e., LND or SLNB) is preferred in the USA.[25] In addition, while the ASTRO guideline strongly recommends EPRT for patients with grade 3 deeply invasive endometrioid type EC regardless of LVSI or type of LN assessment, the ESGO/ESTRO/ESP 2021 guideline recommends EPRT for patients in the HIR group, particularly with a substantial LVSI, but VBT alone for patients without LVSI that underwent LND.[4,8] Similar to the practice pattern in the USA, our gynecologic oncology surgeons prefer complete surgical staging in patients with HIR criteria. The majority of our patients were treated with both pelvic and para-aortic LND and the median number of dissected LNs in our study was 37 with a range of 12–110. In the case of inadequate LND as having dissected LNs less than at least 10, all our patients are being treated with EPRT when HIR criteria are present. We could not find a difference in terms of LRR between the treatment groups in patients with positive LVSI which might be responsible for pelvic recurrence. LVSI was present in 47% of our patients treated with VBT alone,

while it was present in 50% of patients treated with EPRT. The information about LVSI was absent for 24% patients with VBT and 10% with EPRT in our cohort and we do not know the extent of LVSI in the majority of our patients. We retrospectively analyzed pathology specimens for the extent of LVSI and of the 42 patients with LVSI, 7 (17%) had substantial LVSI and 6 (14%) patients were with focal LVSI. For the remaining 29 patients, we could not get information about the extent of LVSI. Since we have the adequate data of either having LVSI present or absent, we stratified our patients having LVSI or not and found no difference in terms of oncological outcomes between the treatment groups. However, when compared to seven patients with substantial LVSI with the other ones known with focal or no LVSI, there was statistically significant difference favoring the patients with focal or no LVSI in terms of OS, DFS, LRRFS and DMFS. However, due to the low number small of our patients with substantial LVSI, we cannot make a definitive conclusion in terms of the efficacy of VBT alone or the need for EPRT after comprehensive surgical staging in these patients. In the ongoing PORTEC-4a study, HIR patients are being stratified into risk groups according to molecular subtypes and presence of substantial LVSI and are being randomized to receive either EPRT or VBT.[26] The results of this study might give us a clearer response and change of adjuvant treatment decisions for HIR patients especially when they have substantial LVSI. Furthermore, our findings are consistent with the PORTEC studies and subsequent prognostic analyses, which have consistently shown that increasing age is associated with worse survival outcomes in EC.[10,27] Likewise, patients aged ≥60 years in our cohort had inferior DFS and DMFS despite comparable locoregional control.

The current study has several limitations. First, the frequency of two parameters which may affect the survival rates, that is, the rate of LND and chemotherapy administration are different between the two groups due to the retrospective nature of the study. In addition, the type of LVSI (substantial vs. focal) which is of utmost importance for the decision-making according to the current guidelines was unknown in the majority of patients, since the study included patients treated between 1994 and 2018. Yet, we still found that the prognosis of patients with substantial LVSI was poorer despite comprehensive surgical staging. Another limitation of our study is that molecular classification could not be performed as this study included patients treated before the introduction of the molecular classification for EC. On the other hand, our findings are important since this is the largest study with a very long follow-up period in the literature comparing VBT alone and EPRT±VBT in FIGO 2009 stage IB grade 3 endometrioid-type EC patients. Another strength of our study is that all our patients were treated with complete surgical staging and the median number of dissected LNs was 37 with a minimum number of 12. Even with this comprehensive surgical staging patients with substantial LVSI showed deterioration in terms of locoregional control and survival rates.

CONCLUSION

In conclusion, there is no difference between VBT alone and EPRT±VBT regarding LRR, DM, and survival rates in patients with grade 3 deeply invasive endometrioid type EC that underwent a comprehensive surgical staging. VBT alone seems an effective and safe treatment with minimal toxicity in this group of patients. However, although the LRR and DM rates are similar in patients with no/focal and substantial LVSI, all survival outcomes are inferior in the latter group. Consequently, with limited and perplexing data in hand, a large prospective randomized study is needed to determine the optimal treatment modality in patients with grade 3 deeply invasive endometrioid type EC , and particularly in patients with substantial LVSI in this subset.

Ethics Committee Approval: The study was approved by the Hacettepe University Ethics Committee (no: 2023/07/12, date: 21/11/2023).

Informed Consent: All patients consented to their anonymized data being used for research and educational purposes.

Conflict of Interest Statement: None declared.

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ORIGINAL ARTICLE

Immune-Related Adverse Events in Patients with Solid Tumors Treated with Nivolumab: A Retrospective Single-Center Cohort Study

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OBJECTIVE

Immune checkpoint inhibitors have substantially improved outcomes in multiple solid tumors but are associated with immune-related adverse events (irAEs). However, the incidence, risk factors, and prognostic implications of irAEs in real-world settings remain unclear.

METHODS

This retrospective single-center study included 223 patients with solid tumors who were treated with nivolumab. irAEs were identified and graded according to the Common Terminology Criteria for Adverse Events Criteria for Adverse Events, version 5.0. The baseline demographic, clinical, and laboratory parameters were also evaluated. Cox proportional hazards models were used to assess factors associated with irAE development and overall survival (OS).

RESULTS

Among the 223 nivolumab-treated patients, 56 (25.1%) developed 64 irAEs. Endocrine toxicities were predominant, with hypothyroidism being the most frequent (43.8%). The median time to irAE onset was 13 weeks, and 20.4% of events were grade 3–4. Corticosteroids were required for 14.1% of the events, and permanent treatment discontinuation occurred in 7.8%. Prior radiotherapy was independently associated with an increased risk of first irAE development (hazard ratio [HR] 2.23, 95% confidence interval [CI] 1.14–4.34, p=0.019). In the multivariable OS analysis, higher body mass index was independently associated with improved survival (HR 0.950, 95% CI 0.913–0.988, p=0.011), whereas elevated lactate dehydrogenase (LDH) was associated with increased mortality (HR 1.020 per 10 U/L increase, 95% CI 1.008–1.031, p<0.001). irAEs, modeled as a time-dependent covariate, were not independently associated with OS (HR 0.747, 95% CI 0.488–1.144, p=0.180).

CONCLUSION

In this real-world cohort study, irAEs occurred in approximately one-quarter of patients during nivolumab therapy, with endocrine toxicities representing the predominant spectrum. Prior radiotherapy was independently associated with the development of irAEs. When analyzed as a time-dependent variable, irAE occurrence was not independently associated with OS. Baseline body mass index and LDH remained independent prognostic factors for survival.

Keywords: Immune checkpoint inhibitors; immune-related adverse events; nivolumab; overall survival; solid tumors.
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INTRODUCTION

Immune checkpoint inhibitors have reshaped modern cancer treatment by counteracting inhibitory signals that restrain antitumor immunity, thus enabling more effective immune attack against tumors.[1] Immune checkpoint inhibitors disrupt inhibitory signaling mediated by the PD-1/PD-L1 and CTLA-4 pathways, thereby enhancing T-cell activation and effector function, which ultimately promotes immune-mediated tumor cell apoptosis and sustained antitumor responses.[2]

Over the past decade, immune checkpoint inhibitors have become integral to the management of multiple solid tumors and have demonstrated meaningful improvements in clinical outcomes across diverse malignancies. Evidence from large retrospective cohorts and systematic reviews indicates that immune checkpoint inhibitors (ICIs) confer significant survival and response benefits in cancers, such as non-small cell lung cancer, malignant melanoma, renal cell carcinoma, urothelial carcinoma, and head and neck squamous cell carcinoma, with reported objective response rates ranging from approximately 30% to over 40% and substantial gains in progression-free and overall survival (OS) compared with historical outcomes.[3,4] As a result, the indications for ICIs continue to expand rapidly, and these agents are increasingly being incorporated into routine clinical practice, both as monotherapy and in combination regimens.

Despite their substantial clinical efficacy, immune checkpoint inhibitors are associated with a distinct spectrum of toxicities, termed immune-related adverse events (irAEs), which arise from non-specific immune activation and breakdown of immune self-tolerance. Large-scale pharmacovigilance analyses comprising more than 50,000 reported irAE cases have shown that these toxicities can involve nearly every organ system, with the most commonly affected being the skin (approximately 22–25%), lungs (18–20%), gastrointestinal tract (14–15%), and endocrine organs, particularly the thyroid (around 12%).[5] Across different immune checkpoint inhibitor regimens, the median time to onset of irAEs has been reported to range from approximately 30 to 45 days, although onset times vary widely from as early as 1–2 weeks to beyond 6–9 months. Delayed events occurring after treatment discontinuation have also been documented.[6] While the majority of irAEs are low to moderate in severity, real-world data indicate that severe or life-threatening toxicities account for a substantial proportion of cases, with reported fatality rates of approximately 20–28% for myocarditis, 20–23% for myositis and myasthenia-like syndromes, and 20–21% for pneumonitis.[5–7]

irAEs are most commonly graded using the Common Terminology Criteria for Adverse Events (CTCAE); however, complementary consensus-based frameworks, such as those proposed by the Society for Immunotherapy of Cancer, have been developed to better capture the unique clinical features of immune-mediated toxicities.[8,9] Management of irAEs is guided by toxicity grade and organ involvement, and may involve treatment interruption, systemic corticosteroids, additional immunosuppressive therapy, or permanent discontinuation of immune checkpoint inhibitors. Early recognition and appropriate management are essential, as inadequately controlled irAEs may lead to significant morbidity, treatment non-adherence, and, in rare cases, mortality, whereas timely intervention often allows safe continuation or reintroduction of immunotherapy.

Moreover, the identification of patients at an increased risk of developing irAEs remains an unresolved clinical challenge. Although previous studies have explored demographic, clinical, and laboratory parameters as potential predictors of irAE susceptibility, the results have been heterogeneous, and no reliable predictive model has been universally adopted. Importantly, variations in genetic background, environmental factors, comorbidity profiles, and treatment practices across populations may contribute to differences in the incidence and presentation of irAEs, underscoring the need for real-world data from diverse clinical settings. Although several studies have evaluated irAEs across heterogeneous immune checkpoint inhibitor regimens, real-world data focusing specifically on nivolumab-treated populations remain comparatively limited, particularly in routine clinical practice settings.

In this context, we conducted a single-center retrospective cohort study to characterize the incidence, spectrum, and timing of irAEs in adult patients with solid tumors treated with nivolumab. We further aimed to identify clinical and laboratory factors associated with the development of irAEs and evaluate the relationship between irAE occurrence and OS using time-to-event analyses. We hypothesized that specific baseline clinical and laboratory characteristics would be associated with an increased risk of irAE development, and sought to determine whether irAE occurrence was associated with survival outcomes in routine clinical practice.

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MATERIALS AND METHODS

Data Curation and Study Cohort

Patients initiating nivolumab between January 2014 and March 2025 were included. Follow-up data were censored on March 31, 2025. Between 2014 and 2025, 233 adult patients with solid malignancies who initiated nivolumab therapy were identified. Three patients who received nivolumab for hematologic malignancies were excluded. Seven patients were excluded because of incomplete baseline or follow-up data. The remaining 223 patients constituted the final study cohort. Patients were included irrespective of treatment duration; therefore, individuals who discontinued nivolumab early because of death, treatment discontinuation, or loss to follow-up remained in the analysis until the time of censoring or event occurrence.

Follow-up started on the date of nivolumab initiation. During the observation period, 56 patients developed a total of 64 irAEs. Multiple adverse events occurred in a subset of patients. Follow-up time was calculated from nivolumab initiation until death or the last clinical contact. Total person-time was calculated as the sum of individual follow-up times, and the incidence rate of first irAEs was expressed per 1,000 patient-weeks with 95% confidence intervals based on the Poisson distribution.

irAEs were identified through retrospective review of electronic medical records, laboratory results, imaging findings, and oncology clinic documentation. Potential irAEs were assessed by review of the treating oncologists' clinical records. When uncertainty regarding causality existed, classification was based on the documented multidisciplinary clinical assessment and available diagnostic work-up recorded in the medical records. The diagnosis of endocrine, hepatic, gastrointestinal, neurological, pulmonary, and dermatological irAEs was based on the treating oncologist's clinical assessment together with laboratory, imaging, and specialist consultation findings, after exclusion of alternative etiologies whenever appropriate. irAEs were identified and graded according to the CTCAE, version 5.0.[8,9]

Patients with previously documented endocrine disorders were not classified as having endocrine irAEs unless a new immune-related event was clinically diagnosed after nivolumab initiation.

History of radiotherapy was defined as any radiotherapy administered before initiation of nivolumab treatment. Radiotherapy delivered after nivolumab initiation was not considered in the analyses.

Ethics

Ethics committee approval was obtained from the Izmir Katip Çelebi University Institutional Review Board on April 9, 2026 (approval no: 0280). The requirement for informed consent was waived by the ethics committee because of the retrospective design of the study. This study was conducted in accordance with the principles of the Declaration of Helsinki and adhered to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for observational cohort studies.

Statistical Analysis

All statistical analyses were performed using Statistical Package for the Social Sciences version 27.0 (IBM Corp., Armonk, NY). Continuous variables are summarized as means with standard deviations or medians with interquartile ranges, whereas categorical variables are presented as frequencies and percentages. The incidence of irAEs has been described overall and by organ-specific subtypes. For patients who experienced more than one irAE, only the time to the first irAE was used in time-to-event analyses.

Patients with incomplete baseline or follow-up data were excluded before analysis. Therefore, all analyses were performed using complete-case data without further imputation.

The association between baseline clinical and laboratory parameters and the risk of developing irAEs was evaluated using Cox proportional hazards regression models. Hazard ratios (HRs) with 95% confidence intervals (CIs) are reported. Candidate variables were selected a priori based on clinical relevance and univariate associations. To minimize overfitting, only a limited number of covariates were entered into the final multivariable model, considering the number of observed first irAE events. Age and sex were retained as clinically relevant adjustment variables irrespective of statistical significance, whereas prior radiotherapy and lactate dehydrogenase (LDH) were included because of their potential biological relevance and univariate associations.

LDH values were scaled per 10-U/L increment before inclusion in Cox regression models to improve the interpretability of hazard ratios. To avoid model overfitting, the number of covariates included was restricted based on the number of observed events. Multicollinearity was assessed using variance inflation factors (VIFs) and condition indices. Variables demonstrating substantial collinearity (VIF >3 or condition index >10) or conceptual redundancy were

excluded from the final models. The proportional hazards assumption was assessed by visual inspection of log-minus-log survival plots for categorical variables and by testing time-dependent interactions between selected continuous covariates and log(time). No meaningful violation of the proportional hazards assumption was identified. Because of substantial conceptual overlap and shared components among laboratory-derived inflammatory indices (neutrophil-to-lymphocyte ratio [NLR], derived neutrophil-to-lymphocyte ratio [dNLR], platelet-to-lymphocyte ratio [PLR], and systemic immune-inflammation index [SII]), only one representative inflammatory marker was included in the multivariable model to minimize multicollinearity. SII was selected a priori based on its broader representation of systemic inflammatory status and previous literature.

OS was defined as the interval from nivolumab initiation to death from any cause or the past follow-up. Cox proportional hazards regression was used to evaluate factors associated with OS. To minimize immortal time bias, the occurrence of irAEs was modeled as a time-dependent covariate such that patients contributed person-time to the non-irAE group until the first irAE occurred and to the irAE group thereafter.

The multivariable model evaluating first irAE included 56 first irAE events, whereas the OS model included 153 deaths. The number of covariates was restricted according to the number of observed events to reduce the risk of model overfitting.

All statistical tests were two-sided, and a $p<0.05$ was considered statistically significant.

RESULTS

Clinical and Laboratory Characteristics of the Study Cohort According to Adverse Event Development

Among the 223 patients treated with nivolumab, 56 (25.1%) developed irAEs (Table 1). The median observation time was 92 weeks (interquartile range [IQR], 56–184), corresponding to a total follow-up of 32,136 patient-weeks. The incidence rate of first irAEs was 1.74 per 1,000 patient-weeks (95% CI, 1.31–2.26). Baseline characteristics were largely comparable between patients with and without irAEs, including age (65.3±8.5 vs. 64.8±9.5 years), sex distribution (male: 78.6% vs. 78.4%), Eastern Cooperative Oncology Group (ECOG) performance status, body mass index, Charlson comorbidity index, tumor histology, and number of prior systemic therapies.

Connective tissue disorders were more frequent among patients who developed irAEs (8.9% vs. 1.2%), while the rates of diabetes mellitus and chronic obstructive pulmonary disease were comparable. Mortality occurred in 60.7% and 71.3% of the patients with irAEs and without irAEs, respectively.

irAEs

Five patients experienced multiple irAEs (three patients had three irAEs each and two patients had two irAEs each). These patients accounted for 13 irAEs in total, including eight additional events beyond the first event (Table 2).

Endocrine toxicities were predominant, with hypothyroidism being the most common (43.8%), followed by hyperthyroidism (14.1%), adrenal insufficiency (12.5%), and hypophysitis (9.4%). Non-endocrine irAEs included dermatitis or rash (10.9%), neurological toxicity (optic neuritis, 3.1%), immune-related hepatitis (3.1%), colitis (1.6%), and myositis (1.6%).

The median time to irAE onset was 13 weeks (range, 1–182 weeks), with an earlier onset of hyperthyroidism (10 weeks) and later onset of adrenal insufficiency (44 weeks). Most events were grade 2 (56.3%), and grades 3 and 4 events accounted for 14.1% and 6.3%, respectively. Systemic corticosteroids were used in nine events (14.1%), and permanent nivolumab discontinuation occurred in five patients (7.8%).

Factors Associated with irAEs

Factors associated with the development of irAEs were evaluated using Cox proportional hazards models, considering the time to the first irAE (Table 3). In univariate analyses, a history of radiotherapy was associated with an increased risk of adverse events (HR 1.877, 95% CI, 1.012–3.478; p=0.046), whereas age, sex, body mass index, ECOG performance status, Charlson comorbidity index, and most baseline laboratory parameters showed no clear association with irAE occurrence.

In the multivariable analysis, prior radiotherapy remained independently associated with an increased risk of first irAE (HR 2.23, 95% CI 1.14–4.34; p=0.019). Baseline LDH showed a borderline association with irAE risk (HR 1.012/10 U/L increase, 95% CI 0.999–1.024; p=0.055). No other evaluated baseline characteristics were independently associated with first irAE occurrence.

Factors Associated with OS

OS was evaluated using Cox proportional hazards models, with irAEs entered as a time-dependent covariate (Table 4).

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Table 1 Study cohort characteristics

Variables	Adverse event (n=56)	No adverse event (n=167)	Total (n=223)	p
Age, mean±SD	65.3±8.5	64.8±9.5	65.0±9.2	0.724
Sex, n (%)				0.984
Male	44 (78.6)	131 (78.4)	175 (78.5)	
Female	12 (21.4)	36 (21.6)	48 (21.5)	
BMI, mean±SD	25.2±4.2	24.2±4.8	24.4±4.7	0.159
ECOG-PS scale, n (%)				0.400
0	46 (82.1)	124 (74.3)	170 (76.2)	
1	10 (17.9)	41 (24.6)	51 (22.9)	
2	0 (0)	2 (1.2)	2 (0.9)	
CCI, mean±SD	9.5±1.6	9.2±1.7	9.3±1.7	0.409
Histopathological types, n (%)				0.187
Lung adenocarcinoma	16 (28.6)	58 (34.7)	74 (33.2)	
Lung SSC	14 (25.0)	43 (25.7)	57 (25.6)	
Malign melanoma	10 (17.9)	33 (19.8)	43 (19.3)	
Renal cell carcinoma	15 (26.8)	26 (15.6)	41 (18.4)	
Other	1 (1.7)	7 (4.2)	8 (3.5)	
Comorbidities, n (%)				
Hypertension	32 (57.1)	66 (39.5)	98 (43.9)	**0.021**
Diabetes mellitus	15 (26.8)	41 (24.6)	56 (25.1)	0.739
COPD	14 (25.0)	43 (25.7)	57 (25.6)	0.912
Connective tissue disorder	5 (8.9)	2 (1.2)	7 (3.1)	**0.004**
Observation duration, weeks, median (IQR)	150 (81-250)	84 (48-164)	92 (56-184)	**<0.001**
Number of treatment regimens before nivolumab, n (%)				0.766
1	37 (66.1)	118 (70.6)	155 (69.5)	
2	13 (23.2)	34 (20.4)	47 (21.1)	
3	6 (10.7)	11 (6.6)	17 (7.6)	
>3	0 (0)	4 (2.4)	4 (1.8)	
History of radiotherapy, n (%)	14 (25.0)	34 (20.4)	48 (21.5)	0.465
Nivolumab duration, weeks, median (IQR)	34 (13–83)	14 (8–31)	16 (10–42)	**<0.001**
Creatinine, mg/dL, median (IQR)	0.99 (0.83–1.14)	0.90 (0.80–1.11)	0.92 (0.80–1.11)	0.371
FBG, mg/dL, mean±SD	112±35	116±41	116±40	0.885
ALT, U/L, median (IQR)	16 (11–21)	14 (9–20)	14 (10–20)	0.235
AST, U/L, median (IQR)	19 (15–24)	16 (13–21)	17 (14–21)	**0.023**
GGT, U/L, median (IQR)	28 (18–52)	27 (19–45)	27 (19–46)	0.823
ALP, U/L, median (IQR)	77 (66–101)	88 (69–111)	85 (67–109)	0.101
LDH, U/L, median (IQR)	188 (158–243)	183 (152–232)	185 (154–235)	0.420
Albumin, g/dL, mean±SD	4.0±0.4	3.9±0.5	3.9±0.5	0.300
WBC, 109/L, mean±SD	7.2±3.0	8.0±3.5	7.9±3.6	0.123
NEU, 109/L, median (IQR)	3.6 (2.7–5.0)	5.0 (3.6–6.5)	4.7 (3.3–6.3)	0.001
LYM, 109/L, median (IQR)	1.7 (1.2–2.3)	1.4 (1.0–2.0)	1.5 (1.0–2.1)	0.064
Hemoglobin, g/dL, mean±SD	12.5±1.9	12.1±2.0	12.2±2.0	0.272
Platelets, 109/L, mean±SD	260±101	293±117	286±115	0.111
TSH, mU/L, median (IQR)	1.72 (0.81–2.63)	1.38 (0.89–2.50)	1.41 (0.87–2.52)	0.765
fT4, ng/dL, median (IQR)	0.95 (0.81–1.17)	0.99 (0.84–1.20)	0.97 (0.83–1.18)	0.403
Mortality, n (%)	34 (60.7)	119 (71.3)	153 (68.6)	0.141

ALP: Alkaline phosphatase; ALT: Alanine transaminase; AST: Aspartate transaminase; BMI: Body mass index; CCI: Charlson comorbidity index; COPD: Chronic obstructive pulmonary disease; ECOG: Eastern Cooperative Oncology Group; eGFR: Estimated glomerular filtration rate; FBG: Fasting blood glucose; fT4: Free thyroxine; GGT: Gamma-glutamyl transferase; LDH: Lactate dehydrogenase; LYM: Lymphocytes; NEU: Neutrophil; N/A: Not applicable; IQR: Interquartile range; SD: Standard deviation; TSH: Thyroid stimulating hormone; WBC: White blood cells.

Table 2 Immune-related adverse events (event-based analysis) (n=64)

Adverse event category	n (%)	Time to onset, weeks, median (min -max)	CTCAE Grade, n	Steroid use, n (%)	Permanent nivolumab discontinuation, n (%)
Hypophysitis	6 (9.4)	27 (4–76)	G1: 0; G2: 5; G3: 1; G4: 0	1 (1.6)	0 (0)
Hypothyroidism	28 (43.8)	13 (4–90)	G1: 14; G2: 12; G3: 1; G4: 1	2 (3.1)	0 (0)
Hyperthyroidism	9 (14.1)	10 (5–24)	G1: 1; G2: 8; G3: 0; G4: 0	0 (0)	0 (0)
Adrenal insufficiency	8 (12.5)	44 (9–136)	G1: 0; G2: 4; G3: 2; G4: 2	3 (4.7)	1 (1.6)
Hepatitis (immune-related)	2 (3.1)	41 (11–70)	G1: 0; G2: 0; G3: 1; G4: 1	1 (1.6)	1 (1.6)
Dermatitis/rash	7 (10.9)	13 (3–182)	G1: 0; G2: 5; G3: 2; G4: 0	0 (0)	1 (1.6)
Neurologic (optic neuritis)	2 (3.1)	26 (1–51)	G1: 0; G2: 0; G3: 2; G4: 0	2 (3.1)	2 (3.1)
Colitis	1 (1.6)	10 (10–10)	G1: 0; G2: 1; G3: 0; G4: 0	0 (0)	0 (0)
Myositis	1 (1.6)	7 (7–7)	G1: 0; G2: 1; G3: 0; G4: 0	0 (0)	0 (0)
Total*	64 (100)	13 (1–182)	G1: 15; G2: 36; G3: 9; G4: 4	9 (14.1)	5 (7.8)

A single patient may have experienced more than one immune-related adverse event; therefore, counts represent the total number of events, not patients. Grade, steroid use, and treatment discontinuation are reported per event. *: Five patients experienced multiple irAEs (three patients had three irAEs each and two patients had two irAEs each), accounting for a total of 13 irAEs. Because five of these were first events, the remaining eight represented additional irAEs beyond the first event. Overall, 64 irAEs occurred in 56 patients. AE: Adverse effect; CTCAE: Common Terminology Criteria for Adverse Events; IQR: İnterquartile range; SD: Standard deviation.

Table 3 Cox proportional hazards model evaluating associated factors for the first irAE

Variables	Univariate			Multivariate		
	HR	95% CI	p	HR	95% CI	p
Age (per a year increase)	1.012	0.981–1.045	0.438	1.013	0.980–1.046	0.449
Female sex (vs male)	1.114	0.585–2.120	0.742	1.213	0.624–2.357	0.569
BMI (per one-point increase)	0.992	0.939–1.048	0.785	—	—	—
ECOG-PS (per one-point increase)	0.928	0.482–1.787	0.823	—	—	—
CCI (per one-point increase)	1.080	0.919–1.270	0.351	—	—	—
History of radiotherapy (yes)	1.877	1.012–3.478	**0.046**	2.225	1.140–4.342	**0.019**
Connective tissue disorder (yes)	1.932	0.760–4.914	0.167	—	—	—
DM (yes)	0.890	0.483–1.638	0.707	—	—	—
HT (yes)	1.527	0.895–2.604	0.120	—	—	—
WBC (per 1×10^9/L increase)	0.970	0.882–1.066	0.526	—	—	—
NEU (per 1×10^9/L increase)	0.944	0.836–1.067	0.351	—	—	—
LYM (per 1×10^9/L increase)	1.107	0.790–1.553	0.554	—	—	—
Hemoglobin (per 1 g/dL increase)	0.996	0.878–1.130	0.949	—	—	—
Platelets (per 1×10^9/L increase)	0.998	0.996–1.001	0.239	—	—	—
LDH (per 10 U/L increase)	1.010	0.998–1.023	0.099	1.012	0.999–1.024	0.055
AST (per 1 U/L increase)	1.010	0.998–1.022	0.112	—	—	—
ALT (per 1 U/L increase)	1.005	0.998–1.013	0.182	—	—	—
TSH (per 1 mU/L increase)	0.980	0.914–1.051	0.572	—	—	—
NLR (per one-point increase)	0.983	0.893–1.082	0.730	—	—	—
dNLR (per one-point increase)	0.956	0.789–1.158	0.646	—	—	—
PLR (per one-point increase)	0.988	0.966–1.011	0.306	—	—	—
SII (per 100-point increase)	1.301	0.913–1.856	0.146	—	—	—
HALP (per one-point increase)	1.001	0.990–1.013	0.816	—	—	—

For patients who developed more than one irAE, only the time to the first irAE was used in the survival analyses. irAE: Immunotherapy-related adverse event ALT: Alanine transaminase; AST: Aspartate transaminase; BMI: Body mass index; CCI: Charlson comorbidity index; CI: Confidence interval; DM: Diabetes mellitus; dNLR: Derived neutrophil-to-lymphocyte ratio; ECOG: Eastern Cooperative Oncology Group; HALP: Hemoglobin–albumin–lymphocyte–platelet; HR: Hazard ratio; HT: Hypertension; LDH: Lactate dehydrogenase; LYM: Lymphocyte ; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; TSH: Thyroid stimulating hormone; SII: Systemic immune-inflammation index; WBC: White blood cell.

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Table 4 Cox proportional hazards model evaluating associated factors for overall survival

Variables	Univariate			Multivariate		
	HR	95% CI	p	HR	95% CI	p
Age (per a year increase)	1.004	0.986–1.022	0.695	1.024	0.994–1.055	0.117
Male sex (vs. female)	1.131	0.758–1.689	0.541	1.213	0.755–1.949	0.425
BMI (per one-point increase)	0.943	0.909–0.978	**0.001**	0.950	0.913–0.988	**0.011**
ECOG-PS (per one-point increase)	1.281	0.940–1.746	0.128	1.088	0.741–1.596	0.667
CCI (per one-point increase)	1.029	0.932–1.137	0.567	0.858	0.725–1.015	0.075
Histopathological type						
Lung cancer		Reference			Reference	
RCC	0.757	0.507–1.130	0.757	0.648	0.399–1.054	0.081
Melanoma	0.308	0.187–0.509	**<0.001**	0.306	0.178–0.526	**<0.001**
irAE, (yes)*	0.693	0.469–1.025	0.066	0.747	0.488–1.144	0.180
DM, (yes)	1.133	0.795–1.614	0.489	—	—	—
HT, (yes)	0.819	0.594–1.128	0.222	—	—	—
COPD, (yes)	1.232	0.855–1.776	0.263	—	—	—
LDH (per 10 U/L increase)	1.018	1.009–1.028	**<0.001**	1.020	1.008–1.031	**<0.001**
NLR (per one-point increase)	1.053	1.020–1.087	**0.002**	—	—	—
dNLR (per one-point increase)	1.087	1.018–1.161	**0.012**	—	—	—
PLR (per one-point increase)	1.009	1.003–1.015	**0.004**	—	—	—
SII (per 100-point increase)	1.647	1.250–2.189	**0.002**	—	—	—
HALP (per one-point increase)	0.988	0.980–0.996	**0.005**	0.993	0.985–1.001	0.087

*: irAE is evaluated as a time-dependent variable. İrAE: Immunotherapy-related adverse event; ALT: Alanine transaminase; AST: Aspartate transaminase; BMI: Body mass index; CCI: Charlson comorbidity index; CI: Confidence interval; DM: Diabetes mellitus; dNLR: Derived neutrophil-to-lymphocyte ratio; ECOG: Eastern Cooperative Oncology Group; HALP: Hemoglobin–albumin–lymphocyte–platelet; HR: Hazard ratio; HT: Hypertension; LDH: Lactate dehydrogenase; LYM: Lymphocyte ; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; SII: Systemic immune-inflammation index; WBC: White blood cell.

In the univariate analysis, a higher body mass index was associated with lower mortality (HR 0.943, 95% CI, 0.909–0.978; p=0.001). Melanoma histology was associated with improved survival compared with lung cancer (HR 0.308, 95% CI, 0.187–0.509; p<0.001). Higher baseline LDH levels and inflammatory indices (NLR, dNLR, PLR, and SII) were associated with an increased mortality risk, whereas higher hemoglobin–albumin–lymphocyte–platelet (HALP) scores were associated with reduced mortality. The occurrence of irAEs, modeled as a time-dependent variable, was associated with a numerically lower hazard of death, but did not reach statistical significance (HR 0.693, 95% CI, 0.469–1.025; p=0.066).

In the multivariable analysis, a higher body mass index remained independently associated with improved OS (HR 0.950, 95% CI 0.913–0.988, p=0.011), whereas higher baseline LDH levels were independently associated with an increased risk of mortality (HR 1.020 per 10 U/L increase, 95% CI 1.008–1.031, p<0.001). Melanoma histology was also independently associated with improved survival compared with lung cancer (HR 0.306, 95% CI 0.178–0.526, p<0.001), while renal cell carcinoma was not significantly associated with survival (HR 0.648, 95% CI 0.399–1.054, p=0.081). Higher HALP scores showed a trend toward improved survival after multivariable adjustment, although the association did not reach statistical significance (HR 0.993, 95% CI 0.985–1.001, p=0.087). irAEs, modeled as a time-dependent covariate, were not independently associated with OS (HR 0.747, 95% CI 0.488–1.144, p=0.180).

DISCUSSION

In this real-world cohort of patients with solid tumors treated with nivolumab, irAEs were observed in approximately one-quarter of the patients and were predominantly endocrine in nature, with thyroid dysfunction representing the most frequent toxicity. The development of irAEs was associated with distinct baseline clinical and laboratory features, including prior exposure to radiotherapy. Although patients who developed irAEs demonstrated a numerically lower mortality risk, this association was not statistically significant when the irAE occurrence was modeled as a time-dependent covariate. Baseline LDH levels, body

mass index, and melanoma histology remained independently associated with OS, whereas HALP showed a non-significant trend toward improved survival.

In our cohort, irAEs developed in 25.6% of patients receiving nivolumab, a rate comparable to that of previous retrospective studies reporting irAE frequencies of approximately 20–35% with PD-1 inhibitors and other immune checkpoint inhibitors.[8,9] Baseline demographic and clinical characteristics were largely similar between patients with and without irAEs, including age, performance status, comorbidity burden, tumor histology, prior treatment exposure, and nivolumab duration, in line with previous reports indicating that routine baseline features have limited value in anticipating irAE development.[10,11] The pronounced male predominance in our cohort (approximately 79%) is attributable to the high proportion of lung cancer cases and reflects the established epidemiologic patterns in thoracic malignancies.[12] Overall, the consistency of irAE prevalence and demographic distribution with the existing literature supports the representativeness of our real-world population.

Endocrine toxicities were predominant in our cohort, with hypothyroidism (43.8%), hyperthyroidism (14.1%), adrenal insufficiency (12.5%), and hypophysitis (9.4%) being the most frequent irAEs. These findings are broadly consistent with those of previous studies, which reported that thyroid dysfunction is the most common endocrine toxicity associated with PD-1 inhibition.[13] The median time to irAE onset was 13 weeks, with earlier thyroid dysfunction and later adrenal insufficiency, paralleling the previously described temporal patterns.[13–15] Most irAEs were low to moderate in severity, and permanent nivolumab discontinuation was required in only 7.8% of the events, supporting the generally manageable nature of endocrine-predominant toxicity profiles observed during PD-1 inhibitor therapy.

In the present study, prior radiotherapy was the only independent factor associated with irAE development. Demographic characteristics, performance status, comorbidity burden, and routinely proposed hematologic or inflammatory indices did not demonstrate a significant predictive value. These findings are consistent with contemporary reviews emphasizing the absence of robust and universally applicable biomarkers for irAE prediction, despite extensive investigation of blood counts, inflammatory ratios, and composite immune indices.[16] Although several studies have suggested associations between irAEs and markers, such as NLR, PLR, sex, or nutritional status, these findings have not been consistently replicated across different populations and tumor types.[10,16]

Although baseline LDH showed a borderline association with first irAE development, this association did not remain statistically significant after multivariable adjustment. Elevated LDH may nevertheless reflect greater tumor burden, enhanced immune activation, or increased systemic inflammation. Previous studies have linked elevated LDH levels to adverse oncologic outcomes and, in some settings, to the severity of immune-mediated toxicities.[17,18] Furthermore, prior radiotherapy was independently associated with a more than two-fold increase in the irAE risk. While some pooled analyses have not demonstrated a clear increase in toxicity among patients previously exposed to radiotherapy,[19,20] other real-world investigations have reported similar findings.[21,22] Radiation-induced tissue injury, persistent inflammatory signaling, and immune priming within irradiated tissues may contribute to the enhanced susceptibility to subsequent immune-mediated toxicity during checkpoint blockade.[23]

The relationship between irAEs and survival remains a subject of debate. Numerous retrospective studies have reported improved survival in patients who develop irAEs during immune checkpoint inhibitor therapy.[24,25] However, conventional analyses comparing patients with and without irAEs are susceptible to immortal time bias because patients must survive long enough to experience adverse events. To address this issue, we modeled irAE occurrence as a time-dependent covariate in the survival analysis. Although the hazard ratio remained below 1 (HR 0.747), irAE occurrence was not independently associated with OS after accounting for event timing, suggesting a possible trend toward improved survival. This finding suggests that at least part of the apparent survival advantage observed in previous studies may be attributable to methodological bias, rather than a direct biological effect. Nevertheless, the direction of the observed association remains consistent with the hypothesis that irAEs may reflect enhanced immune activation. Larger prospective studies are needed to clarify whether a true causal relationship exists.

In contrast, several baseline characteristics remained independently associated with OS. Melanoma histology was associated with significantly better survival than lung cancer, consistent with the well-established long-term efficacy of PD-1 inhibition in advanced melanoma.[3,4] Elevated baseline LDH was independently associated with increased mortality, supporting its role as a surrogate marker of tumor burden and aggressive disease biology. Conversely, a higher body mass index was independently associated with improved survival, in line with previous reports suggesting that nutritional

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status and the so-called obesity paradox may influence outcomes during immunotherapy. Although HALP score showed a favorable trend, it did not retain statistical significance after multivariable adjustment.

Limitations of the Study

This study had several limitations. First, its retrospective single-center design may limit generalizability and introduce the possibility of selection and information bias. Second, low-grade or subclinical irAEs may have been under-recognized, resulting in an underestimation of the true incidence of immune-mediated toxicity. Third, although management strategies, such as corticosteroid use and treatment discontinuation, were recorded, detailed information regarding treatment intensity and duration was not consistently available. Fourth, the modest sample size and limited number of adverse events restricted the statistical power for subgroup analyses and the evaluation of individual toxicity categories. In addition, prior radiotherapy may also reflect underlying disease characteristics, such as tumor type, metastatic burden, or previous treatment strategies, rather than representing a direct causal determinant of irAE development. Moreover, detailed radiotherapy characteristics (dose, fractionation, treatment intent, and irradiated site) were not consistently available because of the retrospective design and therefore were not analyzed. The relatively high proportion of endocrine irAEs may partly reflect routine thyroid function monitoring in patients receiving nivolumab, potentially increasing detection of asymptomatic endocrine abnormalities compared with other organ toxicities. Finally, multiple candidate clinical and laboratory variables were evaluated without formal adjustment for multiple comparisons. Accordingly, borderline associations, particularly those involving baseline biomarkers, should be interpreted cautiously and considered exploratory.

CONCLUSION

In this real-world cohort of patients with solid tumors treated with nivolumab, irAEs occurred in approximately one-quarter of patients and were predominantly endocrine. Prior radiotherapy exposure was independently associated with an increased risk of irAEs. When the timing of adverse events was appropriately accounted for using time-dependent survival analysis, irAE occurrence was not independently associated with OS, although a non-significant trend toward improved outcomes was observed. Baseline LDH level and body mass index were independently associated with OS, whereas HALP showed a non-significant trend toward improved survival. These findings highlight the importance of rigorous methodological approaches when evaluating the prognostic significance of irAEs and support further prospective studies incorporating clinical, laboratory, and immunological biomarkers to better characterize the toxicity risk and treatment outcomes during immune checkpoint inhibitor therapy.

Ethics Committee Approval: The study was approved by the Izmir Katip Çelebi University Ethics Committee (no: 0280, date: 09/04/2026).

Informed Consent: The requirement for informed consent was waived by the ethics committee because of the retrospective design of the study.

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ORIGINAL ARTICLE

Global Research Trends in Post-operative Radiotherapy for Non-Small Cell Lung Cancer: A Bibliometric Analysis (2000–2024)

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OBJECTIVE

The role of post-operative radiotherapy (PORT) in non-small cell lung cancer (NSCLC) remains controversial despite advances in radiotherapy techniques and systemic therapies. This study aimed to evaluate global research trends, citation impact, and thematic evolution in PORT research using bibliometric analysis.

METHODS

A bibliometric analysis was conducted using the Web of Science Core Collection database. Original research articles published between 2000 and 2024 on PORT in NSCLC were included. Bibliometric indicators, including publication trends, citation counts, citation rates, journal impact factors, country and institutional productivity, and collaboration networks, were analyzed. Studies were categorized by research objectives using a multilabel classification system. Citation impact was compared between prospective and retrospective studies.

RESULTS

A total of 82 studies met the inclusion criteria, including 7 prospective and 75 retrospective studies. Survival outcomes and oncologic efficacy were the most frequently studied topics, followed by prognostic factor analysis and radiotherapy technique optimization. Prospective studies had significantly higher total citations and annual citation rates compared with retrospective studies ($p<0.001$). These studies were also published in journals with higher impact factors and more frequently in Q1 journals. Collaboration network analysis showed increasing research output from Chinese academic institutions and limited intercontinental collaboration. Recent research trends focused on predictive modeling, biomarker-driven patient selection, and reducing cardiopulmonary toxicity through advanced radiotherapy techniques.

CONCLUSION

Bibliometric patterns reflect ongoing clinical uncertainty regarding PORT in NSCLC. Research has shifted toward individualized treatment strategies and risk-adapted PORT. Future progress will likely depend on prospective trials integrating modern radiotherapy techniques with systemic therapies and biologically informed patient selection.

Keywords: Bibliometric analysis; non-small cell lung cancer; post-operative radiotherapy.

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INTRODUCTION

Non-small cell lung cancer (NSCLC) remains the leading cause of cancer-related mortality worldwide, accounting for approximately 85% of all lung cancer cases.[1] Surgery is the preferred treatment for early-stage NSCLC; however, post-operative recurrence remains a significant challenge. Post-operative radiotherapy (PORT) has been investigated as an adjuvant treatment strategy, particularly for patients with mediastinal lymph node involvement (pN2 disease), to improve local control and overall survival.[2] Despite advancements in radiotherapy techniques, the role of PORT in NSCLC has been debated due to concerns regarding potential toxicity and conflicting evidence from clinical trials.[3,4] Over the past two decades, significant efforts have been made to optimize PORT in NSCLC, including improved patient selection criteria, advanced imaging techniques, and the introduction of intensity-modulated radiotherapy (IMRT) and proton therapy to minimize toxicity.[5,6]

Recent randomized trials have further contributed to the debate regarding the role of PORT in pN2 disease, showing improved locoregional control but no clear overall survival benefit and increased cardiopulmonary toxicity in some settings.[2] These findings have reinforced the need for better patient selection and modern radiotherapy techniques. As a result, research activity in this field has expanded, focusing on prognostic factors, toxicity reduction, and individualized treatment strategies. This study aimed to conduct a bibliometric analysis of the literature on PORT in NSCLC, evaluating research productivity, citation impact, and thematic evolution over time.

MATERIALS AND METHODS

Database and Search Strategy

A bibliometric analysis was conducted to evaluate research trends related to PORT in non-small cell lung cancer (NSCLC). The literature search was performed using the Web of Science Core Collection database, which is widely used for bibliometric studies due to its standardized indexing and citation tracking capabilities.

The search strategy included predefined combinations of disease-related and treatment-related keywords. The search was performed using title-based search terms related to NSCLC and post-operative or adjuvant radiotherapy. The publication period was restricted to studies published between January 01, 2000, and December 31, 2024. The citation search was extended to January 2025 to allow adequate time for citation accumulation for recently published articles. Only original research articles were considered eligible for inclusion. No restrictions were applied regarding country, institution, or study design.

Eligibility Criteria

Studies were included if they met the following criteria: they included patients diagnosed with NSCLC, evaluated post-operative or adjuvant radiotherapy, reported clinical outcomes, toxicity, prognostic factors, recurrence patterns, or treatment-related analyses, and were published as original research articles.

Studies were excluded if they were review articles or systematic reviews, meta-analyses, editorials or letters, conference proceedings, study protocols without reported outcomes, guideline statements, or non-English publications.

The study selection process was conducted in multiple stages. The initial search results were screened by document type, followed by title and abstract screening. Full-text evaluation was performed for potentially eligible studies. Studies that did not report original analytical data were excluded after full-text review.

The initial search yielded 190 records. After exclusion of non-article document types, 102 articles remained. Proceedings papers were then removed, leaving 92 studies. After excluding non-English publications, 90 studies underwent full-text evaluation. Eight studies were excluded after full review due to a lack of original outcome data or being non-analytical publications. A total of 82 studies met the inclusion criteria (Fig. 1).

Data Extraction and Objective Classification

For each included study, the following information was extracted: Publication year, study design (prospective or retrospective), journal name, journal impact factor and 5-year impact factor, journal citation report quartile, country of origin, number of citations, citation rate per year, research objective and study topic, and reported clinical outcomes and toxicity. Citation counts were obtained from the Web of Science database at the time of data extraction.

Bibliometric Indicators and Analysis

Bibliometric indicators were used to evaluate research productivity, citation impact, and collaboration patterns in the field of PORT in NSCLC. The following bibliometric parameters were analyzed: annual publication output, total citation counts, average citations per article, citation rate per year, journal impact factors,

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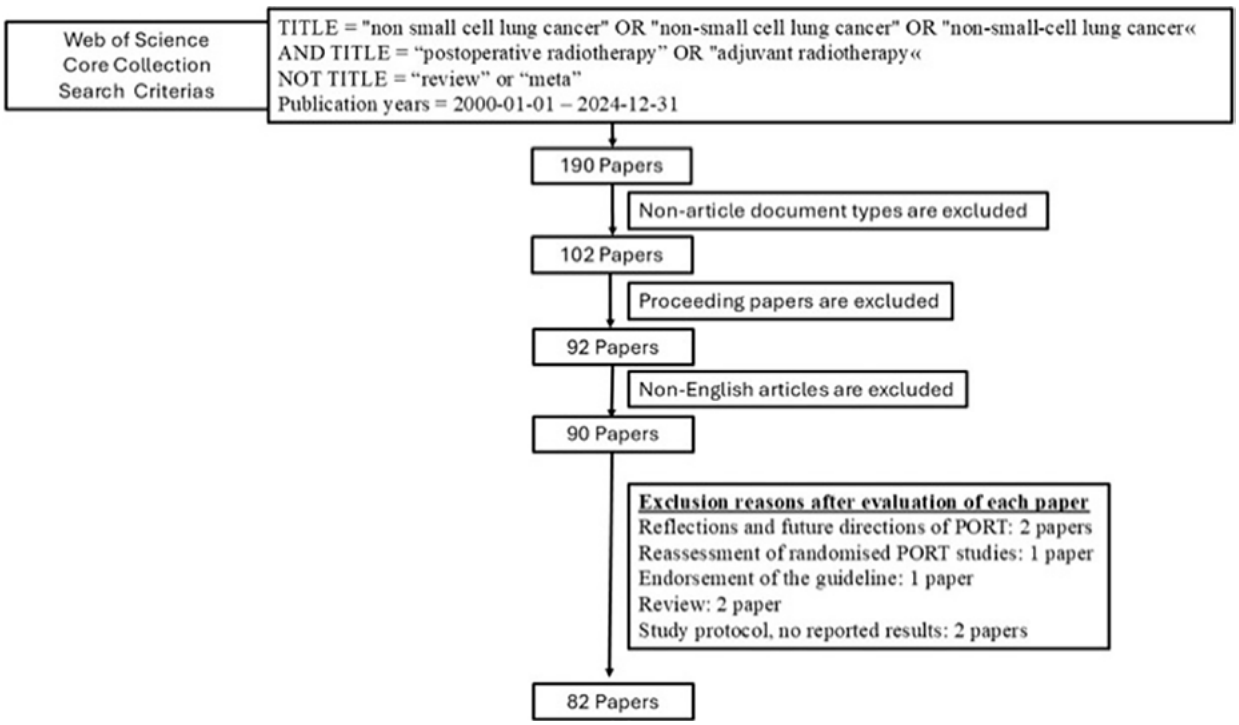

Fig. 1. The PRISMA diagram shows the selection criterias and phases of the studies.

journal quartile distribution, collaboration networks between institutions and countries, and research objective distribution and thematic trends. Citation rate per year was calculated by dividing the total number of citations by the number of years since publication.

Research Objective Classification

To better understand the thematic distribution of research topics, each study was categorized according to its primary research objective. Because many studies addressed multiple research questions, a multilabel classification system was used. Studies could therefore be assigned to more than one objective category.

Objective domains included survival and oncologic outcomes, prognostic or predictive clinical factors, toxicity and safety outcomes, radiotherapy techniques and dosimetry, recurrence patterns and failure analysis, prediction models, nomograms, or artificial intelligence, timing and sequencing of PORT, biomarkers and molecular predictors, practice patterns and database analyses, and quality of life and functional outcomes.

Collaboration and Network Analysis

Collaboration patterns between countries and institutions were analyzed using co-authorship and institutional collaboration networks. Network visualization maps were generated to illustrate relationships between research institutions and countries contributing to PORT research. These analyses were used to identify major research clusters and collaboration patterns within the field.

Statistical Analysis

Statistical analyses were performed to compare bibliometric indicators between study groups, particularly prospective and retrospective studies. Continuous variables were summarized using mean and standard deviation or median and interquartile range, depending on data distribution. Normality of distributions was assessed using the Shapiro–Wilk test.

For comparisons between two groups, the independent samples t-test was used for normally distributed variables, and the Mann–Whitney U test was used for non-normally distributed variables. Categorical variables were compared using the Chi-square test.

Spearman's rank correlation was performed to assess the association between publication year and citation rate. All statistical tests were two-sided, and a $p<0.05$ was considered statistically significant. Statistical analyses were performed using statistical software.

Table 1 Distribution of studies by research objective (n=82)

Objective group	Description of objective domain	Number and percentage of studies (n, %)
Survival benefit of PORT	Overall survival, cancer-specific survival, subgroup survival benefit, comparative effectiveness	35 (42.7)
Prognostic/predictive clinical factors	Clinicopathologic factors (LNR, nodal features, margins, histology, pulmonary function, and subgroup selection) associated with PORT benefit	27 (32.9)
Toxicity and safety outcomes	Radiation pneumonitis, lymphopenia, cardiopulmonary toxicity, treatment morbidity	15 (18.3)
Radiotherapy techniques/dosimetry	IMRT versus 3D-CRT versus proton therapy, dosimetric comparisons, contouring protocols, treatment delivery analysis	12 (14.6)
Recurrence patterns/failure analysis	Patterns of locoregional failure, recurrence risk mapping, and control rates	8 (9.8)
Prediction models/nomograms/AI	Survival prediction tools, dosimetric models, risk calculators, scoring systems	7 (8.5)
Timing and sequencing of PORT	Optimal timing, interval from surgery/chemotherapy, treatment sequencing strategies	5 (6.1)
Biomarkers/molecular predictors	Immune markers, gene mutations, miRNA, angiogenic markers, tumor microenvironment	5 (6.1)
Practice patterns/database analyses	National registry studies, utilization trends, and real-world practice patterns	5 (6.1)
Quality of life/functional outcomes	Quality of life, long-term pulmonary function, survivorship outcomes	2 (2.4)

PORT: Post-operative radiotherapy; LNR: Lymph node ratio; IMRT: Intensity-modulated radiotherapy; 3D-CRT: Three-dimensional conformal radiotherapy; AI: Artificial intelligence. Studies could be classified into more than one objective domain; therefore, totals exceed 100%.

RESULTS

The selection process yielded 82 eligible studies. Most focused on survival outcomes and oncologic effectiveness of PORT, followed by prognostic factors, radiotherapy techniques, and toxicity. Because many studies addressed multiple objectives, totals across domains exceeded the number of included studies. Survival benefit was the dominant theme, with increasing attention to risk stratification and technical optimization (Table 1). Figure 2 illustrates the keyword co-occurrence network generated using VOSviewer. PORT emerged as the central and most strongly connected keyword, demonstrating its pivotal role in the literature.

Among the 82 studies, 7 (8.54%) were prospective, and 75 (91.46%) were retrospective. The total citation count was 1972, with a mean of 24.04 citations per article. Prospective studies had a significantly greater

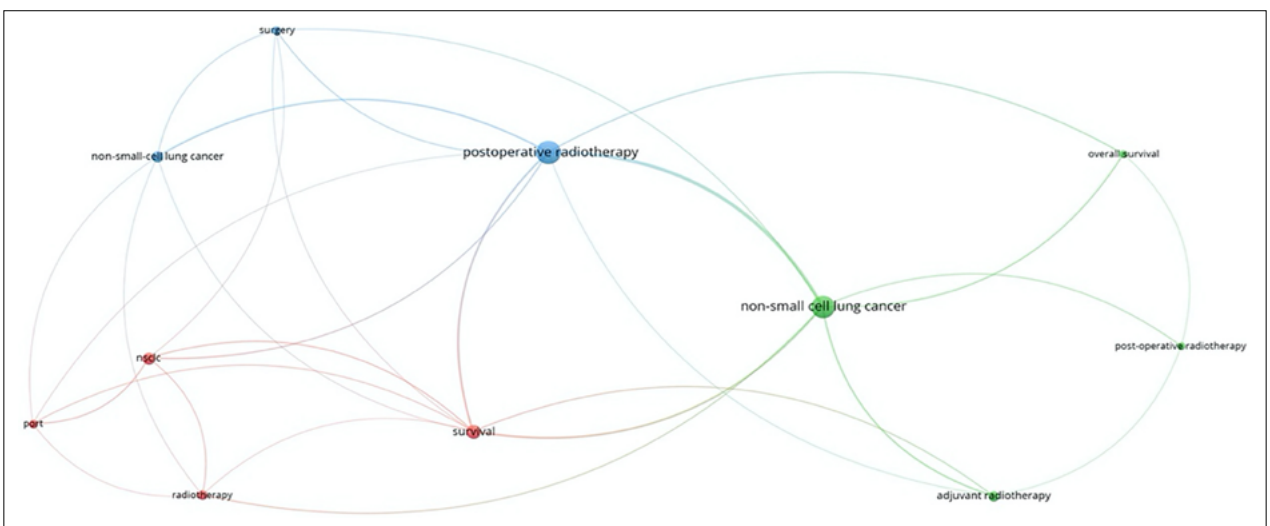

Fig. 2. Illustration of keyword co-occurrence network map analysis.

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Table 2 Comparison of total citations and average citations per year according to the study design

	Total citation count	Average citation per year	p*
Prospective (n=7)			
Mean	95.00	3.65	<0.05
Median	85.00	3.26	
Range	0.00–197.00	0.00–7.58	
Retrospective (n=75)			
Mean	17.42	0.67	<0.05
Median	9.00	0.34	
Range	0.00–106.00	0.00–4.98	

*: Student's t-test.

impact than retrospective studies, with higher total citations (mean 95.0 vs. 17.4) and higher annual citation rates (mean 3.65 vs. 0.67; p<0.001) (Table 2). They were also published in higher-impact journals, with greater 2024 and 5-year JIF values (p=0.002 and p<0.001, respectively) (Table 3). While journal subject categories were similar between groups, prospective studies appeared more often in Q1 journals (71.4% vs. 24.0%; p=0.035) (Table 4).

Collaboration analysis showed that PORT research is concentrated in major academic centers, particularly in China, where dense intra-national collaborations were observed. Intercontinental links were less common. Country-level mapping confirmed China as the leading contributor, with strong connections to several European nations, whereas earlier research activity was more prominent in Europe and Japan (Figs. 3, 4). Co-authorship networks formed distinct institutional clusters linked by a limited number of bridging investigators. Recent years have seen the expansion of research teams and a growing emphasis on predictive modeling, advanced radiotherapy techniques, and individualized treatment strategies (Fig. 5).

DISCUSSION

This bibliometric analysis provides a comprehensive overview of the scientific literature on PORT in NSCLC published between 2000 and 2024. The findings demonstrate that research activity in this field has been driven by persistent clinical uncertainty regarding the survival benefit of PORT, concerns about treatment-related toxicity, and ongoing efforts to improve patient selection through risk stratification and predictive modeling.

Table 3 Comparison of the 2024 journal impact factor and 5-year journal impact factor according to the study design

	2024 journal impact factor	5-year journal impact factor	p*
Prospective (n=7)			
Mean	13.14	15.82	0.002
Median	6.50	9.90	
Range	0.70–35.90	3.70–42.00	
Retrospective (n=75)			
Mean	5.00	5.02	<0.05
Median	3.30	3.40	
Range	0.50–43.40	0.50–38.20	

*: Student's t-test.

Table 4 Comparison of JCR category and JCR category quartile according to the study design

	Prospective (n=7), n (%)	Retrospective (n=75), n (%)	p*
JCR Category			
Oncology	6 (85.7)	64 (85.3)	N.S.
Non-oncology	1 (14.3)	11 (14.7)	
JCR category quartile			
Q1	5 (71.4)	18 (24.0)	0.035
Q2	0	28 (37.3)	
Q3	1 (14.3)	23 (30.7)	
Q4	1 (14.3)	6 (8.0)	

*: Chi-square. JCR: Journal Citation Reports.

One of the most notable findings of this study is the overwhelming predominance of retrospective studies in the literature. More than 90% of the included studies were retrospective in design, highlighting the difficulty of conducting prospective and randomized studies in the post-operative setting. Despite their small number, prospective studies had significantly higher citation counts and higher annual citation rates and were more frequently published in high-impact journals. This suggests that prospective trials have a disproportionate influence on the scientific direction of the field and play a major role in shaping clinical guidelines and treatment recommendations. The high citation impact of prospective studies likely reflects the influence of landmark randomized trials evaluating PORT in pN2 disease, including the Lung ART and PORT-C trials, which have significantly influenced modern clinical decision-making.[2,7]

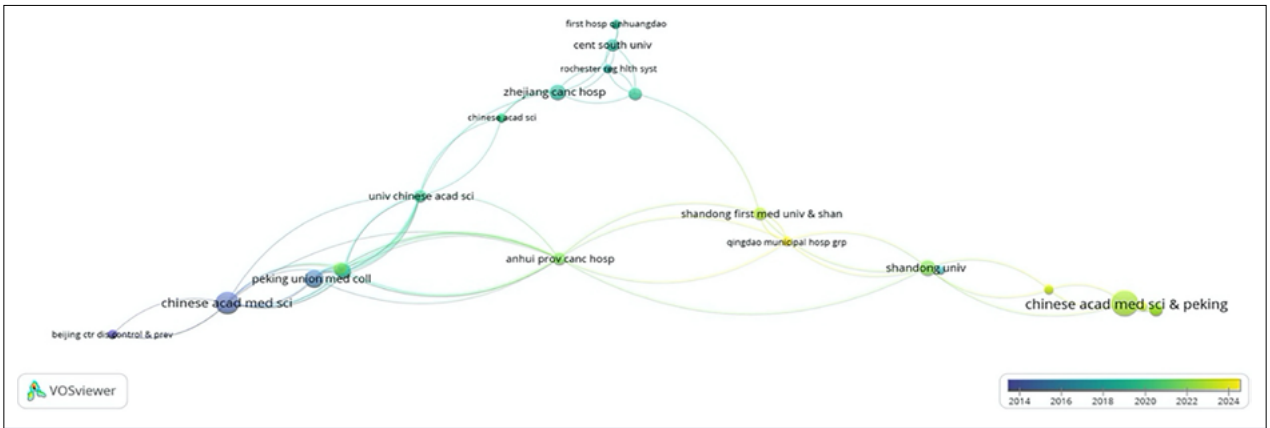

Fig. 3. Illustration of institutional collaboration network map analysis.

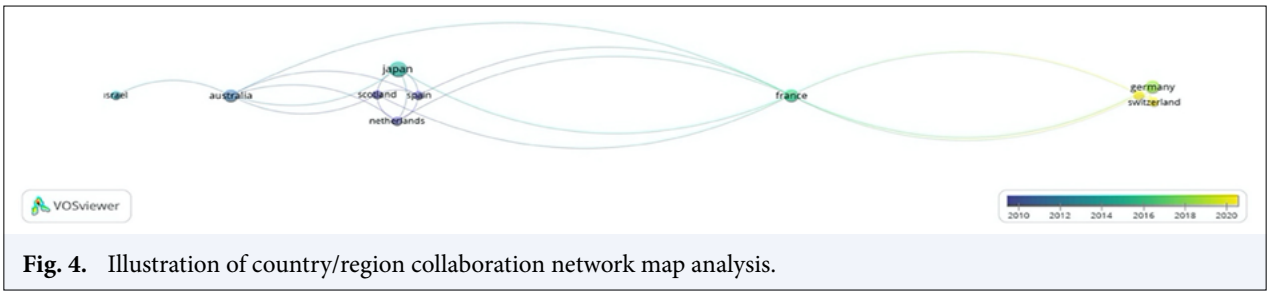

Fig. 4. Illustration of country/region collaboration network map analysis.

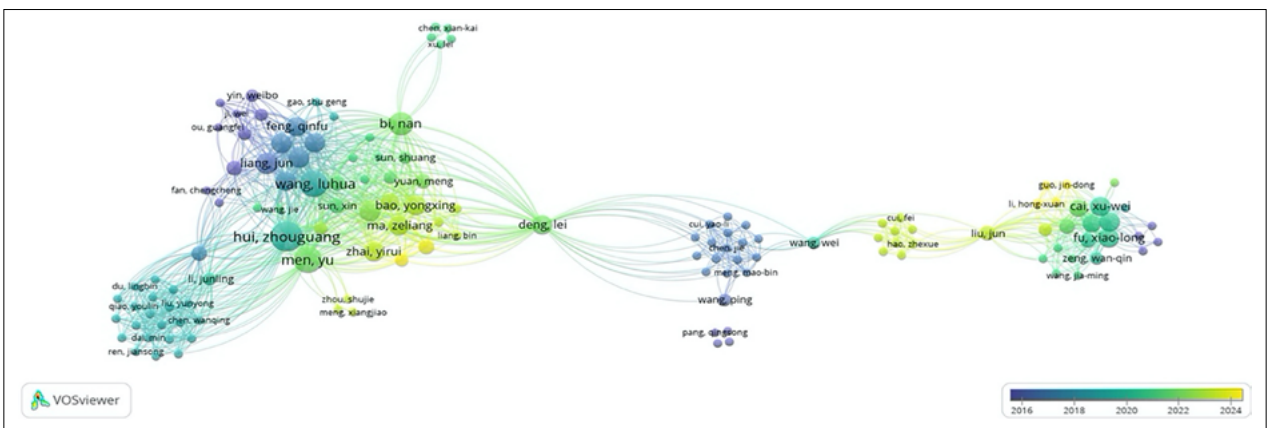

Fig. 5. Illustration of co-authorship network showing investigator clusters and bridging researchers.

The thematic distribution of research objectives demonstrates that the primary focus of PORT research has remained survival outcomes and oncologic efficacy. This finding reflects the central clinical question that has persisted for decades: whether PORT improves overall survival in patients with resected NSCLC, particularly in those with mediastinal lymph node involvement. Earlier meta-analyses suggested a potential detrimental effect of PORT, largely attributed to outdated radiotherapy techniques and increased cardiopulmonary toxicity.[3] However, more recent studies using modern radiotherapy techniques have reported improved locoregional control and possible survival benefits in selected high-risk patients.[8,9] The continued dominance of survival-focused studies in the literature indicates that the survival impact of PORT remains unresolved.

Over time, research focus has shifted toward identifying subgroups of patients most likely to benefit from PORT rather than evaluating PORT as a uniform treatment approach. A substantial number of studies have investigated prognostic factors such as lymph node ratio, number of involved lymph nodes,

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extracapsular extension, surgical margin status, histological subtype, and pulmonary function as predictors of PORT benefit.[10–14] This reflects a broader paradigm shift in oncology toward personalized treatment strategies. Instead of applying PORT uniformly to all patients with nodal disease, current research increasingly supports a selective approach based on individual risk factors and expected toxicity.

The strongest co-occurrence relationship was observed between PORT and non-small cell lung cancer, indicating that most publications primarily focus on the role of PORT in surgically treated NSCLC. Three major thematic clusters were identified. The blue cluster represents studies focusing on surgery and PORT, the green cluster emphasizes clinical outcomes including overall survival and adjuvant radiotherapy, whereas the red cluster reflects traditional research centered on radiotherapy, survival, and PORT. Overall, the network demonstrates that survival outcomes and the integration of PORT into multimodal treatment strategies constitute the dominant research themes in this field.

Another important emerging research area is the development of prediction models, nomograms, radiomics, and dosiomic analyses. These approaches aim to integrate clinical, pathological, and dosimetric variables to estimate survival benefit or toxicity risk on an individual patient basis. Several recent studies have focused on predictive modeling and artificial intelligence-based decision support systems for PORT patient selection.[15–18] The increasing number of studies in this area suggests that future decision-making regarding PORT may rely more on predictive modeling and data-driven tools rather than traditional staging parameters alone. This trend also reflects the growing integration of data science and radiation oncology research.

Toxicity and treatment safety remain important research themes in the PORT literature. Historical studies suggested increased cardiopulmonary toxicity associated with PORT, which contributed to the decline in its routine use in earlier decades.[3] However, advances in radiotherapy techniques, including IMRT, image-guided radiotherapy, and proton therapy, have significantly reduced radiation exposure to organs at risk and improved the therapeutic ratio.[6,19,20] The continued presence of toxicity-focused studies in recent years indicates that safety considerations remain a major factor influencing PORT utilization, particularly in patients with limited cardiopulmonary reserve.

The collaboration network analysis demonstrated that research activity in this field has increasingly shifted geographically over time. Earlier studies were predominantly conducted in European and Japanese institutions, whereas more recent research output is dominated by Chinese academic centers. This shift likely reflects increased research funding, expanding radiotherapy infrastructure, and the availability of large national cancer databases that facilitate retrospective analyses. Despite the overall increase in research productivity and institutional participation, international collaboration networks remain relatively limited. Greater international cooperation may improve study quality, increase sample sizes, and facilitate prospective multicenter trials.

Overall, the bibliometric patterns observed in this study mirror the clinical evolution of PORT in NSCLC. Early research focused on determining whether PORT should be used at all, whereas more recent studies focus on identifying which patients may benefit, how toxicity can be minimized, and how treatment decisions can be individualized. This transition reflects a shift from a uniform treatment paradigm toward precision radiotherapy and biologically guided treatment strategies.[15–18,21]

This study has several limitations inherent to bibliometric analyses. First, the analysis was limited to the Web of Science database, and relevant publications indexed in other databases, such as Scopus or PubMed, were not included. Second, the search strategy was restricted to title-based search terms, which may have resulted in the exclusion of relevant studies that did not include specific keywords in the title. Third, citation counts are influenced by publication year, journal impact factor, and research visibility, and therefore do not necessarily reflect methodological quality or clinical importance. Fourth, self-citations were not excluded from citation analysis. Finally, the relatively small number of prospective studies limited the statistical power of comparisons between study designs.

CONCLUSION

This bibliometric analysis demonstrates that research on PORT in NSCLC has been dominated by retrospective studies, whereas prospective studies, although limited in number, have had a greater scientific impact. The literature has primarily focused on survival outcomes and patient selection, reflecting ongoing clinical uncertainty regarding the role of PORT, particularly in patients with mediastinal nodal disease. Over time, research trends have shifted toward risk stratification, predictive modeling, and toxicity reduction using modern radiotherapy techniques. These findings indicate that the role of PORT is becoming increasingly individualized rather than routine.

Ethics Committee Approval: Since this study is a bibliometric analysis based entirely on publicly available secondary data and does not involve any human participants or animal subjects, ethics committee approval was not required.

Informed Consent: Informed consent was obtained from all participants.

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ORIGINAL ARTICLE

Prolonged Fraction Duration Reduces Tumoricidal Efficacy in a Breast Cancer Cell Line: A Simulated Model of Gated Radiotherapy

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OBJECTIVE

Respiratory-controlled radiotherapy (breath-hold and gating) reduces cardiac exposure in breast cancer but prolongs and fragments intrafraction delivery, lowering the effective dose rate, an effect that is accentuated when patient compliance is imperfect. We tested whether prolonging the delivery of a single 2 Gy fraction compromises tumoricidal efficacy in breast cancer cells, independent of total dose.

METHODS

Michigan Cancer Foundation-7 (MCF-7) cells received 2 Gy delivered rapidly and continuously (reproducing tangential treatment) or as intermittent pulses over 10 or 20 min (reproducing gating), with a non-irradiated control. Viability was assessed by WST-1 at 24 and 48 h, and DNA double-strand break signaling by γH2AX immunofluorescence and flow cytometry (γH2AX and phospho-ATM [pATM]) at 6, 12 and 24 h.

RESULTS

Continuous delivery produced the lowest viability, significantly below control at 24 h (81.2%, p=0.0072) and 48 h (79.7%, p=0.0047); viability rose with delivery time (24 h: 88.4% and 93.3% for 10 and 20 min). Immunofluorescence γH2AX foci were highest after continuous delivery and decreased with delivery time, exceeding control at all-time points. Flow-cytometric γH2AX and pATM were biphasic (peak 6 h, nadir 12 h, rise 24 h), with continuous and 10-min groups above control and fewest undamaged cells after continuous delivery.

CONCLUSION

Prolonging fraction delivery reduced tumoricidal efficacy in MCF-7 cells, consistent with sublethal damage repair at lower, pulsed dose rates. Intrafraction delivery time is a potentially modifiable parameter that warrants consideration when gating or breath-hold extends beam-on time.

Keywords: Breast neoplasms; cell survival; DNA damage; dose-response relationship; radiation; gated radiotherapy, histones (γH2AX).

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INTRODUCTION

Breast cancer is the most frequently diagnosed cancer in women worldwide,[1] and radiotherapy is integral to its locoregional management, reducing recurrence and improving survival.[2] These gains are tempered by a recognized risk of late cardiac toxicity. The risk of ischemic heart disease rises with the mean heart dose, by approximately 7.4% per gray in the analysis of Darby et al.[3] and by about 4% per gray as estimated by Sardaro et al.,[4] and the contribution of radiotherapy to non-cancer mortality has been confirmed in modern dose- and trial-based analyses.[5]

To limit cardiac exposure, respiratory-controlled techniques (deep inspiration breath-hold and respiratory gating) have become standard for left-sided breast irradiation, exploiting displacement of the heart away from the chest wall during deep inspiration to lower heart dose.[6,7] Their effectiveness, however, depends on the patient consistently reproducing the target respiratory phase. In conventional tangential treatment, the prescribed dose is delivered rapidly and without interruption (continuous delivery). Under gating, by contrast, the beam is enabled only during the appropriate part of the breathing cycle, so that delivery becomes intermittent; when patient compliance is imperfect, due to anxiety or an irregular breathing pattern, the correct respiratory window is harder to capture and the beam-on time can be substantially prolonged.[7]

Prolonging and fragmenting the delivery of a fixed dose lowers the effective dose rate and converts a single rapid exposure into a series of pulses. Dose rate is an established modifier of radiobiological effect: at lower dose rates, sublethal damage repair operating during irradiation can reduce cytotoxicity.[8–11] Consistent with this, *in vitro* and modeling studies of protracted delivery have reported increased clonogenic survival and a reduced biological effect as delivery time lengthens.[12–16] This raises a clinically important concern, that the very prolongation introduced to spare the heart might, in some patients, diminish the tumoricidal effect on breast cancer cells, yet this scenario has not been examined in a cell-culture model that reproduces gated delivery one-to-one.

To address this gap, we developed an *in vitro* model that simulates the range of beam-on times encountered in practice. A single 2 Gy dose was delivered to Michigan Cancer Foundation-7 (MCF-7) breast cancer cells under three schedules: a rapid, uninterrupted (continuous) exposure reproducing conventional tangential treatment; an intermittent delivery over 10 min representing a compliant gated patient; and an intermittent delivery over 20 min representing a patient with greater difficulty maintaining the gating window. Cell viability and the DNA double-strand break response were assessed, using γH2AX, a sensitive and specific marker of double-strand breaks,[17,18] together with phospho-ATM (pATM), to determine whether prolonged, intermittent delivery compromises tumoricidal efficacy.

MATERIALS AND METHODS

Cell Culture

The human breast cancer cell line MCF-7 was cultured in RPMI 1640 with high glucose, supplemented with 10% fetal bovine serum and 1% penicillin, at 37°C in a humidified atmosphere with 5% CO_2. At 80–90% confluence, cells were subcultured with 0.5% trypsin-EDTA according to the manufacturer's protocol, resuspended in fresh medium, and seeded onto sterile plates. Cells were incubated for 24 h before irradiation to allow attachment.

Irradiation and Experimental Groups

Irradiation was performed with a TrueBeam STx linear accelerator (Varian Medical Systems, Palo Alto, CA, USA) using 6 MV photons at a source-to-surface distance of 100 cm over a 20×20 cm field, at a single fraction dose of 2 Gy. Delivery schedules were modeled on breast cancer patient treatment plans with the assistance of a medical physicist to reproduce, at the cellular level, the beam-on profiles encountered in clinical practice. Four groups were studied (Fig. 1): A non-irradiated control; a continuous group, in which 2 Gy was delivered rapidly and without interruption to simulate conventional two-field tangential breast irradiation (the beam itself was brief; the total time on the machine was approximately 1 min and was attributable to gantry rotation between the two tangential fields rather than to protraction of the dose); an intermittent group, in which the same 2 Gy was delivered as interrupted beam pulses over a total of 10 min to simulate a compliant patient treated with respiratory gating; and a second intermittent group, in which 2 Gy was delivered over 20 min to simulate a patient with greater difficulty maintaining the gating window. The control was handled identically and transported alongside the irradiated groups.

Cell Viability (WST-1 Assay)

Cells were seeded at 5×10^3 cells/100 µL per well in 96-well plates. At 24 and 48 h after irradiation, 10 µL/well of WST-1 reagent (ScienCell Research Laboratories, Carlsbad, CA, USA) was added and the plates were

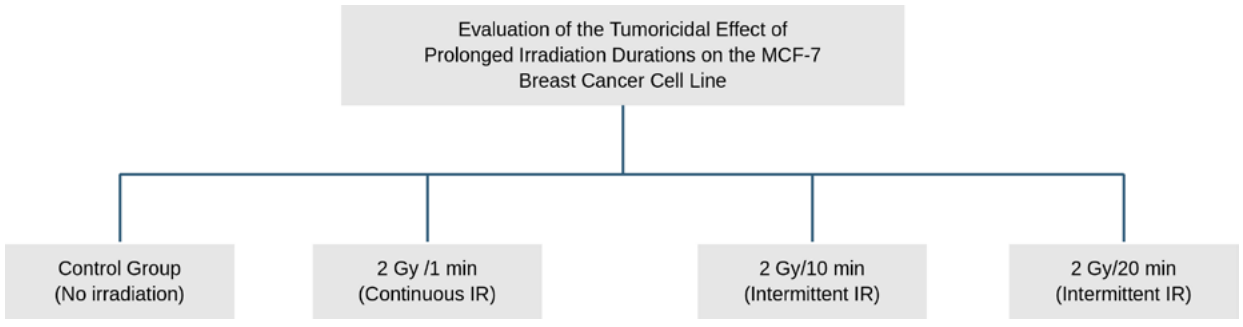

Fig. 1. Experimental groups and irradiation protocol. Michigan Cancer Foundation-7 cells received 2 Gy delivered rapidly and continuously (simulating conventional tangential treatment), or as intermittent pulses over 10 or 20 min (simulating respiratory gating), with a non-irradiated control.

incubated for 2 h at 37°C. Absorbance was measured at 450 nm on a microplate spectrophotometer (Thermo Scientific, Waltham, MA, USA). Viability was expressed as a percentage of the time-matched control.

γH2AX Immunofluorescence

At 6, 12 and 24 h after irradiation (1×10^4 cells per coverslip in 12-well plates), cells were fixed in 4% formaldehyde for 15 min at room temperature, washed with PBS, and blocked with Super Block protein blocking reagent (ScyTek Laboratories, Logan, UT, USA) for 60 min. Coverslips were incubated overnight at 4°C in a humidified chamber with anti-phospho-histone H2A.X (Ser139) primary antibody (1:200), then for 1 h at room temperature with a Texas Red-X-conjugated goat anti-mouse IgG secondary antibody (1:500). Nuclei were counterstained with DAPI-containing mounting medium, and slides were imaged by fluorescence microscopy at ×100. γH2AX foci were quantified with ImageJ.

γH2AX and pATM flow Cytometry

The DNA damage response was assessed with the Muse Multi-Color DNA Damage Kit (MCH200107, Luminex, Austin, TX, USA) according to the manufacturer's protocol. At 6, 12 and 24 h after irradiation (3×10^5 cells per well in 6-well plates), cells were harvested with trypsin, fixed and permeabilized, and stained with anti-pATM (Ser1981)-PE and anti-phospho-histone H2A.X (Ser139)-PECy5 for 30 min at room temperature in the dark. After washing, cells were resuspended in assay buffer and analyzed on a Muse Cell Analyzer.

Statistical Analysis

Analyses were performed in GraphPad Prism v8 (GraphPad Software, Boston, MA, USA). Data are presented as mean±standard deviation of at least three independent experiments. Normality and homogeneity of variance were checked before parametric testing. Differences between groups were evaluated by two-way ANOVA (factors: Irradiation group and time), with Dunnett's post hoc test comparing each irradiated group with the control. $P<0.05$ was considered statistically significant.

RESULTS

Experimental Design and Included Data

Several independent experiments were performed. Experiments with protocol deviations affecting the control group – those in which the control was not transported to the irradiation area together with the other groups, or in which plates were not collected at the prescribed time after preparation – were excluded. The analyses below are based on the experiments in which all four groups, including the control, were prepared, transported, and irradiated under identical conditions.

Continuous Delivery Produced the Greatest Loss of Cell Viability

WST-1 viability showed a consistent, delivery-time-dependent pattern at both time points. Relative to the time-matched control (set to 100%), viability at 24 h was 81.2% for the continuous (tangential) group, 88.4% for the intermittent 10-min group, and 93.3% for the intermittent 20-min group; at 48 h, the corresponding values were 79.7%, 89.8%, and 96.0%. Viability increased monotonically with delivery time at both time points, with the 20-min group closest to control levels; the continuous group was the only group significantly below control (24 h, $p=0.0072$; 48 h, $p=0.0047$), whereas neither intermittent group differed significantly from control. The ordering was preserved between 24 and 48 h, indicating a stable rather than transient effect (Fig. 2).

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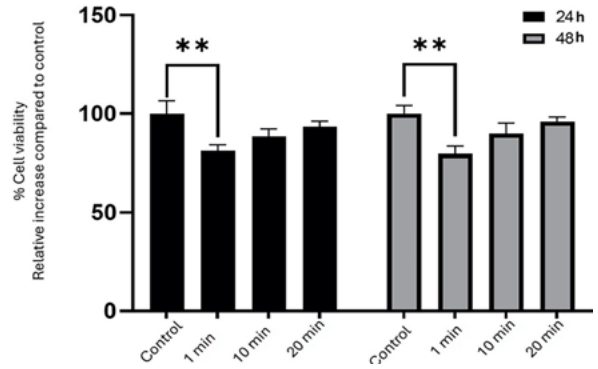

Fig. 2. Cell viability (WST-1) at 24 and 48 h, expressed as a percentage of the time-matched control. Only continuous delivery was significantly below control (**p<0.01); viability increased with delivery time. Bars show mean±standear deviation.

γH2AX foci by Immunofluorescence Decreased as Delivery Time Increased

All irradiated groups contained markedly more γH2AX foci than control at every time point (p<0.05), and the number of foci decreased monotonically from the continuous group through the 10-min to the 20-min group. Foci counts (total per 50 analyzed cells) for the control, continuous, 10-min and 20-min groups were 118, 277, 262, and 248 at 6 h; 113, 266, 251, and 240 at 12 h; and 98, 205, 187, and 162 at 24 h, respectively. Irradiated groups thus carried approximately twice the foci burden of control, with the continuous group consistently highest. In every group, foci declined from 6 to 24 h, consistent with progressive resolution of double-strand breaks, while a low background level of foci persisted in the non-irradiated control (Table 1; Figs. 3, 4).

γH2AX and pATM by Flow Cytometry

Flow cytometry quantified the proportions of undamaged (negative) cells and of γH2AX- and pATM-positive cells. The proportion of undamaged cells was lowest after continuous delivery and highest in the control at every time point (e.g., 58.4% vs. 82.2% at 24 h), with the intermittent 10-min and 20-min groups intermediate, indicating that the greatest DNA damage occurred after continuous delivery. Both γH2AX and pATM followed a biphasic time course, with the signal highest at 6 h, declining at 12 h and rising again at 24 h. Across the 3 time points, the continuous and intermittent 10-min groups were significantly increased relative to

Table 1 γH2AX foci counts (total per 50 analyzed cells) by irradiation group and time point

Group	6h	12h	24h
Control	118	113	98
Continuous (tangential)	277	266	205
Intermittent, 10 min	262	251	187
Intermittent, 20 min	248	240	162

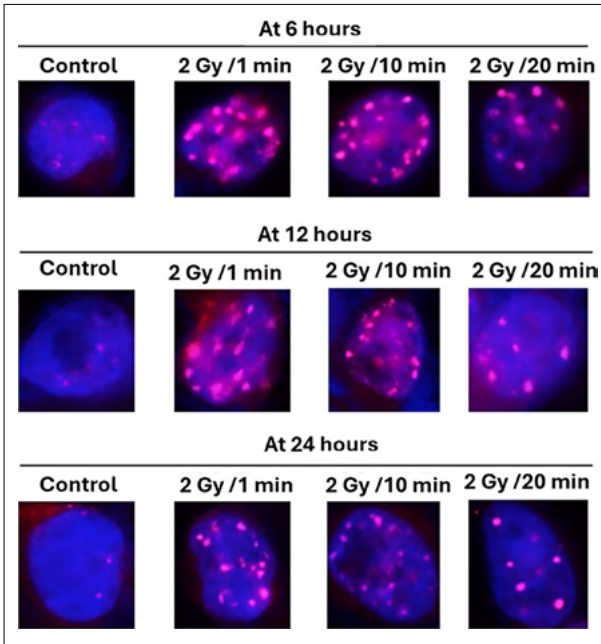

Fig. 3. Representative fluorescence microscopy images of γH2AX foci (red) and DAPI-stained nuclei (blue) across groups and time points.

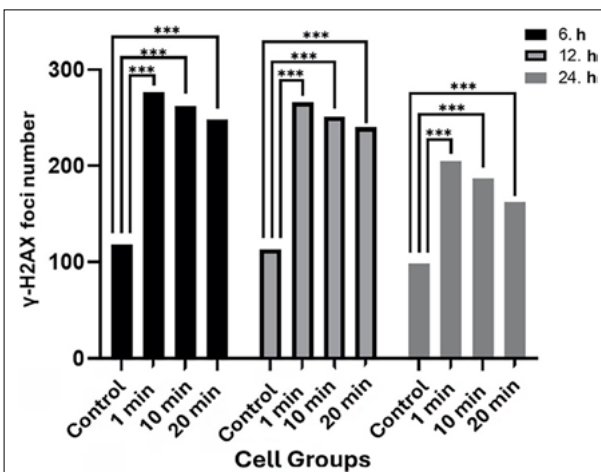

Fig. 4. Quantification of γH2AX foci (total per 50 cells) over time. Foci were highest after continuous delivery and decreased with longer delivery time; all irradiated groups exceeded control at every time point (p<0.05).

control ($p<0.05$), and the overall rank order of damage paralleled the viability and immunofluorescence findings (control lowest, followed by the 20-min, 10-min, and continuous groups) (Fig. 5).

DISCUSSION

In this one-to-one *in vitro* simulation of gated breast radiotherapy, prolonging the delivery of a single 2 Gy fraction reduced its tumoricidal efficacy. Rapid, continuous delivery (reproducing conventional tangential treatment) produced the greatest loss of viability and the most DNA double-strand break signal, whereas fragmenting the same dose over 10 or 20 min, as occurs during respiratory gating, was associated with progressively higher viability and fewer residual γH2AX foci. This pattern is consistent with the classical inverse dose-rate effect, in which lower, protracted dose rates allow sublethal damage repair to proceed during irradiation and thereby reduce cytotoxicity.[8,11]

The three independent readouts were mutually concordant. Viability was lowest, immunofluorescence γH2AX foci were highest, and the undamaged (negative) flow-cytometric fraction was smallest after continuous delivery, with the intermittent groups intermediate and the 20-min group closest to control. This internal consistency strengthens the central observation that intrafraction delivery time, independent of total dose, modulates the biological effect on breast cancer cells, and it provides a cellular correlate for the clinical scenario, in which patient non-compliance prolongs the gating window.

Our findings extend a body of radiobiological work on protracted delivery to a breast cancer model. Sterzing et al.[12] reported increased clonogenic survival of TK6 and MeWo cells with dose protraction. Shibamoto et al.[13] observed a 9–14% reduction in biological effect during intermittent exposure of EMT6 and SCCVII cells, estimating that an 8–16% dose increase would be required to compensate. Moiseenko et al.[14] showed that extending delivery time increased survival and decreased residual γH2AX. Wang et al.[15] predicted clinically meaningful reductions in effective dose for fraction times of 15–45 min, particularly for tumors with low α/β and short repair half-times. Keall et al.[16] demonstrated a reproducible survival increase with prolonged gated- and IMRT-type delivery, identifying overall delivery time as the dominant determinant.

Mechanistically, delivering 2 Gy over 10 or 20 min corresponds to mean dose rates of approximately 0.2 and 0.1 Gy/min, within the low-dose-rate range, while

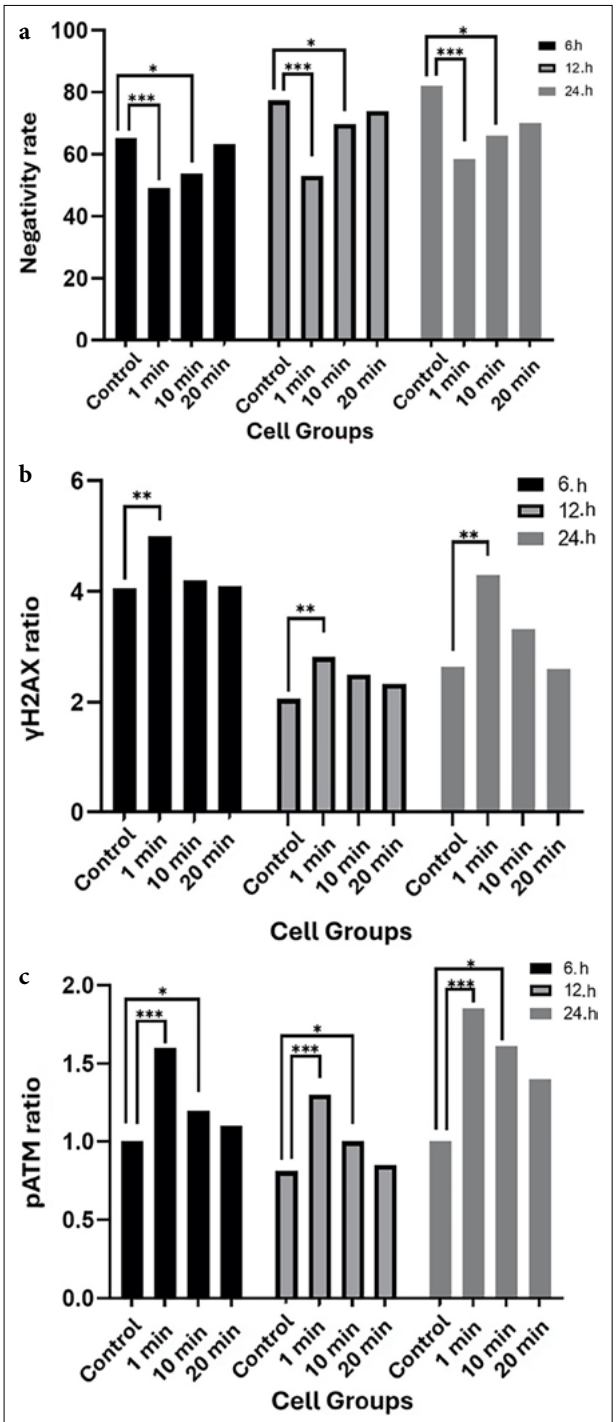

Fig. 5. Flow-cytometric analysis at 6, 12 and 24 h: (a) Negativity (undamaged cells), (b) γH2AX, and (c) phospho-ATM (pATM). The undamaged fraction was lowest after continuous delivery; γH2AX and pATM followed a biphasic course (peak 6 h, nadir 12 h, secondary rise 24 h), with the continuous and 10-min groups elevated above control. Bars show mean±standard deviation.

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the on–off beam pattern of gating further resembles a pulsed low-dose-rate exposure, in which inter-pulse intervals permit partial recovery.[8,11] Lower dose rates have been associated with attenuated accumulation of double-strand breaks and reduced damage signaling over time in both tumor and normal cells,[8–10] providing a plausible basis for the reduced tumoricidal effect seen with longer delivery.

γH2AX and pATM displayed a biphasic time course, peaking at 6 h, declining at 12 h, and rising again at 24 h. The early peak and subsequent decline are consistent with rapid recognition of double-strand breaks followed by effective repair.[17] A secondary rise at 24 h may reflect unrepaired or misrepaired damage, secondary oxidative injury, or progression to apoptosis, during which internucleosomal DNA fragmentation can itself elevate γH2AX.[18] The two methods captured complementary aspects of the response: flow cytometry quantified the total signal across the population, whereas immunofluorescence enumerated discrete nuclear foci, and their combined use provides a more complete picture of damage dynamics.[18] A low level of γH2AX was present in the non-irradiated control, as expected for a transformed cell line with intrinsic genomic instability, and this did not alter the consistent ranking of damage across delivery schedules.

These results have a direct clinical corollary. Respiratory-controlled techniques are adopted specifically to reduce cardiac dose,[3,4,6,7] but they inherently lengthen and fragment beam delivery, and our data suggest that this prolongation may, in turn, attenuate the tumoricidal effect on breast cancer cells. The effect was modest and, in formal testing, reached significance only for the continuous group relative to the non-irradiated control; nonetheless, the consistent trend across three concordant endpoints indicates that intrafraction delivery time is a potentially modifiable parameter. Where clinically feasible, minimizing beam-on time – through patient coaching, stable breath-hold, and efficient gating – may help preserve tumor control while retaining the cardiac benefit and the trade-off may be most relevant in patients who struggle to maintain the gating window.

Limitations of the Study

This study has limitations. It used a single cell line (MCF-7), a single dose (2 Gy), and three delivery durations, with viability and marker-based DNA damage endpoints rather than clonogenic survival; these choices were made to isolate the effect of intrafraction delivery time under clinically relevant conditions. The number of analyzable replicates was limited for some flow-cytometric endpoints, so those comparisons should be regarded as supportive rather than definitive. Statistical testing compared each irradiated group with the non-irradiated control (Dunnett's test); the irradiated groups were not compared directly with one another, so the delivery-time gradient across the viability and DNA-damage endpoints represents a consistent numerical trend across three concordant readouts rather than a formally tested between-group difference. Clonogenic assays, apoptosis markers (e.g., Annexin V and caspase-3), reactive oxygen species measurement, and repair-pathway profiling (e.g., Rad51 and Ku70/80) would further define the underlying mechanisms, and breast cancer subtypes with differing fractionation sensitivity should be examined before clinical extrapolation.[11]

CONCLUSION

Prolonging fraction delivery reduced the tumoricidal efficacy of 2 Gy irradiation in MCF-7 breast cancer cells, with higher viability and fewer residual DNA double-strand breaks as delivery time increased. Because respiratory-controlled techniques inherently extend and fragment beam delivery, intrafraction delivery time merits consideration as a potentially modifiable parameter, and the radiobiological consequences of protracted gated delivery warrant further preclinical and clinical study.

Ethics Committee Approval: Ethics committee approval was not required, as this study was conducted exclusively *in vitro* using a commercially available, established cell line.

Informed Consent: Not applicable.

Conflict of Interest Statement: None declared.

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ORIGINAL ARTICLE

Outcomes of Radiotherapy and Chemoradiotherapy in Patients Aged ≥70 Years with Stage III Non-Small Cell Lung Cancer: A Retrospective Single-Center Analysis

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OBJECTIVE

The aim of the study is to evaluate overall survival (OS) and radiation pneumonitis (RP) in patients aged ≥70 years with stage III non-small cell lung cancer (NSCLC) treated with definitive radiotherapy (RT) or concurrent chemoradiotherapy (CRT).

METHODS

A retrospective analysis included 104 patients. Clinical, dosimetric, and treatment-related factors were assessed. Survival was analyzed using Kaplan–Meier and Cox regression models.

RESULTS

Median OS was 21 months (95% confidence interval: 17–24). Univariate analysis showed associations between OS and Karnofsky Performance Status, tumor volume, total mean lung dose (tMLD), histopathology, chemotherapy use and regimen, RP grade, and RT response. Multivariate analysis identified planning target volume, tMLD, RT response, and RP as independent predictors of OS. RP severity was significantly associated with comorbidities, lymph node location, chemotherapy regimen, and higher lung dose-volume parameters (tV50–60, iV45–60).

CONCLUSION

OS in elderly stage III NSCLC patients is influenced by tumor response and lung dosimetry. RP independently worsens survival. Treatment decisions should rely on functional status rather than age, and concurrent CRT is feasible in selected patients.

Keywords: Concurrent chemoradiotherapy; definitive radiotherapy; geriatric patients; non-small cell lung cancer; overall survival.

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INTRODUCTION

Lung cancer is one of the most common malignancies in the elderly population and has the highest mortality rate.[1] Approximately 85% of lung cancer patients have non-small cell lung cancer (NSCLC), and about 25% of these patients are in the locally advanced stage. [2] Due to the median age at diagnosis being over 70 years, a significant portion of NSCLC patients are in the geriatric patient group. Looking at the entire NSCLC patient group, more than 50% of patients are over 65 years old, and 30–40% are over 70 years old.[3] This situation makes the question of how and under what conditions curative approaches in the treatment

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of stage III NSCLC can be applied in the geriatric patient population even more clinically important.

At present, treatment for stage III NSCLC involves multimodal approaches aimed at curative outcomes, but common comorbidities in patients aged 70 and over, and age-related physiological reserve loss, lead to clinical uncertainties regarding patient tolerance of standard treatment approaches and the risk of treatment-related toxicity.[4,5] Therefore, treatment decisions in geriatric NSCLC patients should be carefully evaluated not only in terms of oncological efficacy but also in terms of treatment tolerance and toxicity risk.

The median age of patients diagnosed with lung cancer is 71 years, and although a significant proportion of patients diagnosed with lung cancer are in the geriatric group, these patients are often excluded from clinical trials, making it difficult to provide evidence-based treatment to the elderly population.[6] Furthermore, the exclusion of elderly patients from studies may lead to inadequate treatment in this age group due to concerns about potential toxicity. As expected, physiological reserve decreases with aging, and the incidence of many comorbid diseases and the use of multiple drugs increase. Such factors can also hinder elderly patients from tolerating standard treatment. However, treatment decisions for elderly patients should not be made solely based on chronological age; the expected lifespan, patient preferences, functional age, and additional diseases should be considered, and the expected benefit and potential side effects of the treatment should be evaluated together.[7]

Treatment decisions for elderly lung cancer patients have mostly been derived from retrospective studies or subgroup analyses of randomized trials. Some of these studies have shown that elderly patients benefit from chemoradiotherapy (CRT), while others have shown no difference in oncological outcomes between CRT and radiotherapy (RT).[8,9] This makes treatment selection difficult for clinicians.

In this study, overall survival (OS) outcomes and factors affecting OS were evaluated in patients aged ≥70 years with stage III NSCLC diagnosed with definitive RT and concurrent CRT, and the development of radiation-induced pneumonia was investigated.

MATERIALS AND METHODS

Patients

This retrospective study evaluated 104 geriatric patients diagnosed with stage III NSCLC who received definitive RT or CRT between January 2014 and December 2024. Inclusion criteria were age 70 years or older at diagnosis, histopathological diagnosis of NSCLC, TNM stage III, Karnofsky performance status (KPS) ≥60, completion of RT or CRT, and attendance at regular follow-up appointments. Patients with multiple primary tumors or missing clinical, treatment, dosimetric, or follow-up data required for the analyses were excluded from the study. Follow-up data were censored on June 30, 2025. The median follow-up duration, measured from the 1st day of RT to the date of death or last clinical follow-up, was 19 months (range, 3–94 months). OS was defined as the time from diagnosis to death or the last follow-up date. None of the patients received consolidation durvalumab during the study period, and chemotherapy administered before or after definitive RT/CRT (induction or sequential regimens) was not separately categorized in the present analysis.

Thoracic computed tomography (CT), 18F-fluorodeoxyglucose positron emission tomography-CT (18F-FDG-PET-CT), and brain magnetic resonance imaging were ordered for staging.

Tumor staging was performed according to the TNM classification system valid at the time of diagnosis. For uniformity, all patients were retrospectively reclassified according to the 8th edition of the TNM staging system for lung cancer.[10] Staging, treatment decision, and post-treatment response evaluation were performed multidisciplinarily at the Lung Oncology Council. OS was defined as the time from diagnosis to death or the last follow-up date. Treatment response evaluation was performed according to the response evaluation criteria in solid tumors version 1.1 (RECIST 1.1) using the first CT images obtained within the first 6 months after completion of RT.[11]

Radiation pneumonitis (RP) was classified according to the Radiation Therapy Oncology Group (RTOG) grading systems. Patients were graded in terms of their need for clinical support, along with imaging and examination findings.[12] Patients with a preliminary diagnosis of RP were again evaluated multidisciplinarily in the Lung Cancer Board.

This study was approved by the Eskişehir Osmangazi University Non-Interventional Clinical Research Ethics Committee (Decision No. 70, decision date: January 06, 2026).

The study was conducted in accordance with the principles of the Declaration of Helsinki.

Treatment

Patients were immobilized in a supine position with their hands above their heads on a T-bar/Wingboard. Images with a thickness of 2–3 mm were obtained be-

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tween the cricoid cartilage and the upper border of the L2 vertebra using Siemens Somatom Definition AS (Siemens Healthineers) and GE Discovery RT (GE Healthcare) CT devices. Diagnostic Thoracic CT and 18F-FDG-PET-CT were fused with planning CT.

Gross tumor volume (GTV) was contoured for the tumor, based on the post-CT volume in patients receiving chemotherapy (ChT) before definitive RT. Lymph node GTV (GTV_nod) was defined based on the pre-treatment volume in patients receiving ChT. For clinical target volume (CTV), a margin of 0.6 cm was given for squamous cell carcinoma (SCC) and 0.8 cm for adenocarcinoma (ACC); 0.5 cm was added to the GTV_nod volume. CTV_node and CTV_tumor volumes were combined to create CTV_total, and a 0.5 cm margin was added to CTV_total for the planning target volume (PTV). Treatment planning in all patients was performed using intensity-modulated RT or volumetric modulated arc therapy techniques, and treatments were administered under image-guided RT. Treatment planning was performed using the Varian Eclipse treatment planning system (Varian Medical Systems, Palo Alto, CA, USA) and the Anisotropic Analytical Algorithm. Patients were treated with Varian Trilogy and Varian TrueBeam linear accelerators (Varian Medical Systems).

Most patients received conventionally fractionated RT (60–66 Gy). In selected elderly patients, a hypofractionated regimen of 45 Gy in 15 fractions was used according to multidisciplinary clinical judgment.

Platinum-based regimens were used as concurrent ChT. The chemotherapy regimen consisted of weekly cisplatin (40 mg/m^2) or carboplatin (AUC 2) + paclitaxel (50 mg/m^2). Before the decision for concurrent ChT, patients were evaluated based on numerous parameters including blood values, additional comorbidities, cardiomyopathy, medications used, and smoking history. Consultations were requested from relevant departments (cardiology, gastroenterology, nephrology, etc.) for patients deemed necessary.

Patients receiving only RT were seen in the outpatient clinic at least once a week during their RT treatment. Patients receiving concurrent ChT were evaluated in the outpatient clinic at least three times a week. Blood values were recorded before and after concurrent ChT, and close monitoring was performed during the application of concurrent ChT.

Variables İncluded in the Analysis

The variables evaluated were age, gender, KPS, smoking history, history of chronic disease, histopathological subtype, tumor location, central or peripheral tumor location, tumor size, location of pathological lymphadenopathy (LAP), pathological LAP level (single level, multilevel, or none), T stage, N stage, TNM stage, presence of concurrent ChT, concurrent ChT regimen, GTV, PTV, RT dose, RP grade, total lung volumes receiving ≥5–60 Gy dose (tV5–V60), total mean lung dose (tMLD), ipsilateral lung volumes receiving ≥5–60 Gy dose (iV5–V60), ipsilateral mean lung dose (iMLD), contralateral lung volumes receiving ≥5–60 Gy dose (cV5–cV60), and contralateral mean lung dose (kMLD).

Statistics

IBM Statistical Package for the Social Sciences for Windows 21.0 and MEDCAL 20.106 were used for data analysis. Shapiro–Wilk's test was used to determine the normality of the distribution of variables. Parametric and non-parametric tests were used to compare groups. One-way analysis of variance and Kruskal–Wallis tests were used to compare groups. Post hoc tests were used to identify different groups. Mann–Whitney U test was used to determine the difference between the medians of two groups. Chi-square tests were used to analyze the created cross-tables. Kaplan–Meier test was used to compare median survival times, and the log-rank test was used to determine group differences. Univariate and multivariate stepwise Cox proportional hazards regression were used to determine the effects of prognostic variables on survival time. For summarizing the data, number (%) statistics were used for qualitative data, and Mean±SD or Median (Q1; Q3) statistics were used for quantitative data. $P<0.05$ was considered statistically significant.

RESULTS

The median age was 74 (min: 70, max: 85). The median KPS was 80 (min: 60, max: 100). 100 patients (96.2%) were male and 4 (3.8%) were female. Seventy (67.3%) patients had a history of chronic disease, while 34 (32.7%) patients did not have a history of chronic disease. The median RT dose was 60 Gy (min: 45, max: 68), and 60 (57.7%) patients received concurrent ChT. Patient, tumor, and treatment characteristics are summarized in Table 1.

The rate of concurrent ChT was statistically significantly higher in patients with higher KPS ($p<0.001$). The median KPS was 80 (Q1–Q3: 80–90) in patients receiving concurrent ChT, while the median KPS was 70 (Q1–Q3: 70–80) in patients not receiving ChT. A box-plot graph showing the relationship between KPS and concurrent ChT is presented in Figure 1.

Table 1 Patient, tumor, and treatment characteristics

Features	n (%) / Median (min, max)	Features	n (%) / Median (min, max)
Age	74 (70–85)	Mediastinal	29 (27.9)
Karnofsky performance status	80 (60–100)	Hilar+mediastinal	45 (43.3)
Gender		Hilar+mediastinal+supraclavicular	3 (2.9)
Female	4 (3.8)	Lymph node level involvement	
Male	100 (96.2)	None	15 (14.4)
History of smoking		Single-level	31(29.8)
+	100 (96.2)	Multilevel	58 (55.8)
–	4 (3.8)	T Stage	
Chronic comorbidity		T2	10 (9.6)
+	70 (67.3)	T3	24 (23.1)
–	34 (32.7)	T4	70 (67.3)
Histopathology		N Stage	
Squamous cell carcinoma	75(72.1)	N0	16 (15.4)
Adenocarcinoma	29 (27.9)	N1	11 (10.6)
Tumor Location		N2	60 (57.7)
Right lower lobe	19 (18.3)	N3	17 (16.3)
Right middle lobe	10 (9.6)	TNM Stage	
Right upper lobe	34 (32.7)	3A	35 (33.7)
Left lower lobe	15 (14.4)	3B	55 (52.9)
Left upper lobe	26 (25)	3C	14 (13.5)
Tumor size (cm)	5.7 (2–16)	Radiation dose (Gy)	60 (45–68)
GTV (cc)	99 (4–1581)	Concurrent chemotherapy	
PTV(cc)	302 (43–2334)	+	60 (57.7)
Tumor location		–	44 (42.3)
Peripheral	35 (33.7)	Concurrent chemotherapy regimen	
Central	69 (66.3)	None	44 (42.3)
Pathological lymph node location		Cisplatin-based	27 (26.0)
None	15(14.4)	Carboplatin–paclitaxel	33 (31.7)
Hilar	12 (11.5)		

PTV: Planning target volume; GTV: Gross tumor volume.

A statistically significant inverse relationship was found between age and KPS with KPS decreasing significantly as age increased ($p<0.05$).

Based on thoracic CT assessments performed within the first 6 months after RT, partial response (PR) was detected in 48 patients (46.2%), stable disease in 32 patients (30.7%), and progression in 24 patients (23.1%).

OS

The median OS in the entire patient group determined by the Kaplan–Meier method was 21 months (95% CI: 17–24). The mean survival was found to be 31 months (95% CI: 26–37). At the last follow-up, 22 patients (21.2%) were alive and 82 patients (78.8%) were deceased. The Kaplan–Meier curve for OS is shown in Figure 2. The 1-, 2-, and 5-year OS rates were 79.2%, 49.0%, and 22.9%,

Univariate Cox Regression Analysis Results

In the univariate Cox regression analysis, higher KPS was found to be significantly associated with better OS (HR: 0.97; 95% CI: 0.94–0.99; p=0.018). Conversely, increased GTV shortened OS and increased the risk of all-cause mortality (HR=1.002, 95% CI: 1.001–1.003, p=0.001); this risk corresponds to approximately a 2% increased risk for every 10 cc increase in GTV (HR≈1.02). Similarly, increased PTV was found to be associated with worsening OS (HR: 1.001; 95% CI: 1.000–1.002; p=0.001). This effect indicates that every

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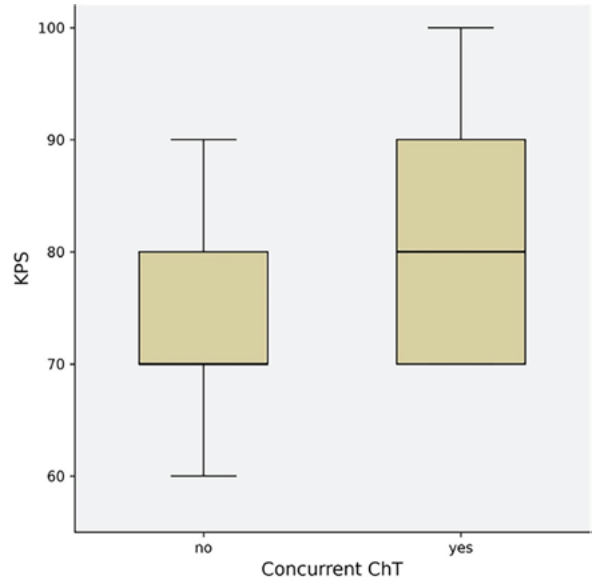

Fig. 1. Box-and-whisker plot showing the distribution of values.

10 cc increase in PTV corresponds to approximately a 1% increase in mortality risk (HR≈1.01).

Increased tMLD was associated with worse OS (HR=1.001, 95% CI: 1.001–1.002, p=0.001). Each 1 Gy (100 cGy) increase in mean lung dose corresponds to approximately a 10.5% increase in mortality risk (HR≈1.105).

When histopathological subgroups were examined, the median OS was 20 months (95% CI: 15–24) in patients with SCC and 27 months (95% CI: 6–47) in those with ACC. In the geriatric group, patients with ACC histopathology had a statistically significantly longer OS (p=0.024).

Concurrent ChT resulted in a significant difference in OS (p=0.020). The median OS was 16 months (95% CI: 12–19) in patients not receiving concurrent ChT, while it was 25 months (95% CI: 19–30) in patients receiving concurrent ChT. The ChT regimen was also associated with OS (p=0.032). When comparing patient groups, the median OS was 16 months (95% CI: 12–19) in the group not receiving ChT, 23 months (95% CI: 14–31) in the cisplatin group, and 27 months (95% CI: 10–43) in the carboplatin-paclitaxel group.

The distribution of OS differed significantly according to RP grade groups (p<0.001). The median OS was 18 months (95% CI: 8–27) in patients without RP, 22 months (95% CI: 17–26 and 15–28, respectively) in patients with grade 1 and Grade 2 RP, 12 months (95% CI: 7–16) in those with Grade 3 RP, and 4 months in those with Grade 5 RP. OS decreased significantly in patients with Grade 3 and above RP.

The distributions of OS according to the CT assessment of RT response (RECIST) showed borderline differences (p=0.051). The median OS was 22 months in the stable response group (95% CI: 15–28), 18 months in the progressive response group (95% CI: 12–23), and 22 months in the PR group (95% CI: 15–28). The difference between groups was more pronounced when considering the mean OS, with 26 months in the stable group (95% CI: 19–32), 20 months in the progressive group (95% CI: 15–24), and 38 months in the PR group (95% CI: 28–48).

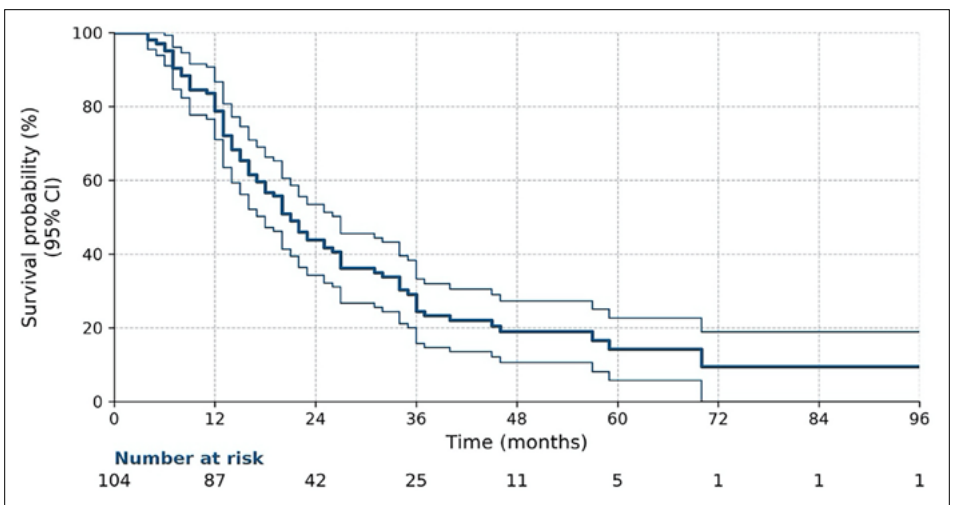

Fig. 2. Overall survival of patients aged ≥70 years with stage III non-small cell lung cancer (Kaplan–Meier analysis).

Table 2 Univariate Cox proportional hazards regression analysis for overall survival

Variable	HR	%95 CI	p
KPS	0.970	0.94–0.990	0.018
PTV	1.001	1.000–1.002	0.001
GTV	1.002	1.001–1.003	0.001
tMLD	1.001	1.001–1.002	0.001
Histopathological subtype	---	---	0.024†
Concurrent ChT (yes/no)	---	---	0.020†
Concurrent ChT regimen	---	---	0.032†
RP	---	---	<0.001†
RT response (RECIST 1.1)	---	---	0.050†

†: Categorical variables were evaluated using the Kaplan–Meier method and log-rank test; global p-values are presented for these variables. HR: Hazard ratio; CI: Confidence interval; KPS: Karnofsky performance status; PTV: Planning target volume; GTV: Gross tumor volume; tMLD: Mean lung dose; ChT: Chemotherapy; RP: Radiation pneumonitis; RT: Radiotherapy; RECIST: Response evaluation criteria in solid tumors.

The univariate Cox regression analysis is summarized in Table 2.

Multivariate Cox Regression Analysis Results

In the multivariate Cox regression analysis, increased PTV was found to be independently associated with worsening OS (HR: 1.001; 95% CI: 1.000–1.002; p=0.026). Furthermore, tMLD was identified as an independent negative prognostic factor for OS (HR: 1.002; 95% CI: 1.001–1.002; p=0.001). RT response (RECIST) (p=0.021) and the presence of RP (p=0.031) were also found to be independently associated with OS in the multivariate analysis. In contrast, KPS and concurrent ChT administration did not maintain their statistical significance in the multivariate analysis (p>0.05). The multivariate Cox regression analysis is summarized in Table 3.

Toxicity

Out of a total of 104 patients, 54 (51.9%) developed Grade 0 RP, 45 (43.3%) developed Grade 1–2 RP, and 5 (4.8%) developed Grade ≥3 RP. The RP distribution graph is given in Figure 3. Among patients with severe RP, four experienced Grade 3 RP, one developed Grade 5 RP, and no Grade 4 events were observed.

23 (67.6%) patients without chronic disease had Grade 0, 11 (32.4%) had Grade 1–2 RP, and no patient had ≥Grade 3 RP. 31 (44.3%) patients with chronic disease had Grade 0, 34 (48.6%) had Grade 1–2, and 5 (7.1%) had ≥Grade 3 RP. A significant relationship was found between the presence of chronic disease and RP grade (p=0.048). Rates of Grade 1–2 and Grade ≥3 pneumonia are higher in patients with chronic disease, and Grade ≥3 pneumonia was observed only in patients with chronic disease (7.1% vs. 0%).

A significant association was found between pathological lymph node location and RP pneumonitis (p=0.015). RP rates were higher in patients with hilar/mediastinal LAP.

A significant association was found between ChT regimen and RP, with higher rates of Gr1–2 and Gr≥3 pneumonia in patients receiving carboplatin-paclitaxel (54.5% and 9.1%, respectively) (p=0.043).

Regarding total lung dosimetric characteristics, tV50 (p=0.026), tV55 (p=0.016), and tV60 (p=0.048)

Table 3 Multivariate Cox proportional hazards regression analysis for overall survival

Variable	HR	%95 CI	p
KPS	0.97	0.94–1.002	0.063
PTV	1.001	1.000–1.002	0.026
tMLD	1.002	1.001–1.002	0.001
Concurrent ChT (yes/no)	0.634	0.380–1.056	0.080
RP (overall)	---	---	<0.031†
Grade 0 RP	Reference	---	---
Grade 1–2 versus Grade 0 RP	0.649	0.402-1.048	0.077
Grade 3–5 versus Grade 0 RP	2.200	0.808-5.993	0.123
RT response (RECIST) (overall)	---	---	0.021†
Partial response	Reference	---	---
Stable disease versus partial response	1.636	0.886–3.020	0.116
Progressive disease versus partial response	0.731	0.424–1.260	0.259

†: For multicategorical variables (RECIST response and radiation pneumonitis), global p-values were calculated using the Wald test. The final multivariate model was constructed using the backward stepwise (Wald) method. HR: Hazard ratio; CI: Confidence interval; PTV: Planning target volume; tMLD: Total mean lung dose; KPS: Karnofsky performance status; ChT: Chemotherapy; RT: Radiotherapy; RECIST: Response evaluation criteria in solid tumors; RP: Radiation pneumonitis.

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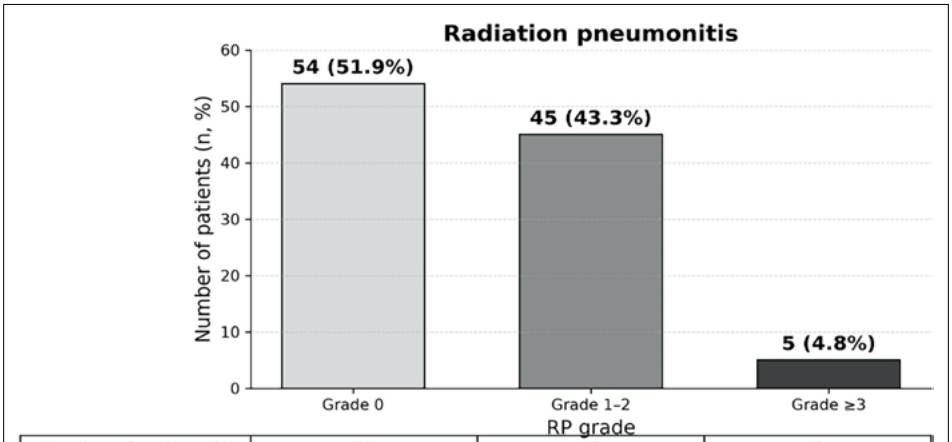

Number of patients (n)	54	45	5
Percentage (%)	51.9%	43.3%	4.8%

Fig. 3. Distribution of radiation pneumonitis grades (n=104).

showed significant differences, while no significant differences were found in tMLD and lower dose volumes. In post hoc analysis, values for all three parameters were found to be higher in the Grade 1–2 pneumonitis group compared to the non-pneumonitis (Grade 0) group (p=0.021 for tV50; p=0.013 for tV55; p=0.043 for tV60). No significant difference was observed between the Grade ≥3 pneumonia group and the other groups.

In the comparison of ipsilateral lung dosimetric values between RP grade groups, significant differences were found in iV45, iV50, iV55, and iV60 values (p=0.039, p=0.025, p=0.008, p=0.042, respectively); however, no significant difference was found at lower dose volumes and in terms of iMLD. Post hoc pairwise comparisons showed that significance stemmed from the difference between Grade 0 and Grade 1–2 groups (iV45 p=0.032; iV50 p=0.020; iV55 p=0.006; iV60 p=0.037); however, no significant difference was observed between Grade ≥3 and the other groups. Significant variables associated with RP are presented in Table 4.

DISCUSSION

Due to the increase in life expectancy, the number of patients diagnosed with lung cancer in the elderly group is also increasing, and the management of geriatric lung cancer patients is becoming increasingly important. However, the recommendations in the current international oncology guidelines are not directly applicable to this patient group. With advancing age, comorbid diseases such as diabetes, chronic

Table 4 Variables significantly associated with radiation pneumonitis

Variable	Grade 0 Median (IQR)	Grade 1–2 Median (IQR)	Grade ≥3 Median (IQR)	p
Chronic comorbidity	–	–	–	0.048
Pathological lymph node location	–	–	–	0.015
Concurrent ChT regimen	–	–	–	0.043
tV50	3.75 (3.65)	5.40 (4.40)	4.70 (2.55)	0.026
tV55	2.25 (2.93)	4.00 (3.40)	3.80 (1.65)	0.016
tV60	0.80 (2.23	1.60 (2.75)	0.70 (2.45)	0.048
iV45	10.60 (9.68)	14.70 (9.65)	13.80 (5.40)	0.039
iV50	7.20 (7.15)	11.70 (8.40)	11.20 (5.15)	0.025
iV55	4.95 (5.73)	8.00 (7.00)	8.90 (4.40)	0.008
iV60	2.00 (4.25)	3.50 (5.45)	**1.40 (5.15)**	0.042

ChT: concurrent chemotherapy; tV50, tV55, tV60: Percentage of total lung volume receiving ≥50 Gy, ≥55 Gy, and ≥60 Gy, respectively; iV45, iV50, iV55, iV60: percentage of ipsilateral lung volume receiving ≥45 Gy, ≥50 Gy, ≥55 Gy, and ≥60 Gy, respectively. (Values are presented as median (interquartile range, IQR). p-values were obtained using the Kruskal–Wallis test followed by post hoc pairwise comparisons where appropriate).

lung diseases, and cardiovascular diseases are also frequently observed. At the same time, geriatric syndromes such as malnutrition and cognitive impairment are more common in this age group. Age-related physiological changes, comorbid diseases and the use of multiple drugs due to them, and malnutrition can alter the metabolism of ChT drugs and cause serious toxicity even at low doses. Exclusion of elderly patients from clinical trials leads to insufficient evidence-based treatment recommendations in this patient group. This causes clinicians to make treatment decisions based on chronological age. This situation can result in functionally fit patients receiving inadequate treatment. The main goal in treatment is to provide treatment with an appropriate therapeutic index, taking into account the patient's functional age.[13]

In our current study, a statistically significant inverse relationship was found between age and KPS, with KPS decreasing as age increases ($p<0.05$). In patients receiving concurrent chemotherapy, KPS was found to be statistically higher ($p<0.001$). In a study conducted by Logtenberg et al.,[14] concurrent or sequential ChT was evaluated in elderly patients, and similarly to our current study, statistically significantly more concurrent ChT was given to younger patients with higher performance scores ($p<0.001$). Functional age, as well as chronological age, actually affects the treatment decision. In conclusion, the patient's performance status must also be evaluated in the decision for concurrent chemotherapy. It should be considered that a patient with a higher KPS despite being older may tolerate concurrent ChT better than a younger patient with a lower KPS.

In our current study, the median OS was 21 months (95% CI: 17–24). The mean survival was found to be 31 months (95% CI: 26–37). The 1-, 2-, and 5-year OS rates were 79.2%, 49.0%, and 22.9%, respectively. In the literature, the median OS in stage III NSCLC receiving curative treatment ranges from 19 to 30 months.[15–17] In the study conducted by Driessen et al.[18] in elderly patients with stage III NSCLC, the median OS, as well as the 1- and 2-year OS rates, were 18 months (95% CI: 9.2–27), 57%, and 21%, respectively, in the concurrent CRT group. In contrast, in the RT -alone group, the median OS and the 1- and 2-year OS rates were 11 months (95% CI: 5.5–16), 49%, and 14%, respectively. In a review of patients diagnosed with stage III NSCLC, the 5-year OS was found to be 30%.[17] Although our study included a geriatric patient population, the median and long-term survival results obtained are consistent with the stage III NSCLC OS data reported in the literature, and it is seen that definitive RT and concurrent CRT for curative purposes may be an effective and feasible treatment option in functionally selected elderly patients. However, patients receiving concurrent CRT had significantly higher baseline KPS. Therefore, the observed survival difference between RT alone and concurrent CRT should be interpreted cautiously, as treatment-selection bias may have influenced this finding.

In this study, factors affecting overall OS in a geriatric patient group were evaluated using univariate and multivariate analyses; in the multivariate analysis, PTV, tMLD, response to RT (RECIST), and RP development were identified as independent determinants of OS. These findings demonstrate that in a geriatric patient group, OS is closely related not only to tumor biology and treatment response but also to treatment volume and lung dosimetric parameters.

Larger PTV volumes indicate both tumor and nodal disease burden and cause organs at risk to receive higher doses. In stage III disease, larger PTV volumes lead to higher lung doses, which increases the risk of pulmonary toxicity and reduces treatment tolerance, leading to poor oncological outcomes. In the RTOG 0617 study, PTV was also evaluated as a prognostic parameter.[19] In the study by Karin et al.,[20] a PTV >700 cc in stage III NSCLC treated with CRT was found to be associated with poor OS. In another study, tumor volume and primary tumor volume were found to statistically significantly affect OS in stage III NSCLC treated with CRT, but nodal volume alone did not.[21] In summary, regardless of T and N stages, OS is poor in large-volume tumors. Similarly, our study found that large tumor volume was associated with poor OS, with each 10 cc increase in PTV resulting in a 1% increase in mortality risk. Larger tumor volume causes an increase in MLD as expected. In stage III NSCLC, the negative impact of increased MLD on OS has been reported in the literature. In a retrospective study evaluating 468 patients diagnosed with stage III NSCLC and treated with RT, MLD was found to be an independent prognostic predictor for OS.[22] Similarly, in the study by Stervik et al.,[23] age and increased MLD were found to be associated with an increased risk of short-term respiratory-related mortality; this was indirectly associated with poor OS.

In our study, a significant relationship was found between RT response and OS. The literature also reports that RT response is closely related to survival; one study showed that the median OS was approximately 33.6 months in patients who achieved complete

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response (CR)/PR, while the median OS was only 7.3 months in patients with progressive disease.[24]

Increased MLD with large PTV volumes facilitates RP development, reducing treatment tolerance. In our study, this interaction was thought to negatively affect OS in geriatric stage III NSCLC patients.

In the present study, RP was not observed in 51.9% of patients, while mild-to-moderate (Grade 1–2) RP was observed in 43.3% and Grade 3 and above RP in 4.8%. In a systematic review and meta-analysis conducted by Kuang et al.[25] with patients diagnosed with stage III NSCLC, the rate of Grade 3 and above RP was reported to range from 0 to 8.3%. Although our study only included geriatric patients, the Grade ≥3 RP rate of 4.8% was found to be consistent with the literature. The risk of radiation pneumonia is associated not only with dosimetric parameters but also with chronic comorbidities. Chronic diseases such as diabetes mellitus and chronic obstructive pulmonary disease have been reported to increase the risk of RP.[26,27] The increased risk of RP due to chronic comorbidities can be largely explained by the increase in the basal inflammatory background of the lung, endothelial/microvascular dysfunction, and decreased pulmonary reserve.[28]

The more frequent occurrence of comorbidities in geriatric patients often leads clinicians to adopt a more protective approach towards this patient group. Our findings suggest that carefully selected elderly patients may tolerate RT and CRT with acceptable toxicity. However, only patients who completed treatment and attended regular follow-up were included in this study.

The addition of concurrent ChT to RT is also known to increase the risk of RP.[29] In our study, concurrent ChT, especially when administered with the carboplatin-paclitaxel regimen, was found to be associated with a higher risk of developing RP. Therefore, this suggests that when planning concurrent treatment in the geriatric patient group, not only oncological efficacy but also pulmonary reserve and comorbidity profile, i.e., functional age, should be carefully evaluated. In our study, a significant relationship was found between the development of RP and high-dose lung volumes (tV50–60 and iV45–60), while no significant relationship was observed with MLD and low-dose volumes. Similar to our study, there are studies that identify high-dose volumes as a risk factor for the development of RP.[30,31] These findings suggest that cellular damage and associated local inflammation developing in high-dose lung portions may contribute to the development of RP. These findings may be particularly relevant in elderly patients because of age-related reductions in pulmonary reserve; however, this hypothesis requires confirmation in larger prospective studies.

In our study, significant associations between RP and high-dose lung dose–volume parameters were observed primarily between patients with Grade 0 and Grade 1–2 RP, whereas no statistically significant differences were identified between patients with Grade ≥3 RP and the other RP groups. Given the limited number of severe RP events, these findings should be considered exploratory and interpreted with caution. Although minimizing high-dose lung volumes during treatment planning remains a reasonable strategy whenever clinically feasible, the present study does not support the definition of elderly-specific lung dose constraints or specific threshold values.

Limitations of the Study

This study has several limitations. Its retrospective and single-center design may have resulted in patient selection and treatment decisions being based on institutional experience rather than standardized, contemporary geriatric guidelines. Furthermore, the lack of routine application of comprehensive geriatric assessment (CGA) parameters (such as frailty scores, cognitive status, and nutritional status) prevented a complete analysis of the difference between chronological age and functional age. Although KPS was used to assess functional status, it primarily reflects performance rather than the multidimensional concept of functional age. Established geriatric assessment approaches, including the Charlson Comorbidity Index, validated geriatric screening tools, and CGA, may provide a more comprehensive evaluation of physiological reserve, frailty, and treatment tolerance in older adults. Future prospective studies incorporating these assessments may improve patient selection and individualized treatment strategies in elderly patients with stage III NSCLC. In addition, RP and RECIST response were assessed after treatment initiation and were analyzed as fixed covariates in the survival analysis. Therefore, the observed associations between these post-treatment variables and OS may have been influenced by time-dependent (guaranteed-time) bias and should not be interpreted as evidence of an independent causal relationship. This consideration is particularly relevant for Grade 5 RP, which by definition represents treatment-related mortality. The presence of chronic disease was considered as a single variable, and chronic lung diseases, cardiovascular diseases, and diabetes mellitus could

not be examined as separate subgroups. Finally, the small number of patients who developed severe RP (Grade ≥3, n=5) limited the statistical power of analyses involving severe toxicity. Therefore, findings related to severe RP should be interpreted cautiously and require validation in larger prospective cohorts.

CONCLUSION

The standard treatment approach for stage III NSCLC patients aged ≥70 years remains unclear. The limited elderly-specific prospective evidence leads to heterogeneity in treatment approaches for this age group, with treatment decisions often relying on clinician judgment. In the geriatric patient group, OS was found to be closely related not only to tumor response but also to treatment volume and lung dosimetric parameters. The development of RP stands out as an independent factor negatively affecting OS in the geriatric patient group. Higher high-dose lung volumes were associated with RP in this cohort. Therefore, minimizing high-dose lung exposure during treatment planning may be considered whenever clinically feasible. However, the present findings are exploratory and do not support the definition of elderly-specific dose constraints or specific threshold values. According to this study, definitive RT and concurrent ChT can be applied with close monitoring in functionally appropriate selected geriatric patients.

Ethics Committee Approval: The study was approved by the Eskişehir Osmangazi University Non-Interventional Clinical Research Ethics Committee (no: 70, date: 06/01/2026).

Informed Consent: This retrospective study.

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ORIGINAL ARTICLE

Hereditary Patterns and Secondary Malignancies in Familial Nasopharyngeal Carcinoma

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OBJECTIVE

This study aimed to evaluate the clinicopathological characteristics and familial aggregation patterns of nasopharyngeal carcinoma (NPC) in a large cohort from a non-endemic region.

METHODS

Medical records of 1,132 NPC patients treated at the Istanbul University Oncology Institute between 1985 and 2020 were retrospectively reviewed. Familial NPC was categorized based on the total number of affected members per cluster: low-frequency (two affected individuals, including the proband) and high-frequency (three or more affected individuals, including the proband). Analysis focused on pathologically confirmed cases, documenting relationships among first-degree relatives (FDRs) and second-degree relatives (SDRs), demographic data, histopathology, and treatment outcomes.

RESULTS

Twenty-four families with ≥2 affected members were identified, representing a familial NPC frequency of 2.1% within the study population. Of these, 18 families (75%) involved FDRs, with 14 probands (58.3%) having affected siblings. Two families met criteria for high-frequency familial NPC (≥3 affected individuals per family). The median age of probands was 42.5 years (range: 12–70), with undifferentiated non-keratinizing carcinoma (World Health Organization type 3) histology being the most prevalent (66.7%). In addition, a family history of non-NPC malignancies among relatives was documented in 20.8% of families (n=5).

CONCLUSION

Familial aggregation occurs in approximately 2.1% of NPC cases in our cohort, predominantly clustering among siblings. These findings highlight that detailed family history evaluation and heightened clinical awareness for siblings are essential in clinical practice.

Keywords: Familial aggregation; frequency; nasopharyngeal carcinoma; non-endemic; secondary malignancy.
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INTRODUCTION

The etiology of nasopharyngeal carcinoma (NPC) involves a complex interplay between environmental triggers and genetic susceptibility.[1,2] Along with Epstein-Barr virus (EBV) infection, environmental risk factors such as dietary nitrosamines, tobacco use, and occupational exposure to wood dust play significant

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roles in the development of the disease. In recent years, a growing body of research has underscored the importance of genetic predisposition, identifying key associations with human leukocyte antigen Class I genes and various molecular markers.[1,2]

While Southeast Asia remains the primary endemic region for NPC, familial aggregation is a well-documented etiological hallmark in these high-incidence areas.[3] Reports from China have described extreme clusters, such as 15 affected individuals across four generations within a single family.[4] In endemic regions, studies indicate that more than 5% of patients have an affected first-degree relative (FDR), who faces a significantly elevated risk.[5–8] Familial NPC is not limited to only endemic populations; but it is also observed in intermediate- or low-incidence regions.[9] Although the overall prevalence is lower in non-endemic cohorts, the risk for immediate family members remains disproportionately high.

Comparative studies between familial and sporadic NPC have evaluated clinicopathological characteristics such as age, sex, histological subtype, and EBV serology. Familial cases typically present at a younger age while preserving the male predominance observed in sporadic cases.[10] Furthermore, an increased incidence of non-NPC malignancies has been observed among these families, particularly in non-endemic areas. For instance, familial clusters in Greenland natives have shown a co-occurrence of NPC and salivary gland tumors, while other reports suggest an increased risk of EBV-related Burkitt lymphoma within NPC-prone lineages.[11,12]

Despite these global insights, data from Türkiye—an intermediate-risk region — remain sparse. In the English literature, there is currently only one reported case of familial NPC from Türkiye.[13] To address this significant data gap, we retrospectively evaluated patients who were treated for NPC at our institution over the past 35 years (1985–2020). This study aims to describe the clinical characteristics and familial aggregation patterns of NPC within a large Turkish cohort, providing essential epidemiological insights from a non-endemic region.

MATERIALS AND METHODS

Definition and Identification of Familial NPC

The familial history of NPC was retrospectively reviewed using patient medical records. Based on the number of affected relatives, patients were categorized into two groups: low-frequency familial NPC, with one additional NPC case within the family; and high-frequency familial NPC, with two or more additional NPC cases within the family consistent with classification approaches used in Cao et al.'s study.[14]

Each patient's NPC diagnosis was pathologically confirmed, and all had a documented family history. All families were identified through a single proband. In cases where more than one family member was treated for NPC at our clinic, the first enrolled patient was designated as the proband.

The family history of the patients was reported by the probands. However, in cases where an affected relative with NPC was not treated at our institution, pathological confirmation of diagnosis was required for inclusion. Family relationships were classified as follows: FDRs included parents, siblings, and children; SDRs comprised aunts, uncles, nieces, nephews, grandparents, and grandchildren.

A total of 26 families with at least two members diagnosed with NPC were identified. Two families were excluded due to only distant blood relations (e.g., cousins), and the remaining 24 families were included in the analysis.

Statistical Analysis

Descriptive statistics were used to summarize the clinicopathological features of the cohort. Categorical variables were presented as frequencies and percentages, while quantitative variables were expressed as medians and ranges.

Baseline demographic and clinicopathological characteristics (age at diagnosis, sex distribution, and WHO histological subtypes) were compared between the familial NPC cohort (n=24 probands) and the sporadic registry (n=1,098). Continuous variables were compared using the Mann–Whitney U test, whereas categorical variables were evaluated using the Chi-square test or Fisher's exact test, as appropriate. Two-sided $p<0.05$ was considered statistically significant.

The median follow-up period was calculated from the date of initial pathological diagnosis to the date of the last clinical visit or death. Statistical analyses were conducted using IBM Statistical Package for the Social Sciences Statistics for Windows, version 26.0 (IBM Corp., Armonk, N.Y., USA). Due to the limited sample size and low event rate within the familial cohort, as well as varying follow-up completeness across the 35-year historical sporadic registry, formal Kaplan–Meier modeling and comparative survival analyses were not conducted; survival outcomes were reported descriptively as exploratory data.

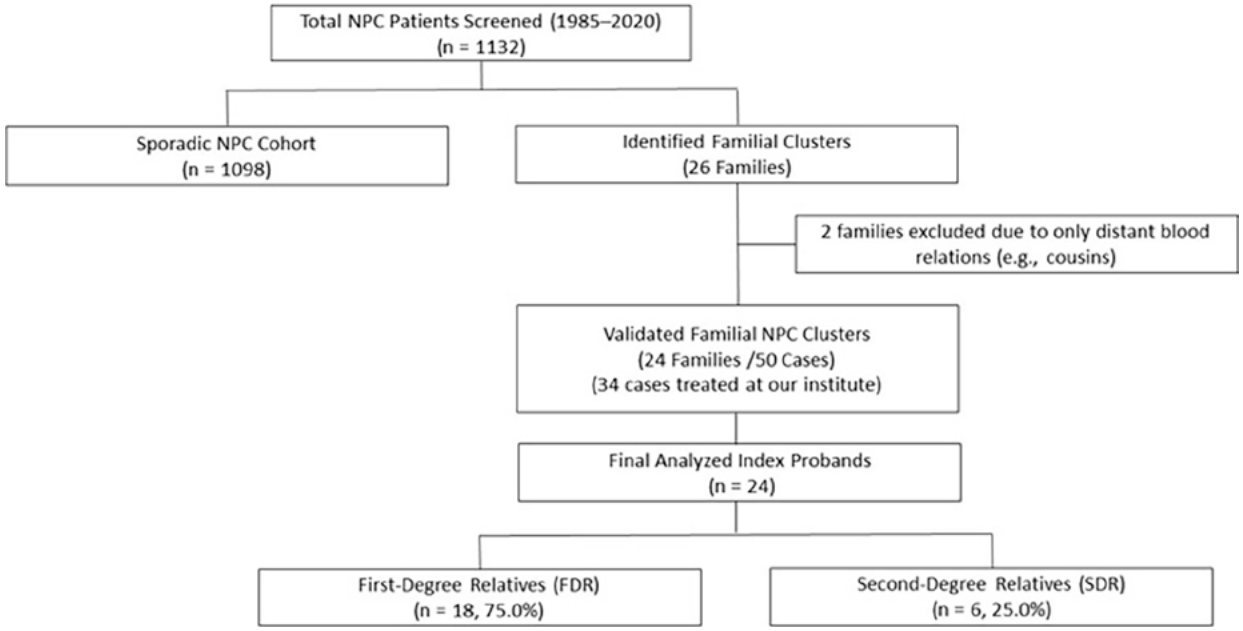

Fig. 1. Flow diagram of patient screening, cohort stratification, and patient selection for familial NPC.
NPC: Nasopharyngeal carcinoma; FDR: First-degree relative, SDR: Second-degree relative.

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Istanbul University, Oncology Institute (Date: April 17, 2026, No:4029480). Informed consent was obtained from all individual participants who were alive at the time of the study.

RESULTS

Among the 1,132 NPC patients screened, 24 familial clusters were identified, representing a familial NPC frequency of 2.1%. Among the 50 familial NPC cases, 34 had received treatment at our institute. After excluding 10 relatives who were part of the same clusters, the final analysis focused on 24 probands (Fig. 1).

Of these 24 families, 18 (75%) involved FDRs, and 6 (25%) involved second-degree relatives (SDRs). Two families met the criteria for high-frequency familial NPC (≥3 affected individuals).

Clinical Characteristics of Probands

The demographic, histopathological, and treatment characteristics of the 24 probands are summarized in Table 1. The majority of familial clusters (18/24) involved FDRs, with a striking predominance of sibling-to-sibling occurrences (14/24, 58.3%). The median age at diagnosis was 42.5 years (range: 12–70). Undifferentiated non-keratinizing carcinoma (World Health Organization type 3) was the most frequent histological subtype (66.7%).

Induction chemotherapy was administered to 79.2% of the probands, while 41.7% received concurrent chemoradiotherapy. After a median follow-up of 57.3 months (range: 4.8–236), 19 patients (79.2%) remained alive. Of the five deaths, four were due to disease progression, and one was related to a second primary malignancy (SPM). Specifically, one patient developed metastatic colon cancer 2 years after the initial diagnosis of NPC and succumbed to the disease a year later. Another patient had a history of seminoma, treated 8 years before the NPC diagnosis.

Comparison between Familial and Sporadic NPC Cohorts

Baseline demographic and clinicopathological features of familial probands (n=24) and the sporadic registry (n=1,098) are summarized in Table 2. Notably, a statistically significant difference was observed in sex distribution: while the sporadic cohort demonstrated a typical male predominance, the familial cohort was characterized by a higher proportion of female patients (p=0.011).

High-Frequency Familial NPC Clusters

In the first high-frequency family, three of six siblings were diagnosed with NPC, two of whom ultimately

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Table 1 Patient characteristics of the probands

	Frequency	%
Sex		
Female	13	54.2
Male	11	45.8
Histopathology		
WHO 1	2	8.3
WHO 2	6	25.0
WHO 3	16	66.7
Relationship		
Proband-Sibling	12	50.0
Proband-Niece/Nephew	5	20.8
Proband (Mother)-daughter	3	12.5
Proband (Father)-son	1	4.2
Proband-Aunt	1	4.2
Proband-Sibling-Sibling	1	4.2
Proband-Son-Sibling	1	4.2
Overall stage		
2	4	16.7
3	12	50.0
4a	8	33.3
IC		
Yes	19	79.2
No	5	20.8
Concurrent ChT		
Yes	10	41.7
No	14	58.3
Treatment response		
CR	20	83.3
PD	1	4.2
PR	3	12.5
Recurrence site		
Distant metastasis	2	8.3
Local recurrence	2	8.3
Locoregional recurrence	2	8.3
Regional recurrence	2	8.3
No recurrence	16	66.7
Last status		
Alive	19	79.2
Ex (Progression)	4	16.7
Ex (SPM)	1	4.2

NPC: Nasopharyngeal carcinoma; WHO: World Health Organization; IC: Induction chemotherapy; ChT: Chemotherapy; CR: Complete response; PD: Progressive disease; PR: Partial response; Ex: Exitus; SPM: Second primary malignancy.

Table 2 Comparison of baseline clinicopathological characteristics between familial probands and the sporadic nasopharyngeal carcinoma cohort

Parameter	Familial cohort (Probands, n=24)	Sporadic cohort (n=1,098)	p
Age at diagnosis (years)			
Median (range)	42.5 (12–70)	48.0 (6–85)	0.415
Sex, n (%)			0.011
Female	13 (54.2)	315 (28.7)	
Male	11 (45.8)	783 (71.3)	
Histological subtype, n (%)			0.902
WHO type 1	2 (8.3)	98 (8.9)	
WHO type 2	6 (25.0)	304 (27.7)	
WHO type 3	16 (66.7)	660 (60.1)	
Unspecified	0 (0.0)	36 (3.3)	—

Continuous variables were compared using the Mann–Whitney U test. Categorical variables were compared using the Chi-square test or Fisher's exact test, as appropriate. Histopathological comparison was performed among cases with documented subtypes (n=1,062 sporadic vs. n=24 familial). WHO: World Health Organization.

died from the disease. Additional malignancies in this family included breast cancer (mother), mesothelioma (father), and gastric cancer (paternal grandfather). In the second high-frequency family, NPC was diagnosed in the proband, the proband's son, and a sibling. No other malignancies were reported in this family (Table 3 and Fig. 2).

Family History of Non-NPC Malignancies in Relatives

In five of the 24 families (20.8%), at least one first- or second-degree relative was diagnosed with a non-NPC malignancy, including breast, prostate, and laryngeal cancers, mesothelioma, gastric cancer, and chronic myeloid leukemia (CML) (Table 4).

DISCUSSION

In this study, we investigated the clinical and demographic characteristics of familial NPC within a large cohort in Türkiye. Our analysis identified a familial frequency of 2.1%. Notably, the majority of familial clusters (75%) involved FDRs, with a striking predominance of sibling-to-sibling occurrences.

The reported rate of familial NPC in endemic regions typically ranges from 5.8% to 19%.[5–8] For instance, in a prospective study involving 200 patients from an en-

Table 3 Patients with high-frequency familial nasopharyngeal carcinoma

Family	Patient	Year of diagnosis	Sex	Age	Stage	Relationship	Last status
Family 1	1.1	1991	F	24	T3N3M0	Proband	NED
	1.2	1992	F	25	T1N2M0	Sibling	Ex
	1.3	2021	M	50	T1N3M1	Sibling	Ex
Family 2	2.1	2007	F	64	T2N1M0	Proband	Ex
	2.2	2007	M	38	Unknown	Son	Ex
	2.3	2012	F	53	T2N2M0	Sibling	NED

F: Female; M: Male; Ex: Exitus; NED: No evidence of disease.

Table 4 History of non-NPC malignancies among family members of probands

Family no	Affected relative	Relation to proband	Malignancy type (non-NPC)
Family 1	Relative 1	Paternal grandfather	Gastric
	Relative 2	Mother	Breast
	Relative 3	Father	Mesothelioma
Family 2	Relative 1	Mother	CML
Family 3	Relative 1	Sibling	Breast
Family 4	Relative 1	Father	Larynx
Family 5	Relative 1	Uncle	Larynx
	Relative 2	Uncle	Prostate

CML: Chronic myeloid leukemia; NPC: Nasopharyngeal carcinoma.

demic region, familial NPC – defined strictly as having an affected FDR – was identified in 15.5% of cases.[15] When applying this same strict definition to our cohort, the rate of familial NPC was 1.6%. Furthermore, while Loh et al.[15] reported 31 FDRs and 4 SDRs among their familial cases, our study identified 18 FDRs and 6 SDRs.

Extensive studies in endemic regions have explored the risk of familial aggregation using large cohorts, often comparing the risk among relatives of NPC patients with that of the general population. Across these large-scale cohort and registry investigations, an elevated familial risk has been consistently demonstrated among FDRs, with estimated risk elevations ranging from 1.2- to 4.6-fold.[16–18]

Family clustering of NPC is uncommon but has been well-documented even among non-endemic populations. One of the few register-based cohort studies to assess familial cancer risk in a low-incidence region was conducted by Liu et al.[19] in Sweden. Their findings revealed that the risk for NPC among FDRs remained significantly elevated (relative risk [RR]: 4.29), a result strikingly consistent with data from endemic cohorts.

The risk of other malignancies in the families of NPC probands varies. In endemic areas, studies generally indicated that the excessive risk is largely restricted to NPC.[16,17] However, a broader perspective is provided by the registry-based study in Sweden, a low-incidence region, where FDRs of NPC probands

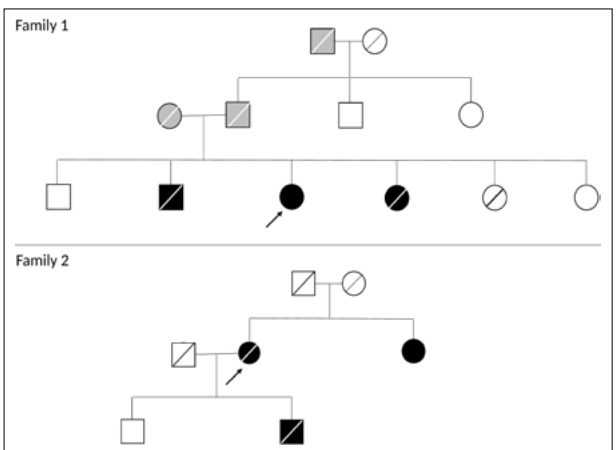

Fig. 2. Pedigrees of high-frequency nasopharyngeal carcinoma (NPC) families. Symbols: Squares indicate males; circles indicate females; black symbols represent NPC; gray symbols represent other malignancies; diagonal lines indicate deceased individuals.

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exhibited increased risks for salivary gland, laryngeal, prostate, and thyroid cancers.[19] The elevated incidence of salivary gland cancer in this cohort mirrors findings from studies in Greenland.[20] Along with salivary gland carcinoma, the RRs of uterine and cervix carcinoma were also significantly increased in the study by Friborg et al.[20] Our cohort displayed a notable diversity of non-NPC malignancies. In five of the 24 families (20.8%), at least one member was diagnosed with a non-NPC cancer. The most prominent example was a high-frequency familial NPC cluster where two siblings of the proband were affected; this family also had a significant history of other cancers, including breast cancer (mother), mesothelioma (father), and gastric cancer (paternal grandfather). Other observed malignancies included CML, prostate cancer, and laryngeal cancer.

Beyond familial clustering, the occurrence of SPMs in NPC patients themselves represents a distinct clinical entity. In the Taiwanese cohort, increased risks of secondary cancers (head and neck, bone, and hematopoietic systems) were primarily attributed to the late effects of radiotherapy (RT) rather than genetic predisposition.[17] These findings underscore the critical need for refining RT techniques, such as the use of intensity-modulated radiation therapy or proton therapy, and maintaining rigorous long-term surveillance. In our study, two patients developed non-NPC malignancies: one was diagnosed with metastatic colon and the other with seminoma.

The distribution of affected relatives within familial clusters is variable, though siblings consistently demonstrate the highest risk.[15,16] In our cohort of 24 families, 14 probands (58.3%) had affected relatives who were their siblings. Similarly, Liu et al.,[18] in their large-scale case-control study in Southern China, noted a significantly stronger association with maternal and sibling histories than with paternal history. The most striking evidence of this risk comes from Huang et al.,[21] who utilized the Taiwan National Health Insurance Research Database to reveal a 9.23-fold increased risk for siblings. Our findings reinforce this global pattern, suggesting that sibling-targeted screening may be the most high-yield strategy in familial NPC management.

An important point of debate in familial NPC is whether the clinical behavior of familial cases differs from that of their sporadic counterparts. While Loh et al.[15] reported no significant differences in clinical characteristics, other large-scale studies suggest a distinct biological profile for familial disease. For instance, Huang et al.[21] demonstrated a younger age of onset in familial cases (35.5 vs. 39.0 years; $p<0.0001$) within a Taiwanese cohort. This was further corroborated by Cao et al.[14] in high-risk Southern Chinese populations, where "high-frequency" familial NPC cases presented significantly earlier than sporadic cases (39 vs. 46 years). In our cohort, although familial probands presented at a younger median age than sporadic patients (42.5 vs. 48.0 years), the difference did not reach statistical significance ($p=0.415$). Interestingly, a distinct and statistically significant female predominance was observed among familial probands compared to the marked male predominance in sporadic cases (54.2% vs. 28.7%, $p=0.011$). Survival comparisons between cohorts were not performed due to historical registry limitations.

Beyond the age of onset, the prognostic significance of familial aggregation is particularly noteworthy.[14] Ouyang et al.[22] identified a first-degree family history as an independent favorable prognostic factor for both overall survival and distant metastasis-free survival. These findings suggest that familial NPC may represent a biologically distinct subset of the disease. While an underlying familial susceptibility may contribute to an earlier onset of malignancy, the resulting tumors may paradoxically exhibit a more indolent clinical course or a more robust response to contemporary therapeutic regimens. Consistent with this, our cohort demonstrated a high complete response rate (83.3%) and favorable survival outcomes (79.2% alive at a median follow-up of 57.3 months).

While high-frequency familial clusters (defined as families with ≥3 affected members) are more common in endemic regions, they remain rare in non-endemic areas.[16] Nevertheless, sporadic reports have documented such occurrences in low-incidence populations.[10] Our series contributes to this rare body of evidence with two distinct high-frequency families. In the first family, three siblings were diagnosed with NPC. In the second family, the disease affected the proband, one of the proband's siblings, and the proband's son. The importance of familial clustering in non-endemic regions, such as Türkiye, is further highlighted by the case report from Kara et al.[13] Although genetic analysis was performed on the proband and two living relatives, no specific germline susceptibility mutation was identified, suggesting that familial aggregation may involve multifactorial genetic or environmental factors rather than a single causative gene. We were unable to perform genetic analysis due to the retrospective nature of the cohort and the long study period beginning in the 1980s, when routine genetic testing was not available.

In addition to genetic susceptibility, environmental and infectious factors are also believed to contribute to familial clustering of NPC.[10,15–17,20,21] Previous studies have suggested that shared EBV exposure within families, combined with host genetic susceptibility, may contribute to the development of NPC. Shared environmental exposures such as dietary factors, tobacco exposure, and occupational carcinogens may also be relevant in families with similar lifestyles and living conditions. Therefore, familial NPC is generally considered a multifactorial disease resulting from the interaction between genetic predisposition, EBV infection, and environmental exposures rather than a purely hereditary cancer syndrome. In our cohort, EBV status and molecular viral analyses were not systematically available due to the retrospective design, the long study period, and the limited availability of historical virological data.

Limitations of the Study

This study represents one of the largest familial NPC cohorts from a non-endemic Mediterranean region, spanning over three decades of follow-up. However, it is not without limitations. As a retrospective, single-center study, the familial NPC rate may be underestimated since family members were not systematically contacted after the probands' death. The EBV status of the patients was not systematically available, which limited our ability to evaluate viral contribution to familial clustering. Furthermore, as our institution is a tertiary referral oncology center, potential referral bias may have enriched the proportion of complex or familial clusters identified in this cohort. In addition, given the limited sample size, long-term survival endpoints were considered exploratory, precluding comprehensive multivariate or Kaplan–Meier survival comparisons. Finally, genetic analysis could not be performed due to the retrospective design and limited availability of biological samples. Future prospective studies incorporating molecular and genomic profiling are needed to understand better the genetic and environmental susceptibility factors of NPC in Türkiye.

CONCLUSION

Our study confirms a familial NPC frequency of 2.1%. While this is lower than that in endemic regions, the high concentration of cases among FDRs – particularly siblings – and the presence of other primary malignancies suggest an underlying genetic susceptibility. Given these findings, siblings of NPC patients in non-endemic regions could be considered a subgroup that may benefit from increased clinical awareness.

Ethics Committee Approval: The study was approved by the Istanbul University, Oncology Institute Ethics Committee (no: 4029480, date: 17/04/2026).

Informed Consent: Informed consent was obtained from all individual participants who were alive at the time of the study.

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ORIGINAL ARTICLE

Investigation of the Molecular Effects of Temperature Change on Cold Shock Domain-containing Protein E1 in Hepatocellular Carcinoma Cells

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OBJECTIVE

Cold shock domain-containing protein E1 (CSDE1) is a multifunctional RNA-binding protein implicated in translation regulation, apoptosis, and cancer progression. While CSDE1 overexpression has been reported in several malignancies, its role in hepatocellular carcinoma under environmental stress conditions remains poorly understood.

METHODS

Human hepatocellular carcinoma hepatoma G2 (HepG2) cells were cultured under standard conditions (37°C) and cold stress (24°C). Morphological changes were assessed using phase-contrast microscopy and hematoxylin and eosin staining. CSDE1 messenger RNA (mRNA) expression was analyzed by reverse transcription quantitative real-time polymerase chain reaction, while protein levels in culture supernatants were measured using enzyme-linked immunosorbent assay (ELISA). In addition, molecular docking simulations were performed to evaluate the interaction of CSDE1 with the tyrosine kinase inhibitors lenvatinib and sorafenib.

RESULTS

Cold stress induced marked morphological alterations, including decreased cell density and disrupted cellular integrity. Although no significant change was observed in CSDE1 mRNA expression, CSDE1 protein levels were significantly elevated (p=0.019), suggesting possible post-transcriptional or post-translational regulation. Docking analysis showed that sorafenib had a more negative predicted binding score compared with lenvatinib; however, this finding does not demonstrate functional modulation of the therapeutic response. This study provides a basis for further studies to clarify the mechanistic and translational significance of CSDE1 under cold stress.

CONCLUSION

These findings show an increase in ELISA-detected CSDE1 signal in the culture supernatant of HepG2 cells under cold-stress conditions. This increase may reflect a passive release associated with the observed decrease in cell density and disruption of cellular integrity and provide direction for further studies aimed at distinguishing it from active secretion. This study provides a basis for further studies to clarify the mechanistic and translational significance of CSDE1 under cold stress.

Keywords: Cold shock protein; cold shock domain containing E1; hepatocellular carcinoma; hepatoma G2; molecular docking.

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INTRODUCTION

Temperature change is one of the most common environmental stressors encountered by living organisms. Organisms exposed to significant shifts in temperature have developed intricate cellular mechanisms to respond and adapt to these challenges, ensuring survival and functionality under stress conditions.[1]

In cancer biology, the tumor microenvironment (TME) plays a critical role in tumor growth, progression, and response to therapy. The TME comprises various components, including stromal cells, immune cells, cytokines, growth factors, extracellular matrix, and physicochemical conditions such as pH and temperature.[2] The TME orchestrates multiple tumorigenic processes, including epithelial-mesenchymal transition (EMT), migration, invasion, apoptosis, and resistance to chemotherapy.[3] Various types of microenvironments are commonly used and identified in *in vitro* cell cultures, including thermal and serum conditions.[4]

One notable environmental factor influencing the TME is temperature. While hypothermia promotes cellular adaptation and survival in non-physiological conditions,[5] hyperthermia can modulate tumor behavior by affecting temperature-sensitive signaling pathways.[6] In clinical oncology, hyperthermia has been used as an adjunct therapy for various cancers, such as prostate, melanoma, bladder, esophageal, and cervical cancers. Although some of the cellular effects of hypothermia and hyperthermia are known, studies on the full explanation of their molecular mechanisms remain limited.[7]

Among the key molecules responding to temperature fluctuations are cold shock proteins (CSPs). These evolutionarily conserved proteins are rapidly upregulated in response to a temperature drop and participate in the regulation of transcription, translation, cell cycle, differentiation, and apoptosis.[1] A hallmark of these proteins is the cold shock domain (CSD), which enables them to bind DNA and RNA and modulate gene expression.[8] CSD proteins can also bind to specific cell surface receptors, inducing various downstream effects.[9] Notably, overexpression of CSPs has been implicated in tumorigenesis by promoting malignant transformation, cell proliferation, inflammatory responses, and resistance to apoptosis. In many cancers, elevated CSP levels are associated with poor clinical outcomes.[10] One of the prominent members of the CSP family is CSD containing E1 (CSDE1), which plays a critical role in translation regulation, cell differentiation, apoptosis, and stress response. CSDE1 controls the initiation of messenger RNA (mRNA) translation and modulates the expression of target genes.[11] In human embryonic stem cells (hESCs), CSDE1 has been shown to bind to fatty acid-binding protein 7 (FABP7) and vimentin mRNAs and has been suggested to be an important post-transcriptional regulator of hESC identity.[12] Dysregulation of CSDE1 has been linked to cancer progression, with studies showing its overexpression in tumors such as melanoma, where it enhances invasion and metastasis.[13] In addition, CSDE1 has emerged as a potential drug target, prognostic biomarker, and anticancer drug sensitizer in various malignancies.[11–14] Hepatocellular carcinoma (HCC) is the most prevalent form of primary liver cancer, ranking fifth among global cancer types and fourth in cancer-related mortality. The pathogenesis of HCC is complex, involving alterations in signaling pathways, DNA methylation patterns, microRNA expression, and cell cycle regulation. Although the role of CSPs in cancer has been explored in several studies, the specific relationship between CSDE1 and HCC remains largely understudied.[15]

Despite increasing interest in CSPs in oncology, limited research exists on the role of CSDE1 in HCC. This study addresses this gap by examining how temperature stress impacts CSDE1 expression and secretion in HCC cells. In addition, molecular docking analysis was conducted to predict the interaction between CSDE1 and potential ligands or regulators which have been used for cancer therapy. Molecular docking is a computational approach used to model the binding between a receptor (e.g., protein) and a ligand, providing insights into binding affinity, interaction specificity, and potential drug-target relationships. In the context of CSDE1, docking simulations may help identify molecules that modulate its function, potentially altering cancer-related signaling pathways under temperature-induced stress.[16]

This study aims to evaluate the molecular effects of temperature variation on CSDE1 in HCC cells and explore its potential as a therapeutic target through expression profiling and computational docking analysis.

MATERIALS AND METHODS

Cell Culture and Study Design

Human HCC cell line hepatoma G2 (HepG2) was obtained from ATCC (American Type Culture Collection, USA). Cells were initially cultured in Dulbecco's Modified Eagle's Medium supplemented with 10% fetal bovine serum and 1% antibiotics (penicil-

lin-streptomycin). Cells reaching 60–70% confluence were treated with trypsin, removed from the culture dish, counted, and divided into two main groups. In the control group, cells were seeded in 12- and 6-well culture dishes containing round coverslips with 50,000 and 300,000 cells, respectively. When HepG2 cells covered 60-80% of the culture surface in an incubator (37°C and 5% carbon dioxide); further, analyses described below were performed. In the experimental group, HepG2 cells were cultured in the same number in appropriate culture dishes and placed in culture conditions at 24°C. To ensure temporal consistency between conditions, the experimental group was initiated simultaneously with the control group, with temperature maintained in a separate incubator set to 24°C, while the control group was maintained under standard culture conditions at 37°C. Further analyses were performed in parallel with the control group.

Monitoring of Morphological Changes

To evaluate the changes in the morphology of HepG2 cells, live images of the cells were examined under an inverted phase microscope (Primovert, Zeiss, AG), and the images were recorded. When the cells in the control group were 60–80% confluent, both groups of cells were fixed simultaneously with appropriate fixative and stained with hematoxylin-eosin stain after fixation. The stained samples were examined and photographed under a light microscope (Primo Star, Zeiss, AG).

Total RNA Isolation and Complementary DNA (cDNA) Synthesis

RNA extraction of the experimental groups was then performed using an RNA Purification kit (innuPREP RNA Mini kit 2.0, Cat. No: 049-21, Innuscreen GmbH, Germany), according to the manufacturer's instructions. The concentration and purity of the extracted RNA samples were subsequently assessed with a BioTek Synergy Microplate Reader (Agilent Technologies, Inc.), utilizing ultraviolet absorbance. The Thermo Scientific RevertAid First Strand cDNA Synthesis kit (Cat. no. Thermo Fisher Scientific, Inc.) was employed to synthesize cDNA from total RNA, following the instructions provided by the manufacturer.

Reverse Transcription Quantitative Real-Time Polymerase Chain Reaction

Quantitative polymerase chain reaction (qPCR) was conducted on a LightCycler® 96 instrument (Roche Diagnostics) using the Ampliqon RealQ Plus Master Mix Green Without ROX kit (cat. no. A323402, Ampliqon A/S) and gene-specific primers for CSDE1 (forward sequence. 5′-CGAGAAATGGGTGTGATTGCT-3′ and reverse sequence 5′- CACGATCCACACACTTGATGAA-3′) and GAPDH (forward sequence, 5′- GCACCGTCAAGGCTGAGAAC-3′ and reverse sequence, 5′- GGATCTCGCTCCTGGAAGATG-3′). qPCR was performed using the following thermocycling conditions: Initial denaturation at 95°C for 10 min, followed by 40 cycles of denaturation at 95°C for 15 s, annealing at 58°C for 15 s, and extension at 72° C for 10 s. qPCR primer sequences were obtained from BMLabosis. The 2-ΔΔCq was employed for the relative quantification of gene expression, with GAPDH serving as the internal control.[17]

Measurement of CSDE1

CSDE1 levels in the supernatant of cell culture of the experimental groups were measured by the use of a commercial colorimetric kit (ELK Biotechnology, Turkey, Cat: ELK6392, Lot:36451010).

Molecular Docking Analysis

In the present study, the molecular interactions between CSDE1 and the drugs lenvatinib and sorafenib were investigated. The full-length, three-dimensional model of the human CSDE1 protein, as predicted by AlphaFold, was obtained from the AlphaFold Protein Structure Database (UniProt accession number: O75534, AlphaFold model ID AF-O75534-F1). In the molecular docking analysis, CSDE1 was used as the receptor, with lenvatinib and sorafenib acting as the anticancer drugs. The CSDE1 structure used is a computationally predicted AlphaFold model. The structures of lenvatinib (PubChem CID: 9823820) and sorafenib (PubChem CID: 216239) were obtained from the PubChem database. Hydrogen atoms were added to the ligand structures and partial atomic charges were then assigned. After the preparation of the ligand and receptor molecules, molecular docking experiments were performed using the AutoDock Vina program.[18] The best binding positions were then selected based on AutoDock Vina scores. The interactions between the receptor and ligand molecules were visualized using BIOVIA Discovery Studio Visualizer (Dassault Systèmes BIOVIA, 2019, San Diego).

Statistical Analysis

The Statistical Package for Social Sciences (SPSS) for Windows 20 (IBM SPSS Inc., Chicago, USA) was used for statistical assessments. All experiments were carried out with at least three independent biological replicates ($n \geq 3$). First, the Shapiro–Wilk test was used to assess whether the obtained data were distributed normally.

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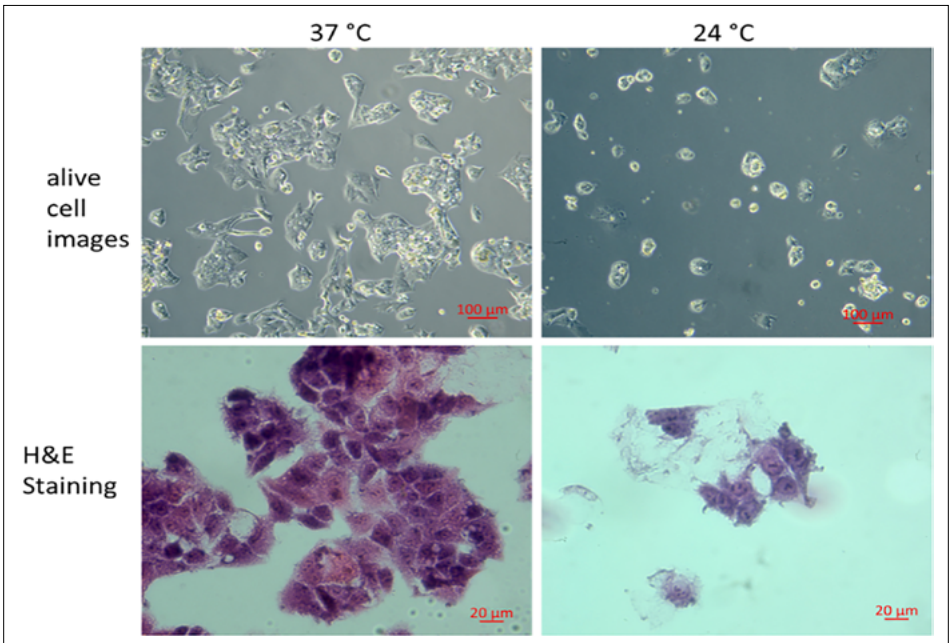

Fig. 1. Morphological images. Hepatoma G2 cells under an inverted microscope and a light microscope, with hematoxylin and eosin staining.

Subsequently, the independent-samples Student's t-test was used to analyze the experimental groups. Relative gene expression was calculated using the $2^{-\Delta\Delta Ct}$ method. P<0.05 was considered statistically significant.

RESULTS

Morphological Change

The morphological findings obtained from phase-contrast live-cell microscopy were consistent with those observed in hematoxylin and eosin-stained sections across both groups; notably, cells in the experimental group cultured at 24°C showed reduced cell density and impaired cellular integrity relative to the control group (Fig. 1).

CSDE1 Gene Expression Level

As shown in Figure 2, the effects of temperature change on CSDE1 gene expression level were higher in the cold-shocked (24°C) group compared to the control group (t(4)=−1.03, p=0.360). However, the difference was not found to be statistically significant.

CSDE1 Protein Level in Culture Supernatant

As shown in Figure 3, CSDE1 protein detected from HepG2 cell supernatants was found to be significantly higher in 24°C cell culture conditions compared to the control group at 37°C (t(4)(6)=−3.81, p=0.009).

Molecular Docking

The predicted interactions between CSDE1 and lenvatinib and sorafenib are illustrated in Figure 4 and 5, respectively. The predicted binding score for lenvatinib and sorafenib were -3.8 kcal/mol and -8.7 kcal/mol, respectively. The drugs lenvatinib and sorafenib are tyrosine kinase inhibitors are used in the treatment of cancer . Sorafenib showed a more negative predicted binding score against CSDE1 than lenvatinib in this in silico analysis; however, no binding assay, drug-treatment experiment, target-engagement analysis, or functional validation was performed, and this computational finding does not demonstrate physical binding or a functional role for CSDE1 in the response to these drugs.

DISCUSSION

CSPs are evolutionarily conserved proteins found across almost all organisms and are known to play critical roles in gene expression regulation, cellular differentiation, proliferation, and survival under environmental stress conditions.[12] Among these, CSDE1 has emerged as a key regulator in several cancers due to its ability to control mRNA translation and modulate oncogenic pathways.[11] In our study, morphological evaluation of HepG2 cells under cold shock (24°C) revealed decreased cell density and disrupted cell in-

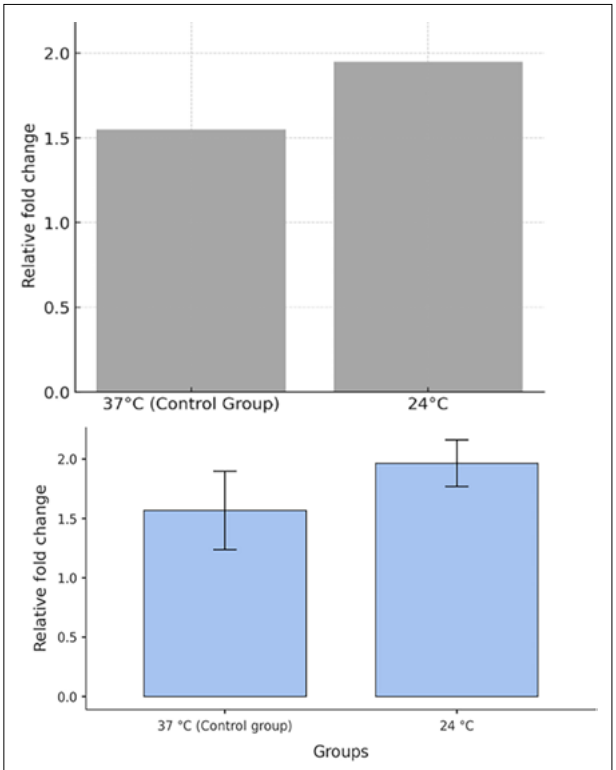

Fig. 2. Cold shock domain-containing protein E1 relative messenger RNA fold change ($2^{-\Delta\Delta Ct}$) in hepatoma G2 cells cultured at 37°C (control) and 24°C (cold shock). Bars represent group means; error bars indicate the standard deviation. Individual biological replicate values are overlaid as dots (n=3/group). Analyzed by independent samples t-test using the Statistical Package for Social Sciences statistical software.

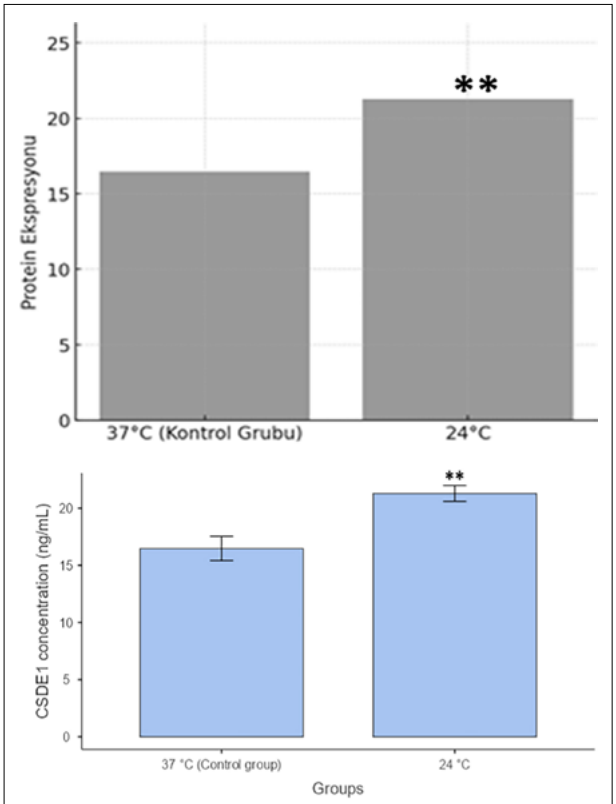

Fig. 3. Cold shock domain-containing protein E1 protein concentration (ng/mL) in hepatoma G2 cell culture supernatants, measured by enzyme-linked immunosorbent assay (450 nm) and calculated from the kit standard curve. Bars represent group means; error bars indicate the standard deviation. Individual biological replicate values are overlaid as dots (n=4/group). Analyzed by independent-samples t-test using the Statistical Package for Social Sciences statistical software (**p<0.01).

tegrity compared to control conditions, together with increased cytoplasmic granularity in some surviving cells; whether this reflects a stress-induced adaptive response or early cytotoxicity cannot be determined from morphology alone. These observations are consistent with reports that temperature-induced stress can lead to apoptosis or trigger adaptive responses in cancer cells,[5] although the present study did not include a dedicated viability or apoptosis assay to distinguish between these possibilities.

Although CSDE1 gene expression showed a nonsignificant increase under cold-shock conditions, the CSDE1 signal detected by enzyme-linked immunosorbent assay (ELISA) in the culture supernatant was significantly higher in the cold-shock group (p=0.019, two-way). A nonsignificant change in mRNA level does not by itself demonstrate that transcription was unaffected, particularly given the small sample size, and the increase in supernatant signal does not by itself establish increased intracellular protein production, stability, or active secretion. Because cold shock also reduced cell density and disrupted cellular integrity in our morphological assessment, passive release of intracellular CSDE1 from damaged or dying cells is a plausible alternative explanation for the elevated supernatant signal, one that could be evaluated in future work using viability and membrane-damage assays, together with parallel measurement of intracellular CSDE1 and normalization to viable cell number or total cellular protein. Cold-stress-associated changes in protein handling have been described in other contexts,[19] but the present data cannot establish which specific mechanism underlies the finding in HepG2 cells.

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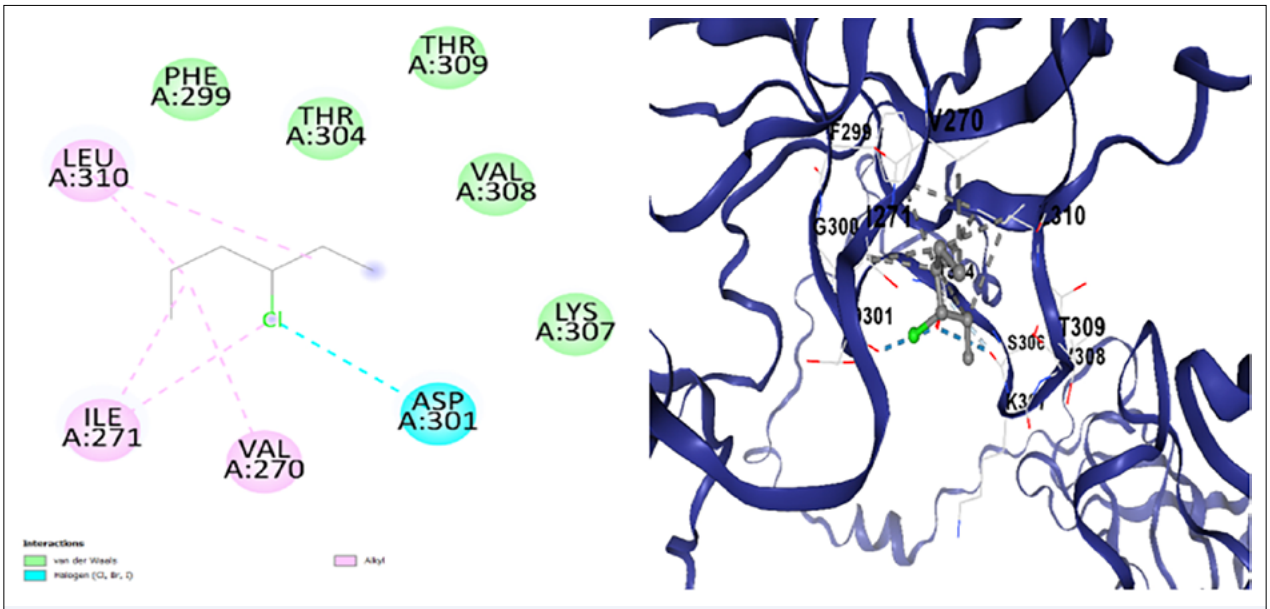

Fig. 4. Interactions of lenvatinib docked to the cold shock domain-containing protein E1.

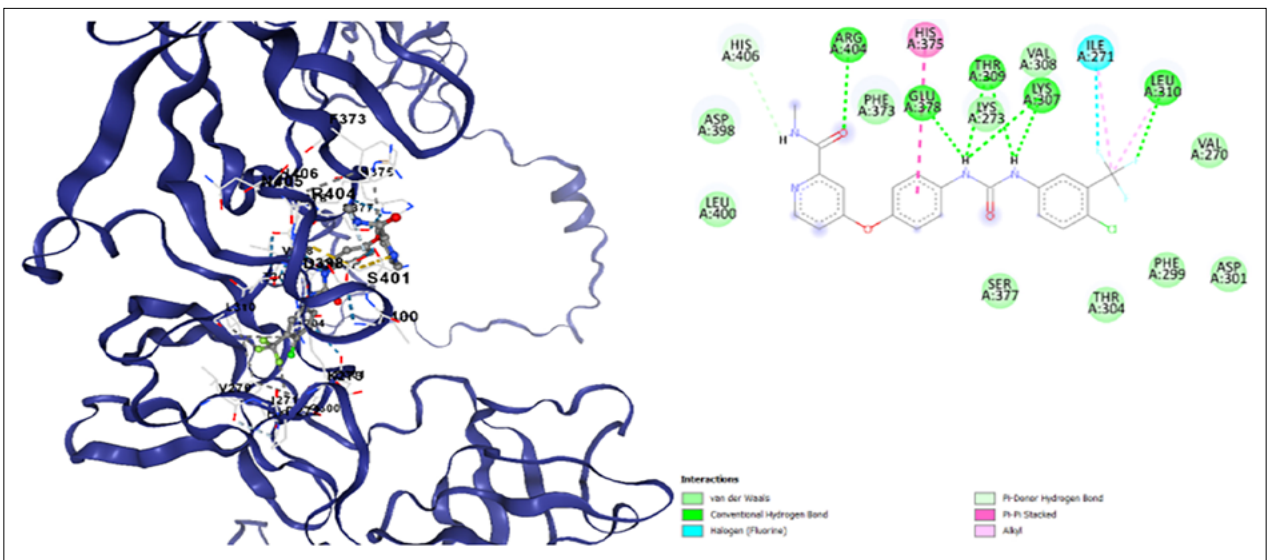

Fig. 5. Interactions of sorafenib docked to the cold shock domain-containing protein E1 macromolecule and amino acid residues involved in hydrogen bonding.

Previous studies have shown that CSDE1 is upregulated in various cancer types, including colorectal, pancreatic, melanoma, and breast cancers, where it promotes proliferation, migration, EMT, and resistance to apoptosis.[11] In triple-negative breast cancer, CSDE1 knockdown has been shown to downregulate RAC1 signaling; whether an analogous CSDE1-RAC1-ERK axis operates in HCC has not, to our knowledge, been directly demonstrated, and our data-based on a single cell line without gene knockdown or pathway-level analysis -do not test this possibility. Any parallel between our findings and RAC1/ERK-mediated oncogenic signaling in HCC should therefore be regarded as a hypothesis for future testing rather than a conclusion supported by the present study.[20]

Interestingly, while CSDE1 is generally described as an oncogene, tumor-suppressive roles have also been reported, such as in pheochromocytoma and paraganglioma[21] and oral squamous cell carcinoma.[22] This duality underscores the context-depen-

dent nature of CSDE1's role across tumor types and argues against extrapolating a single functional role to HCC without direct evidence.

Overall, culturing HepG2 cells at 24°C was associated with morphological changes, a nonsignificant increase in CSDE1 mRNA, and a significant increase in ELISA-detected CSDE1 signal in the culture supernatant. These observations are compatible with, but do not establish, post-transcriptional or post-translational regulation of CSDE1 under cold stress, and they do not distinguish active secretion from passive release associated with reduced cell viability. Given the single-cell-line design, the small number of replicates, and the absence of functional validation (e.g., CSDE1 knockdown or overexpression), we regard these findings as preliminary and hypothesis-generating rather than as evidence that CSDE1 functions as an adaptive survival factor, a prognostic biomarker, or a therapeutic target in HCC.

CONCLUSION

This study examined the effect of cold stress (24°C) on CSDE1 in HepG2 cells. Morphological assessment showed reduced cell density and disrupted cellular integrity at 24°C compared with standard culture conditions. CSDE1 mRNA expression was not significantly altered, whereas ELISA-detected CSDE1 signal in the culture supernatant was significantly higher under cold stress. Because this increase coincided with signs of reduced cell density and disrupted membrane integrity, it may reflect passive release of intracellular protein rather than confirmed active secretion; the present data cannot distinguish between these mechanisms. Molecular docking indicated a more negative predicted binding score for sorafenib than for lenvatinib against CSDE1; in the absence of binding or functional assays, this should be regarded as an exploratory, hypothesis-generating observation rather than evidence of a functional interaction.

Based on a single cell line, without independent biological replication, viability or membrane-damage assays, intracellular CSDE1 measurement, or functional validation, CSDE1 cannot at this stage be presented as an established prognostic biomarker, therapeutic target, or mediator of adaptive survival in HCC. Further studies incorporating independent biological replicates, viability/membrane-integrity assays, parallel intracellular and extracellular CSDE1 measurement, and functional experiments such as CSDE1 knockdown or overexpression are needed to clarify whether the changes observed here reflect a regulated biological response and to evaluate their relevance to HCC biology and therapy.

Ethics Committee Approval: Since this is a cell culture study, an ethics committee approval is not required.

Informed Consent: It is a cell culture study.

Conflict of Interest Statement: The authors declare that they have no conflicts of interest with the contents of this article.

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ORIGINAL ARTICLE

Multicentric Glioblastoma: A Retrospective Analysis of Demographic, Clinical, Molecular and Prognostic Characteristics

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OBJECTIVE

The objective of the study was to compare the demographic, clinical, molecular and prognostic characteristics and survival outcomes of patients with multicentric glioblastoma (GBM) with those of patients with unifocal GBM.

METHODS

Patients with GBM referred to a single radiation oncology department between September 2015 and September 2022 were retrospectively reviewed. All cases were reclassified according to the 2021 World Health Organization Classification of Tumors of the Central Nervous System, and isocitrate dehydrogenase-mutant tumors were excluded. The final cohort comprised 76 patients with unifocal and 20 with multicentric GBM. Survival was analysed with the Kaplan–Meier method and Cox regression.

RESULTS

Median progression-free survival was 6 months in the multicentric group and 9 months in the unifocal group (p=0.031); median overall survival was 8 and 13 months, respectively (p=0.021). Poor performance status (Eastern Cooperative Oncology Group [ECOG] >2: 50% vs. 2.6%), bihemispheric involvement (60% vs. 2.6%) and a higher Ki-67 index were significantly more frequent in multicentric GBM. In the unifocal cohort, ECOG performance status was an independent predictor of progression and, together with age, of mortality; gross total and subtotal resection were associated with better outcomes than biopsy. No independent prognostic factor was identified in the multicentric cohort. The proportion of multicentric cases increased numerically after 2020, coinciding with the COVID-19 pandemic.

CONCLUSION

Multicentric GBM is associated with poorer performance status, higher proliferative activity, more frequent bihemispheric involvement and shorter survival than unifocal GBM. Whether the post-2020 increase in multicentric presentations is related to COVID-19 should be investigated in larger prospective cohorts.

Keywords: Glioblastoma; multicentric glioblastoma; COVID-19.
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INTRODUCTION

Glioblastoma (GBM) is the most common and most aggressive primary malignant brain tumor in adults. Defined in the 2021 World Health Organization (WHO) Classification of Tumors of the central nervous system (CNS) as an isocitrate dehydrogenase (IDH)-wildtype diffuse astrocytic glioma of CNS WHO grade 4, GBM accounts for approximately half of all primary malignant brain tumors.[1] The standard first-line treatment consists of maximal safe resection followed by radiotherapy (RT) with concomitant and adjuvant temozolomide; nevertheless, median overall survival (OS) remains around 15 months.[2]

Within the clinical spectrum of GBM, tumors presenting with more than one lesion pose a particular management challenge. Multifocal GBM refers to multiple lesions connected by a recognizable route of spread, such as white-matter tracts or cerebrospinal fluid and leptomeningeal dissemination, whereas multicentric GBM refers to anatomically separate lesions that cannot be explained by any known pathway of spread.[3] The reported incidence of multifocal/multicentric GBM ranges from 2% to 35%, and true multicentric tumors are estimated to account for approximately 10% of all cases.[4,5] Both subgroups have been associated with a poorer prognosis, lower rates of gross total resection and a higher risk of recurrence than unifocal GBM.[6,7]

In our clinic, an apparent increase in the number of multicentric GBM cases since 2020 drew attention due to its temporal overlap with the COVID-19 pandemic. The aim of this study was to compare the demographic, clinical, molecular and survival characteristics of patients with multicentric and unifocal GBM and to explore this possible association.

MATERIALS AND METHODS

Study Design and Patients

This single-center retrospective study screened 116 patients with GBM who were referred to the radiation oncology department of a tertiary university hospital between September 2015 and September 2022. All cases were re-evaluated according to the 2021 WHO Classification of Tumors of the CNS, and 20 patients with IDH-mutant tumors, which are no longer classified as GBM, were excluded (n=20). The final study population consisted of 96 patients: 76 with unifocal and 20 with multicentric GBM.

Multicentric disease was defined on contrast-enhanced T1-weighted and fluid-attenuated inversion recovery magnetic resonance imaging (MRI) as two or more anatomically separate lesions without a detectable connection or known route of spread.[3] Demographic data, Eastern Cooperative Oncology Group performance status (ECOG PS), tumor location and hemispheric involvement, extent of resection (biopsy, subtotal resection [STR] or gross total resection [GTR]), p53 status, Ki-67 proliferation index, RT dose and survival status were retrieved from medical records. RT was delivered with intensity-modulated RT, volumetric-modulated arc therapy or three-dimensional conformal RT to a total dose of 60 Gy; patients with poor performance status received a hypofractionated regimen of 40 Gy in 15 fractions. All patients received concomitant and adjuvant temozolomide. Follow-up MRI was performed 1 month after the completion of RT and every 3 months thereafter. For patients diagnosed after the onset of the pandemic, history of COVID-19 infection and vaccination was recorded where available.

Ethics

The study was approved by the Şişli Memorial Hospital Ethics Committee (Decision no: 006, Date: December 12, 2023) and was conducted in accordance with the Declaration of Helsinki.

Owing to the retrospective design, informed consent was not obtained from patients. The study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

Statistical Analysis

Analyses were performed with IBM Statistical Package for the Social Sciences Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY, USA). Normality was assessed with the Kolmogorov–Smirnov and Shapiro–Wilk tests. As continuous variables were not normally distributed, they were compared with the Mann–Whitney U test and are presented as median (minimum–maximum) together with mean±standard deviation. Categorical variables were compared with Pearson's Chi-square test, the Chi-square test with Yates' continuity correction or Fisher's exact test, as appropriate, and are presented as number (percentage). Progression-free survival (PFS) was defined as the time from diagnosis to progression, death or last follow-up, and OS as the time from diagnosis to death or last follow-up, both in months. Survival was estimated with the Kaplan–Meier method and compared with the log-rank test. Factors associated with PFS and OS were analysed separately within each cohort using univariate and multivariate Cox proportional hazards regression, and results are presented as hazard ratios (HRs) with 95% confidence intervals (CIs). Variables that made the multivariate

Table 1 Comparison of categorical variables between patients with multicentric and unifocal GBM

	Multicentric GBM (n=20)	Unifocal GBM (n=76)	Test statistic	p
Age group (years)				
<60	9 (45.0)	40 (52.6)	0.127	0.722[b]
≥60	11 (55.0)	36 (47.4)		
Sex				
Female	10 (50.0)	29 (38.2)	0.495	0.482[b]
Male	10 (50.0)	47 (61.8)		
ECOG PS				
0–2	10 (50.0)	74 (97.4)	–	**<0.001**[c]
>2	10 (50.0)	2 (2.6)		
Extent of resection				
Biopsy	1 (5.0)	5 (6.6)	1.726	0.422[a]
GTR	1 (5.0)	12 (15.8)		
STR	18 (90.0)	59 (77.6)		
p53 mutation				
Negative	2 (18.2)	20 (29.0)	–	0.718[c]
Positive	9 (81.8)	49 (71.0)		
RT dose				
<60 Gy	6 (30.0)	15 (19.7)	–	0.366[c]
≥60 Gy	14 (70.0)	61 (80.3)		
Ki-67 index				
≤20%	0 (0)	31 (44.9)	–	**0.005**[c]
>20%	10 (100)	38 (55.1)		
Hemispheric involvement				
Bihemispheric	12 (60.0)	2 (2.6)	–	**<0.001**[c]
Unihemispheric	8 (40.0)	74 (97.4)		
Tumor location				
Infratentorial	0 (0)	1 (1.3)	4.174	0.124[a]
Supratentorial	18 (90.0)	74 (97.4)		
Supratentorial and infratentorial	2 (10.0)	1 (1.3)		
Survival status				
Deceased	14 (70.0)	58 (76.3)	0.084	0.772[b]
Alive	6 (30.0)	18 (23.7)		

Data are presented as n (%); percentages are calculated among patients with available data. [a]: Pearson's Chi-square test; [b]: chi-square test with Yates' continuity correction; [c]: Fisher's exact test. GBM: Glioblastoma; ECOG PS: Eastern Cooperative Oncology Group performance status; GTR: Gross total resection; STR: Subtotal resection; RT: Radiotherapy.

models unstable were not included in them, and tumor location was not entered into the Cox models due to the small number of observations in some categories. A two-sided p<0.05 was considered statistically significant.

RESULTS

Patient Characteristics

Multicentric disease accounted for 20.8% (20/96) of the study population. In the multicentric group, the female-to-male ratio was 1:1, and the median age was 62.5 (range, 27–74) years. ECOG PS 0–2 was observed in 50% of patients with multicentric GBM and in 97.4% of those with unifocal GBM (p<0.001). Bihemispheric involvement was present in 60% of the multicentric group and in 2.6% of the unifocal group (p<0.001). A Ki-67 index >20% was found in all evaluable multicentric tumors (10/10) compared with 55.1% of unifocal tumors (p=0.005). Age group, sex, extent of resection, p53 status, RT dose, tumor location and survival status did not differ significantly between the groups (Table 1).

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Table 2 Comparison of continuous variables between patients with multicentric and unifocal GBM

	Multicentric GBM (n=20)		Unifocal GBM (n=76)		Test statistic	p[a]
	Mean±SD	Median (min–max)	Mean±SD	Median (min–max)		
Age (years)	57.25±13.47	62.5 (27–74)	56.55±12.90	58 (29–77)	712	0.655
Time to progression (months)	6.18±5.42	5 (1–26)	10.16±8.35	7.5 (0.3–39)	740	**0.023**
Follow-up (months)	9.15±10.06	6 (1–48)	16.37±11.52	12 (0.3–51)	1154.5	**<0.001**
ECOG PS	2.35±0.75	2.5 (1–3)	1.12±0.80	1 (0–3)	229	**<0.001**
RT dose (Gy)	55.33±8.58	60 (34–60)	57.30±6.21	60 (39–60)	841	0.312
Ki-67 index (%)	58±15	60 (35–85)	33±21	30 (1–90)	114	**0.001**

[a]: Mann–Whitney U test. GBM: Glioblastoma; SD: Standard deviation; ECOG PS: Eastern Cooperative Oncology Group performance status; RT: Radiotherapy.

Table 3 Kaplan–Meier estimates of progression-free survival according to patient group

Group	Mean (95% CI)	Median (95% CI)	p[a]
Multicentric GBM	7.95 (3.72–12.19)	6 (4.76–7.24)	**0.031**
Unifocal GBM	14.58 (11.45–17.72)	9 (7.15–10.85)	
Total	13.52 (10.76–16.27)	8 (6.66–9.34)	

Survival times are given in months. [a]: Log-rank test. CI: Confidence interval; GBM: Glioblastoma.

Table 4 Kaplan–Meier estimates of overall survival according to patient group

Group	Mean (95% CI)	Median (95% CI)	p[a]
Multicentric GBM	13.99 (4.87–23.12)	8 (4.94–11.06)	**0.021**
Unifocal GBM	19.53 (15.88–23.18)	13 (10.96–15.04)	
Total	18.33 (15.03–21.64)	12 (10.36–13.65)	

Survival times are given in months. aLog-rank test. CI: Confidence interval; GBM: Glioblastoma.

In the comparison of continuous variables, median time to progression was 5 months in the multicentric group and 7.5 months in the unifocal group (p=0.023), and median follow-up was 6 and 12 months, respectively (p<0.001). The median Ki-67 index was 60% in the multicentric group and 30% in the unifocal group (p=0.001) (Table 2).

Survival

Median PFS was 6 months (95% CI: 4.76–7.24) in the multicentric group and 9 months (95% CI: 7.15–10.85) in the unifocal group (p=0.031) (Table 3 and Fig. 1). Median OS was 8 months (95% CI: 4.94–11.06) and 13 months (95% CI: 10.96–15.04), respectively (p=0.021) (Table 4 and Fig. 2).

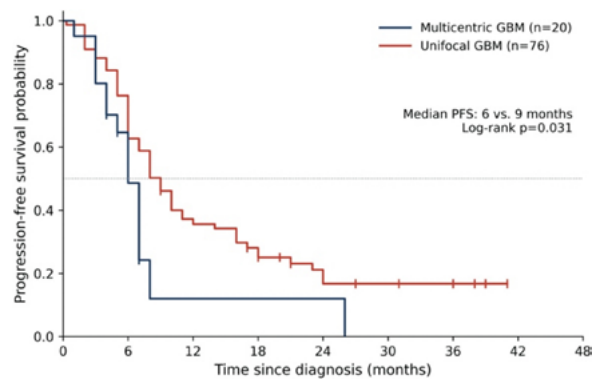

Fig. 1. Kaplan–Meier curves of progression-free survival in patients with multicentric and unifocal glioblastoma. Vertical tick marks indicate censored observations. The dotted horizontal line indicates a survival probability of 0.5.

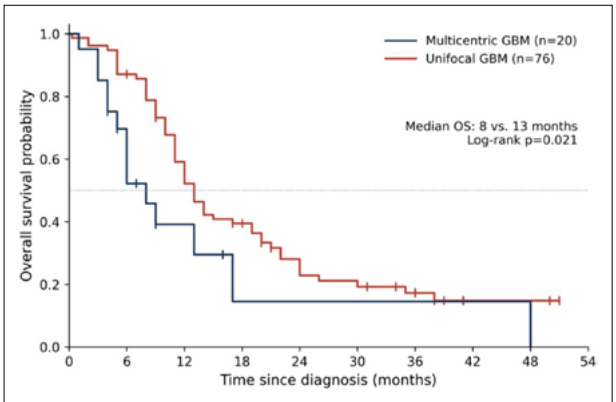

Fig. 2. Kaplan–Meier curves of overall survival in patients with multicentric and unifocal glioblastoma. Vertical tick marks indicate censored observations. The dotted horizontal line indicates a survival probability of 0.5.

Table 5 Cox regression analysis of factors associated with progression-free survival within each patient group

Cohort	Variable	Univariate		Multivariate	
		HR (95% CI)	p	HR (95% CI)	p
Multicentric GBM	Age	1.035 (0.985–1.087)	0.177	0.937 (0.753–1.167)	0.562
	Sex	2.323 (0.689–7.836)	0.174	11.124 (0.639–193.741)	0.098
	ECOG PS	2.027 (0.849–4.837)	0.112	1.692 (0.072–39.739)	0.744
	Ki-67 index	6.192 (0.076–507.376)	0.417	0.001 (<0.001–>1000)	0.463
	p53 mutation	2.036 (0.229–18.066)	0.523	–	–
	RT dose (Gy)	0.963 (0.908–1.021)	0.210	1.052 (0.897–1.235)	0.532
	Extent of resection (ref: biopsy)				
	GTR	0.751 (<0.001–>1000)	0.972	–	–
	STR	24.613 (<0.001–>1000)	0.661	–	–
	Hemispheric involvement	0.658 (0.209–2.071)	0.474	0.004 (<0.001–6.965)	0.145
Unifocal GBM	Age	1.021 (0.997–1.046)	0.084	1.021 (0.992–1.050)	0.158
	Sex	1.317 (0.765–2.266)	0.321	0.958 (0.525–1.748)	0.890
	ECOG PS	3.323 (2.207–5.005)	**<0.001**	3.448 (2.118–5.613)	**<0.001**
	Ki-67 index	1.083 (0.292–4.013)	0.905	0.621 (0.156–2.479)	0.500
	p53 mutation	0.958 (0.517–1.776)	0.893	–	–
	RT dose (Gy)	0.989 (0.944–1.037)	0.656	0.992 (0.940–1.046)	0.761
	Extent of resection (ref: biopsy)				
	GTR	0.013 (0.003–0.058)	**<0.001**	–	–
	STR	0.127 (0.045–0.361)	**<0.001**	–	–
	Hemispheric involvement	0.321 (0.076–1.348)	0.120	0.651 (0.145–2.932)	0.577

–: Not included in the multivariate model. Ki-67 index was entered as a continuous variable (0–1 scale). Extent of resection was analysed with biopsy as the reference category. Confidence limits below 0.001 or above 1000 are shown as <0.001 or >1000 (unstable estimates owing to the small number of events). HR: Hazard ratio; CI: Confidence interval; GBM: Glioblastoma; ECOG PS: Eastern Cooperative Oncology Group performance status; RT: Radiotherapy; GTR: Gross total resection; STR: Subtotal resection.

Prognostic Factors

In the Cox analysis for PFS (Table 5), ECOG PS was an independent prognostic factor in the unifocal cohort (multivariate HR: 3.448, 95% CI: 2.118–5.613, p<0.001). In univariate analysis, both GTR (HR: 0.013, 95% CI: 0.003–0.058, p<0.001) and STR (HR: 0.127, 95% CI: 0.045–0.361, p<0.001) were associated with a significantly lower risk of progression than biopsy. In the analysis for OS (Table 6), age (HR: 1.037, 95% CI: 1.006–1.070, p=0.019) and ECOG PS (HR: 6.184, 95% CI: 3.568–10.719, p<0.001) were independent predictors of mortality in the unifocal cohort. No independent prognostic factor was identified in the multicentric cohort in either analysis (all p>0.05).

Distribution by Year of Diagnosis

Of the 20 multicentric cases, 10 were diagnosed between 2015 and 2019 and 10 between 2020 and 2022. Relative to all screened patients, the proportion of multicentric cases increased from 13.3% (10/75) in 2015–2019 to 24.4% (10/41) in 2020–2022, with the highest annual number (n=6) recorded in 2022; however, this difference was not statistically significant (Fisher's exact test, p=0.197) (Fig. 3). Among patients diagnosed after the onset of the pandemic with available data, four patients had a history of COVID-19 vaccination and four other patients had a history of COVID-19 infection.

DISCUSSION

The management of GBM requires an effective multidisciplinary approach involving neurosurgery, radiation oncology and medical oncology. The reported incidence of multifocal/multicentric GBM ranges from 2% to 35%.[4,5,8] This wide range largely reflects differences in definitions and imaging techniques. The classical criteria of Batzdorf and Malamud defined multicentric gliomas as widely separated lesions, located in different lobes or hemispheres, without any macroscopic or microscopic connection.[9] With modern MRI, and especially FLAIR sequences, connections can be seen between lesions that once appeared separate, so some apparently multicentric tumors are reclassi-

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Table 6 Cox regression analysis of factors associated with overall survival within each patient group

Cohort	Variable	Univariate		Multivariate	
		HR (95% CI)	p	HR (95% CI)	p
Multicentric GBM	Age	1.025 (0.977–1.075)	0.321	0.920 (0.759–1.114)	0.393
	Sex	2.239 (0.661–7.585)	0.195	15.564 (0.722–335.626)	0.080
	ECOG PS	2.126 (0.905–4.996)	0.084	1.944 (0.189–19.983)	0.576
	Ki-67 index	6.778 (0.065–705.004)	0.419	0.001 (<0.001–>1000)	0.435
	p53 mutation	1.676 (0.184–15.243)	0.646	–	–
	RT dose (Gy)	0.973 (0.920–1.029)	0.337	1.024 (0.889–1.180)	0.743
	Extent of resection (ref: biopsy)				
	GTR	0.737 (<0.001–>1000)	0.972	–	–
	STR	24.478 (<0.001–>1000)	0.688	–	–
	Hemispheric involvement	0.852 (0.277–2.618)	0.780	0.004 (<0.001–9.579)	0.166
Unifocal GBM	Age	1.026 (1.001–1.052)	0.045	1.037 (1.006–1.070)	0.019
	Sex	1.389 (0.806–2.394)	0.236	1.001 (0.547–1.834)	0.997
	ECOG PS	5.449 (3.441–8.628)	**<0.001**	6.184 (3.568–10.719)	**<0.001**
	Ki-67 index	1.442 (0.373–5.581)	0.596	1.862 (0.458–7.566)	0.385
	p53 mutation	0.821 (0.442–1.524)	0.532	–	–
	RT dose (Gy)	0.986 (0.941–1.033)	0.547	0.984 (0.933–1.038)	0.553
	Extent of resection (ref: biopsy)				
	GTR	0.002 (<0.001–0.016)	**<0.001**	–	–
	STR	0.042 (0.012–0.149)	**<0.001**	–	–
	Hemispheric involvement	0.604 (0.146–2.501)	0.487	0.880 (0.202–3.830)	0.865

–: Not included in the multivariate model. Ki-67 index was entered as a continuous variable (0–1 scale). Extent of resection was analysed with biopsy as the reference category. Confidence limits below 0.001 or above 1000 are shown as <0.001 or >1000 (unstable estimates owing to the small number of events). HR: Hazard ratio; CI: Confidence interval; GBM: Glioblastoma; ECOG PS: Eastern Cooperative Oncology Group performance status; RT: Radiotherapy; GTR: Gross total resection; STR: Subtotal resection.

fied as multifocal.[3] In a meta-analysis by Di Carlo et al.,[10] multiple lesions were present in 19% of high-grade gliomas, with multicentric and multifocal tumors accounting for 6% and 11%, respectively. Thomas et al.[11] found multiple lesions at diagnosis in 35% of patients with GBM and suggested that improved imaging partly explains the higher rates reported in recent series. In our series, the proportion of multicentric GBM was 20.8%, which is higher than in many previously reported series. We attribute this relatively high rate to the technical capacity of our center and the high volume of referrals from other centres; a referral-related selection bias therefore cannot be excluded.

Age and sex distributions did not differ significantly between the groups. The median age of our multicentric group (62.5 years) was close to the median age at GBM diagnosis reported in population-based registry data (66 years).[12] Although GBM is about 1.6 times more common in men than in women,[12] the sex ratio in our multicentric group was 1:1; given the small number of patients, this finding should not be over-interpreted.

Our survival findings are largely consistent with the literature. Patil et al.[6] reported significantly shorter survival in patients with multifocal GBM than in those with unifocal disease, and Lasocki et al.[3] emphasised

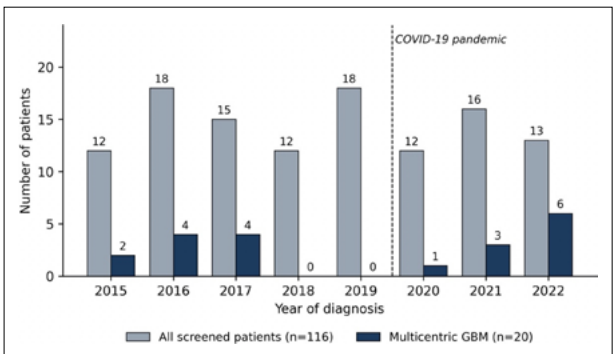

Fig. 3. Annual distribution of all screened patients and of patients with multicentric glioblastoma by year of diagnosis. The dashed line marks the onset of the COVID-19 pandemic. The study period covered September 2015 to September 2022; therefore, 2015 and 2022 represent partial years.

the role of FLAIR imaging in the characterization and prognostic classification of multifocal and multicentric GBM. In the meta-analysis by Di Carlo et al.,[10] the presence of multiple lesions was associated with a 1.71-fold higher risk of death. In contrast, Paulsson et al.[13] found no appreciable difference in survival, patterns of failure, or genomic signatures between single-focus and multiple-lesion GBM, suggesting that the prognostic impact of lesion multiplicity may vary between series. Thomas et al.[11] offered a possible explanation for these conflicting results: patients with multiple lesions had shorter median OS than those with a single lesion (10 vs. 18 months), but this difference was no longer significant after adjustment for age, Karnofsky performance status, and extent of resection. This observation is directly relevant to our findings, because 50% of our patients with multicentric GBM had an ECOG PS >2, compared with only 2.6% of those with unifocal GBM. The shorter survival of the multicentric group may therefore reflect, at least in part, its poorer clinical condition at presentation rather than lesion multiplicity alone. The small size of the multicentric cohort did not allow us to test this hypothesis in a combined multivariate model.

The independent prognostic value of ECOG PS and age in our unifocal cohort is in line with established prognostic models. In the Radiation Therapy Oncology Group recursive partitioning analysis and in later series, age and performance status consistently emerged as the strongest determinants of survival in GBM,[14,15] and the systematic review by Li et al.[16] also supports the prognostic importance of performance status. In our unifocal cohort, both GTR and STR were associated with a lower risk of progression than biopsy, and the favorable association of GTR with survival (univariate HR for OS: 0.002, $p<0.001$) is in line with the findings of Haque et al.[7] Larger series and meta-analyses support this observation: Lacroix et al.[17] reported a significant survival advantage when at least 98% of the tumor volume was removed, and the meta-analysis by Brown et al.[18] showed that GTR improves both OS and PFS compared with STR.

Bihemispheric involvement, present in 60% of the multicentric group, makes GTR technically difficult and often limits surgery to biopsy. Although the extent of resection did not differ significantly between the groups in our series, the literature suggests that surgery should not be abandoned in multicentric disease when it can be performed safely. Hassaneen et al.[19] showed that resection of all lesions through multiple craniotomies in multifocal and multicentric GBM provided survival comparable to that of matched patients with a single lesion, without an increase in complications. Similarly, in the meta-analysis by Di Carlo et al.,[10] surgical resection was an independent predictor of better outcome in multicentric tumors, whereas biopsy alone was associated with a markedly higher risk of death (HR: 7.61). In butterfly GBM, another form of bihemispheric disease, Dziurzynski et al.[20] reported a median survival of 265 days after surgical decompression and 48 days after biopsy, although this difference did not reach statistical significance. The absence of an independent prognostic factor in our multicentric cohort is most likely explained by the small number of patients and events rather than by a true lack of effect.

Showalter et al.[21] reported that local recurrence predominated in multifocal GBM, whereas Syed et al.[22] showed that distant intracranial recurrence was also a substantial problem. These patterns support covering all visible lesions within the RT target volumes, while remaining alert to distant progression during follow-up. In our series, patients with poor performance status received hypofractionated RT (40 Gy in 15 fractions). This approach is supported by randomised data showing that an abbreviated course provides survival similar to that of the standard 60 Gy regimen in older patients,[23] and that adding temozolomide to short-course RT prolongs survival in elderly patients.[24] Because half of our patients with multicentric GBM had an ECOG PS >2, short-course regimens are a practical option that reduces treatment burden in this subgroup.

The higher Ki-67 proliferation index in the multicentric group (median 60% vs. 30%) is consistent with the report by Liu et al.,[25] which pointed to a distinct molecular profile in multifocal and multicentric GBM. Dono et al.[26] also examined the molecular characteristics and clinical features of multifocal GBM. The origin of multiple lesions is still debated. Abou-El-Ardat et al.[27] showed that separate foci in the same patient share early genetic events, such as loss of chromosome 10 and TERT promoter mutations, supporting a monoclonal origin followed by parallel clonal evolution. Lim et al.[28] reported that GBMs in contact with the subventricular zone, a neural stem cell niche, were more often multifocal. A highly proliferative and invasive phenotype may therefore facilitate the development of distant lesions. However, the prognostic value of Ki-67 in GBM remains controversial: Tini et al.[29] found that a Ki-67 index below 15% independently predicted longer survival in IDH-wildtype GBM, whereas Alkhaibary et al.[30] found no significant association with survival. In addition, Ki-67 data were available for only half of our multicentric patients, so this finding should be confirmed in larger series.

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Relationship with the COVID-19 Pandemic

The increase in multicentric GBM observed after 2020 warrants investigation of possible biological mechanisms. Using a Mendelian randomization approach, Dong et al.[31] showed that COVID-19 hospitalisation increased the risk of developing GBM. The expression of angiotensin-converting enzyme 2 (ACE2) in human neurons supports the neuroinvasive potential of SARS-CoV-2,[32] and Jiang et al.[33] reported that the coronavirus receptors ANPEP and ENPEP are significantly overexpressed in GBM tissue and can form protein complexes with ACE2. In a retrospective case–control study from the MD Anderson Cancer Center, patients with GBM showed accelerated tumor progression after COVID-19 infection, and multifocal or leptomeningeal disease at progression was more frequent in infected patients than in controls.[34] Systemic inflammation is another possible link: In experimental models, respiratory viral infections, including SARS-CoV-2, reactivated dormant disseminated cancer cells through an interleukin-6-dependent mechanism, and in human cohorts SARS-CoV-2 infection was associated with higher cancer mortality and lung metastasis in patients with breast cancer.[35] Whether similar inflammatory signaling affects glial tumors remains unknown. On the other hand, delayed presentation during the pandemic, resulting in diagnosis at a more advanced stage, may be an indirect explanation for this increase.[36] It should also be stressed that the increase in our series did not reach statistical significance (p=0.197) and that infection and vaccination histories were available for only some patients; therefore, no conclusion regarding COVID-19 infection or vaccination can be drawn from these data. This observation should be regarded as hypothesis-generating; both possibilities deserve thorough investigation, and this study aims to draw attention to this question.

Limitations of the Study

The main limitations of this study are its retrospective design, the relatively small sample size – particularly in the multicentric group – and the inability to reach some patients during the pandemic. The small number of patients and events in the multicentric cohort limited the statistical power of the Cox models, as reflected by the wide CIs, and the multivariate results in this group should be interpreted with caution. Molecular data were incomplete for some patients, and O6-methylguanine-DNA methyltransferase promoter methylation status, the main predictor of benefit from temozolomide,[37] was not available. Nevertheless, to our knowledge, this is one of the few single-center series focusing specifically on multicentric GBM classified according to the 2021 WHO criteria.

CONCLUSION

Multicentric GBM is associated with a significantly worse prognosis than unifocal disease and is characterised by poor performance status, high proliferative activity, frequent bihemispheric involvement and limited options for complete resection. The increase in incidence that temporally coincided with the COVID-19 pandemic raises a new question that requires investigation of both direct biological and indirect clinical mechanisms. Large multicenter prospective studies are needed to clarify the prognostic determinants specific to this subgroup and to optimize treatment strategies.

Ethics Committee Approval: The study was approved by the Şişli Memorial Hospital Ethics Committee (no: 006, date: 12/12/2023).

Informed Consent: Informed consent was waived due to the retrospective design of the study.

Conflict of Interest Statement: The authors declare no conflicts of interest.

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REVIEW

Emerging Label-Free and Nanoscale Imaging Modalities for Early Detection of Cervical Cancer

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SUMMARY

Cervical cancer remains a major global health challenge, particularly in low- and middle-income countries where organized screening coverage is limited. Current algorithms based on human papillomavirus (HPV) testing and cytology, followed by colposcopy and histopathology, have well-documented limitations in sensitivity, specificity, cost, and turnaround time, and the shift to HPV primary screening has created a large triage population. In parallel, a family of label-free, nanoscale imaging and spectroscopic modalities has matured and is approaching reproducible diagnostic performance: Scanning electron microscopy (SEM) of exfoliated cervical cells, atomic force microscopy (AFM) of cell surface adhesion and mechanical properties, Raman spectroscopy, fluorescence lifetime imaging microscopy, and optical coherence tomography (OCT), coupled to machine learning classifiers. This review describes, discusses, and evaluates current knowledge of these emerging modalities, their diagnostic performance, mechanistic rationale, and readiness for clinical translation. Recent multimodal SEM-AFM pipelines combining discrete wavelet transform-derived features with divergence-based classifiers reached 95.9% classification accuracy; machine learning applied to AFM adhesion maps distinguished precancerous from cancerous cervical cells with an area under the curve (AUC) of 0.93; single-cell Raman spectroscopy with machine learning achieved an AUC of 0.987; and in vivo OCT reached 93.4% accuracy for high-grade lesions, with OCT triage after HPV genotyping reaching an AUC of 0.921. Implementation evidence for HPV self-sampling, the likely specimen source for nanoscale approaches, is also reviewed. The remaining barriers, including small cohorts, absent prospective validation, protocol standardization, and instrumentation cost, are analyzed, and a roadmap toward integration of these biomarkers into risk-based screening programs is proposed.

Keywords: Early detection of cancer; electron, machine learning; mass screening, microscopy, scanning; uterine cervical neoplasms.

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INTRODUCTION

Cervical cancer is a preventable malignancy whose global burden remains concentrated in low- and middle-income countries, and the World Health Organization elimination strategy rests on vaccination, screening, and timely treatment of precancerous lesions.[1] Organized screening based on the Papanicolaou smear, later augmented by liquid-based cytology, automation, human papillomavirus (HPV) primary testing, geno-

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typing, and dual-stain triage, has driven substantial reductions in incidence in high-income settings.[2] HPV vaccination is now reshaping screening paradigms further, with longer intervals and risk-based algorithms replacing uniform cytology-based recall.[3]

Nevertheless, the current gold standard pathway, HPV testing and cytology for screening followed by colposcopy and histopathology for diagnosis, is limited in sensitivity and specificity, is costly and time-consuming, and depends on laboratory and colposcopy capacity that is unevenly distributed worldwide.[4] In premenopausal and older women, epithelial atrophy and migration of the transformation zone into the endocervical canal reduce the sensitivity of conventional cytology, a problem highlighted in recent morphometric and ultrastructural studies of precancerous cervical lesions.[5] These gaps motivate complementary, ideally label-free and minimally invasive, modalities for early detection.

This review describes, discusses, and evaluates the current level of knowledge of a family of emerging, high-resolution imaging and spectroscopic modalities for early cervical cancer detection: Scanning electron microscopy (SEM) and atomic force microscopy (AFM) of exfoliated cervical cells, their multimodal machine learning-assisted combinations, adjacent label-free platforms (Raman spectroscopy, Fluorescence lifetime imaging microscopy [FLIM]), and, as the most clinically advanced optical counterpart, OCT and related endomicroscopic imaging. Because the exfoliated cell is the common specimen of this literature and its collection is being transformed by HPV self-sampling, the implementation evidence for self-sampling is reviewed first, followed by the technology-specific sections. The focus throughout is on diagnostic performance, mechanistic rationale, and readiness for clinical translation.

THE CURRENT SCREENING PATHWAY AND ITS LIMITATIONS

The modern cervical screening algorithm has evolved from the conventional Pap smear through liquid-based cytology and automation to HPV primary screening with cytology triage of HPV-positive women, and most recently to digitalization and artificial intelligence (AI) assistance.[2] In many contemporary programs, HPV testing is now the primary test and cytology is used mainly for triage of HPV-positive women.[6] This shift has improved sensitivity for high-grade lesions but has created a large pool of HPV-positive women requiring triage, increasing the workload of cytology laboratories and colposcopy clinics.[6]

Three specific limitations of the current pathway create space for emerging modalities. First, cytology remains labor-intensive and subject to interobserver variability.[6] Second, HPV testing alone has imperfect specificity, particularly in younger women, and triage markers such as genotyping and dual staining are being introduced to personalize management.[2] Third, in specific clinical scenarios such as the premenopausal period with atrophic epithelial changes, conventional cytology loses sensitivity, and advanced morphometric and ultrastructural methods have been proposed to bridge this diagnostic gap.[5]

HPV SELF-SAMPLING: THE SPECIMEN PIPELINE FOR CELL-BASED TECHNOLOGIES

Cell-based nanoscale and spectroscopic modalities depend on the availability of exfoliated cervical cells, and the collection step is itself undergoing transformation. Self-sampling for HPV testing is now recommended by the World Health Organization, and a systematic review and meta-analysis of six trials involving 29,018 participants in low- and middle-income countries found a small but significant improvement in screening uptake with self-sampling versus provider collection (risk ratio [RR] 1.11, 95% confidence interval [CI] 1.10–1.11), which increased to RR 1.82 (95% CI 1.67–1.99) in a sensitivity analysis of five trials with harmonized uptake definitions.[7] In the United States, the phase 3 MBMT-3 randomized trial showed that mailed HPV self-collection kits with appointment-scheduling assistance increased screening uptake among under-screened low-income women from 37% to 72% (RR 1.93, 95% CI 1.62–2.31).[8] In an internet-based program in China, 20,136 women performed vaginal self-sampling for HPV testing, 95.97% of respondents reported that self-sampling was easy to perform, and the model reached under-screened and remote populations effectively.[9] Self-collected vaginal samples showed HPV positivity statistically similar to provider-collected samples in a Zimbabwean crossover study (26.9% vs. 29.3%), supporting diagnostic comparability.[10]

Acceptability and cost data reinforce these findings. Community-based distribution achieves 20–35% uptake in resource-limited settings while reducing costs by 32–48%, and vaginal brushes achieve a sensitivity of 94.6% (95% CI 92.4–96.8) for HPV detection.[11] In India, HPV self-sampling showed 97% acceptance in urban slum settings with 95.1%

agreement between self-collected and health-worker-collected samples, and pictorial instructions performed as well as personnel-delivered education.[12] A critical review concluded that self-sampling improves participation among women hesitant to attend facility-based screening and reduces provider burden, while noting that best practices for target populations and follow-up protocols remain to be established.[13] Implementation science is catching up: a stakeholder-engaged pre-implementation study in rural China specified four strategy packages for village doctor-delivered self-sampling, and in its pilot, 62.2% of 172 invited women completed self-sampling with 99.1% of samples meeting testing standards.[14] For nanoscale imaging technologies, this evidence is strategically important: self-collected specimens could feed SEM, AFM, and spectroscopic pipelines, extending their reach beyond clinic-based populations, although cell quality and pre-analytical standardization from self-sampling devices require dedicated validation.[11,13]

SEM OF EXFOLIATED CERVICAL CELLS

SEM provides nanometer-scale imaging of the surface ultrastructure of exfoliated cervical cells, including microvilli and surface projections whose density and morphology change during carcinogenesis. Recent work has moved beyond descriptive ultrastructure toward quantitative, computational classification: in a multimodal study, 540 SEM and 540 AFM cell images were analyzed using discrete wavelet transform (DWT)-derived features and three divergence-based classifiers (triangle divergence, Jensen-Shannon divergence, and Hellinger divergence), with feature likelihoods combined using exponential graph regulation.[15] The combined SEM-AFM approach with triangle divergence achieved a classification accuracy of 95.9% for distinguishing normal, benign, and malignant cells, outperforming single-modality analysis.[15]

In a related study applying 16 DWT families (Daubechies, Coiflet, Symlet, and Biorthogonal) to SEM and AFM images of cervical cells, the average classification rates were 98.29% for AFM images and 97.10% for SEM images, with ten texture features calculated for each approximation and detail coefficient.[16] The surface roughness of malignant AFM images was larger than that of normal and benign images, whereas the volume of particles in malignant AFM images was smaller.[16] These studies demonstrate that quantitative texture features of cell surface ultrastructure carry discriminative information, although the cohorts remain small and the imaging workflow requires specialized infrastructure.[15,16]

AFM: ADHESION, MECHANICS, AND FRACTAL ANALYSIS

AFM provides nanoscale topographic, adhesive, and mechanical mapping of individual cells. A key advance was the use of high-resolution AFM adhesion maps: analysis of adhesion between the AFM probe and the cell surface allowed discrimination of normal from cancerous or precancerous cervical epithelial cells using a single parameter, fractal dimension, and subsequent introduction of machine learning (random forest) improved the separation of precancerous from cancerous cells to an area under the curve (AUC) of 0.93, with accuracy, sensitivity, and specificity of 83%, 92%, and 78%, respectively.[17] Because the separation between premalignant and malignant cells is the most clinically significant distinction, the improvement in sensitivity was emphasized as clinically meaningful, and the authors proposed that relatively low specificity could be compensated by combining this approach with existing screening methods.[17]

Mechanical phenotyping is a parallel line of evidence. AFM force-indentation measurements fitted with Hertz and Sneddon models, complemented by stress-relaxation analysis, have shown that elastic and viscoelastic properties of cancer cells, including cervical cancer cells, are lower than those of normal cervical and mammary epithelial cells, and that measured properties depend on probe geometry, tip radius, and loading rate.[18] These findings confirm that biomechanical fingerprints are reproducible and quantifiable, but also that measurement protocols must be standardized for clinical use.[18] Instrument-side progress continues: an adaptive harmonic AFM probe generated stable harmonic signals in atmospheric and liquid environments and improved classification accuracy for normal versus cancer cervical cells by approximately 8% and between HeLa and SiHa cancer subtypes by approximately 13%, using 3,600 cell samples.[19]

MULTIMODAL SEM-AFM PIPELINES AND MACHINE LEARNING

The convergence of SEM and AFM with computational feature extraction represents the most recent method-

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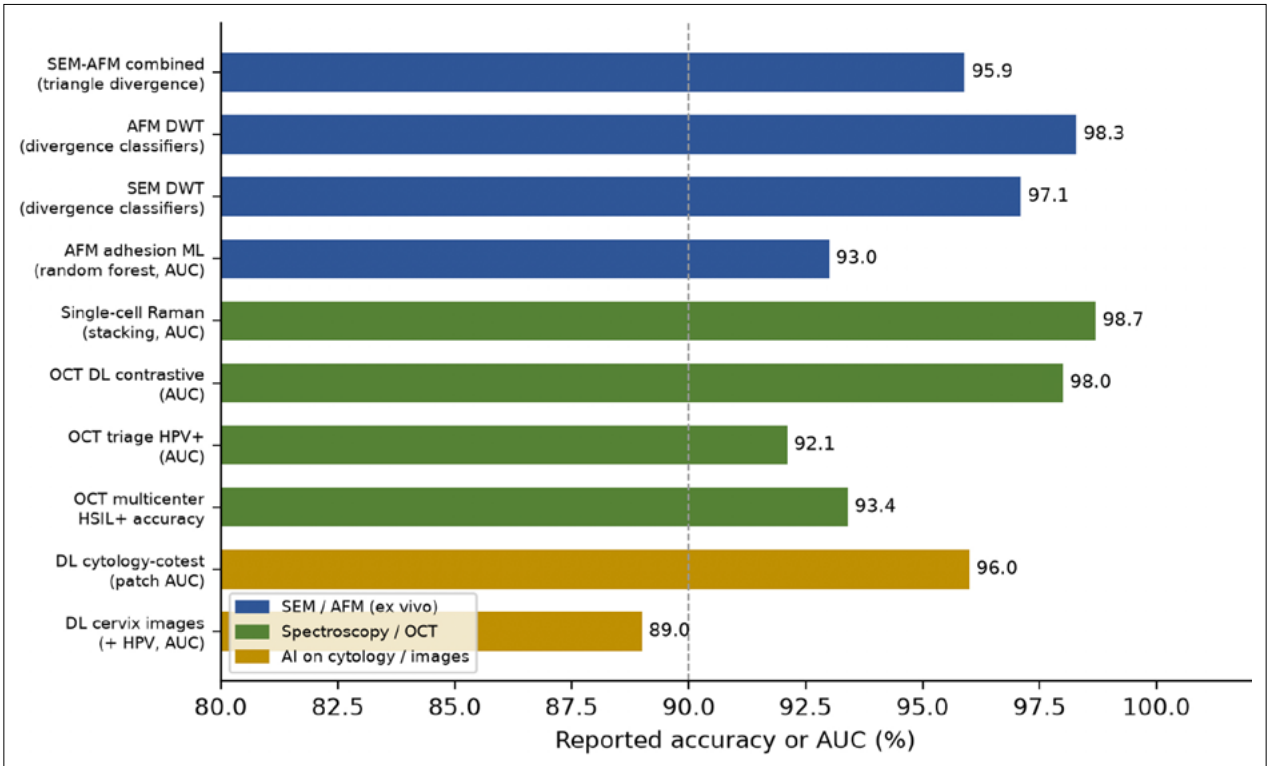

Fig. 1. Reported classification accuracy or area under the curve of the modalities reviewed, grouped by modality family. Values are as reported in the primary studies and are not directly comparable across cohorts.

ological step. The multimodal DWT-divergence pipeline categorized SEM and AFM cells into six groups (normal, benign, and malignant for each modality) and demonstrated that the weighted combination of features improved diagnostic precision over either modality alone.[15] The rationale is that SEM captures surface architecture while AFM captures nanomechanical and adhesive properties, so their combination reduces the diagnostic unreliability inherent in relying on a single imaging technique.[15]

Machine learning is the common denominator across these pipelines. Beyond the divergence-based classifiers of the SEM-AFM studies,[15,16] random forest models applied to AFM adhesion maps achieved an AUC of 0.93 for precancerous versus cancerous discrimination,[17] and unsupervised machine learning applied to FLIM images of exfoliated cells achieved a sensitivity of 90.9% and specificity of 100% for cervical cancer risk prediction, outperforming cytology in the same study.[20] Single-cell Raman spectroscopy combined with seven machine learning algorithms, with a stacking ensemble selected as optimal, achieved an AUC of 0.987, accuracy of 99.2%, sensitivity of 98.9%, and specificity of 99.3% for distinguishing normal from abnormal cervical exfoliated cells.[21] Figure 1 compares the reported classification performance across these modalities, and the proposed multimodal pipeline integrating them is shown in Figure 2. These results, although generated in pilot and single-center settings, establish that label-free nanoscale and spectroscopic data streams are amenable to reproducible computational classification.[15,17,20,21]

ADJACENT LABEL-FREE MODALITIES: RAMAN SPECTROSCOPY AND FLIM

Raman spectroscopy provides molecular fingerprints of tissue and exfoliated cells without labels and has been studied for cervical cancer detection for over two decades using exfoliated cells, biofluids, and tissue *ex vivo* and *in vivo*.[4] A recent pilot multimodal study combined Raman spectroscopy with AFM and SEM on paraffin-embedded cervical squamous cell carcinoma samples, identifying distinct molecular profiles between malignant and healthy tissue regions in the 813–1668 cm−1 range, with AFM and SEM providing supportive morphological

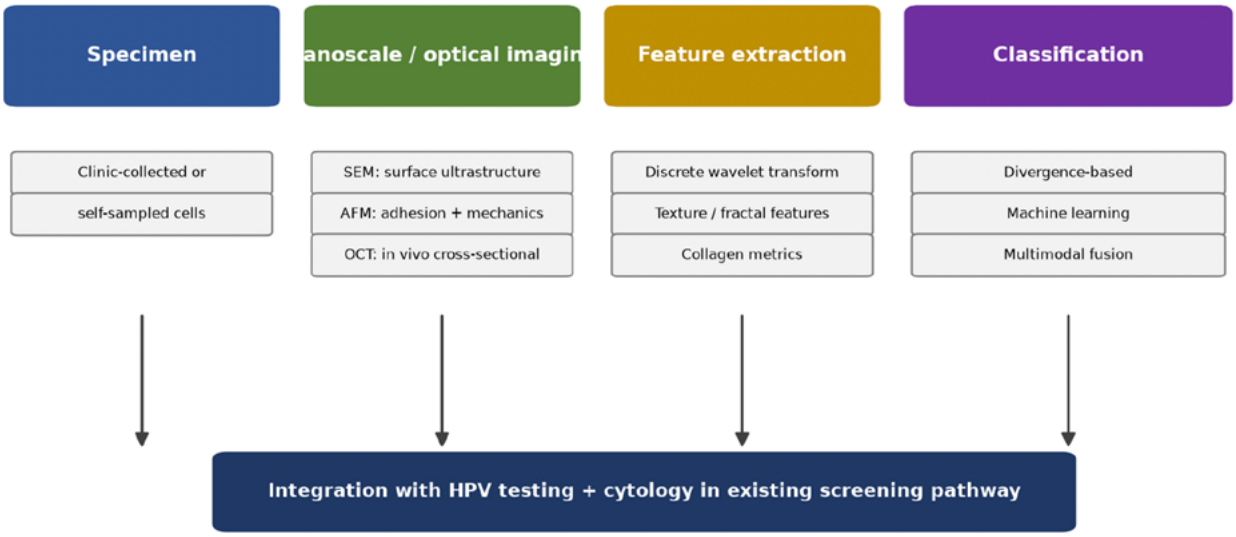

Fig. 2. Proposed multimodal pipeline for early detection of cervical cancer, from specimen collection through nanoscale/optical imaging and feature extraction to classification and integration with the existing screening pathway.

information on structural irregularities associated with malignancy.[22] The authors emphasized that Raman spectroscopy has not yet replaced Pap smears and biopsies in clinical practice due to challenges in standardization, reproducibility, and clinical validation, positioning the multimodal approach as a stepping stone toward minimally invasive, label-free diagnostic workflows.[22]

FLIM, by measuring endogenous NAD(P)H fluorescence lifetime, captures metabolic state changes in exfoliated cervical cells. Combined with unsupervised machine learning, FLIM images from 71 participants yielded a sensitivity of 90.9% and specificity of 100% for cervical cancer risk prediction, significantly higher than cytology, and one cancer recurrence case was flagged months earlier than by current clinical methods.[20] Complementing these optical approaches, single-cell transcriptomic profiling of cervical exfoliated cells has identified molecular biomarkers of progression, including a lipid-associated macrophage subset that predicted progression from low-grade to high-grade squamous intraepithelial lesion (HSIL) and an SPP1-CD44 protumor signaling axis between epithelial cells and macrophages, verified by immunofluorescence.[23] Together, these modalities illustrate a converging trend: the exfoliated cervical cell can now be interrogated at nanoscale, metabolic, and single-cell transcriptomic levels, each yielding quantitative biomarkers of carcinogenesis.[20,22,23]

OPTICAL COHERENCE TOMOGRAPHY AND ENDOMICROSCOPY: THE *IN VIVO* FRONTIER

OCT is the most clinically advanced *in vivo* counterpart to the *ex vivo* nanoscale modalities, providing non-invasive, real-time, cross-sectional imaging of cervical epithelium and stroma. In a multicenter study of 1,214 patients with cervical lesions examined by *in vivo* OCT, the accuracy, sensitivity, specificity, positive predictive value, and negative predictive value of OCT for diagnosing HSIL or worse (HSIL+) were 93.4%, 88.5%, 95.0%, 85.0%, and 96.2%, respectively, with strong consistency with histopathology (kappa 0.701); for low-grade lesions, the corresponding values were 84.7%, 61.7%, 96.3%, 89.3%, and 83.2%.[24] In the same study, OCT screening outperformed combined HPV and ThinPrep cytologic test screening, with accuracy 83.7% versus 64.9%, sensitivity 77.8% versus 64.5%, and specificity 91.8% versus 65.4% (all $p<0.001$).[24] Figure 3 presents these diagnostic metrics.

OCT also functions as a triage tool. In a cross-sectional study of 883 women referred for colposcopy, HPV combined with OCT showed higher specificity for detecting CIN2+ and CIN3+ than HPV combined with cytology (96.1% vs. 93.2%, $p=0.002$; 93.8% vs. 91.3%, $p=0.013$), and OCT triage after HPV genotyping achieved the highest AUC for detecting CIN2+ and CIN3+ among women with high-risk HPV infection (0.921 and 0.920, respectively).[25] Figure 4 summarizes this triage evidence. AI is being layered

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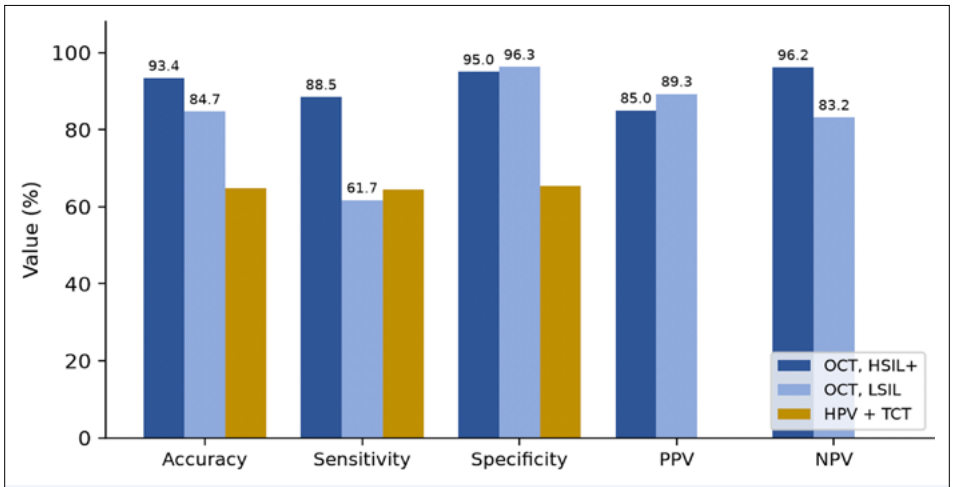

Fig. 3. Diagnostic metrics of *in vivo* optical coherence tomography for high-grade squamous intraepithelial lesion + and low-grade squamous intraepithelial lesion versus combined human papillomavirus and ThinPrep cytologic test screening in the multicenter study. Positive predictive value and negative predictive value for the combined screening arm were not reported.

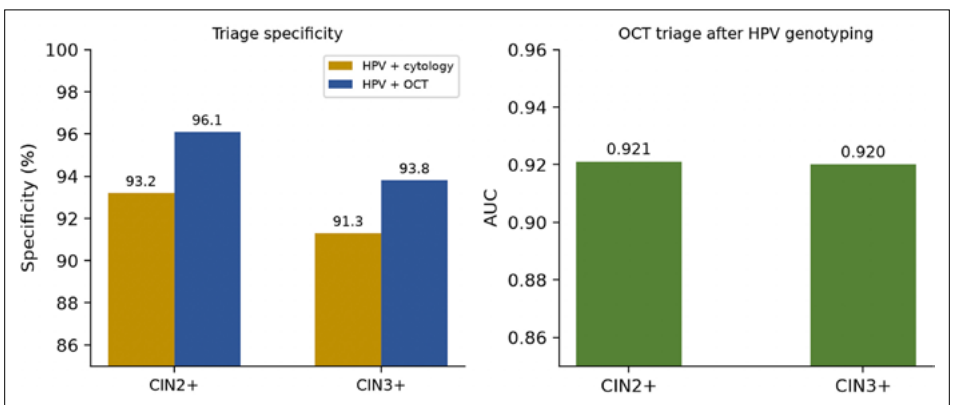

Fig. 4. Optical coherence tomography (OCT) as a human papillomavirus (HPV) triage tool: Specificity of HPV combined with OCT versus HPV combined with cytology (left) and area under the curve of OCT triage after HPV genotyping (right).

onto OCT rapidly: A contrastive self-supervised texture learning model achieved an AUC of 0.98 for detecting high-risk lesions on OCT image patches, with 91.5% sensitivity and 97.4% specificity on an external validation set of 287 three-dimensional OCT volumes from 118 patients,[26] and a feature-pyramid deep learning model achieved F1-scores of 81.6% and 84.3% on two clinical datasets, outperforming five experienced medical experts on one.[27]

Technology development continues along three fronts. Probe-based quantitative OCT of collagen fiber organization, using an extended-depth-of-focus quasi-Bessel beam, produced a tumor potential index map that merges multiple metrics to guide biopsy targeting in *ex vivo* human specimens and *in vivo* murine models.[28] Gabor-domain optical coherence microscopy achieved near-histologic resolution of cervical dysplasia *ex vivo*, resolving epithelium, stroma, basement membrane, and HPV-associated changes,[29] and high-resolution optical coherence microscopy has been applied to endocervical canal lesions, addressing a structure poorly visualized by conventional screening.[30] Endoscopic OCT combined with autofluorescence imaging is being evaluated for *in vivo* endocervical canal imaging,[31] and OCT has also been used to map tissue architecture and extracellular matrix abnormalities in human cer-

vix specimens.[32] At the implementation level, a low-cost multiscale system combining portable colposcopy with high-resolution endomicroscopy, coupled to a multiscale imaging fusion network, achieved sensitivity equal to clinical impression (0.98) with significantly higher specificity (0.75 vs. 0.43, p=0.000006), demonstrating that accurate real-time diagnosis of high-grade pre-cancers is feasible in low-resource settings.[33]

AI IN CERVICAL SCREENING AND THE PLACE OF NANOSCALE IMAGING

AI is already reshaping cervical screening through digital cytology, automated image analysis, and colposcopy support.[6,34] Model-based evaluation of AI-assisted digital cytology within the National Health Service (NHS) cervical screening program estimated that reviewing and reporting 479,125 slides annually would require 31,842 staff hours with AI-assisted digital cytology versus 103,151 h with manual microscopy, corresponding to a potential 69% increase in overall productivity.[35] In a clinical evaluation of an AI-assisted cytology system in a high-risk Chinese population, the AI strategy achieved the highest Youden index at both low-grade and HSIL thresholds and outperformed liquid-based cytology plus HPV cotesting at the high-grade threshold.[36] A proof-of-concept deep learning model applied to digitized ThinPrep cytology and HPV cotest results achieved an image-patch-level AUC of 96% in temporal validation, although prospective multicenter studies with patient-level analysis were deemed necessary before clinical implementation.[37]

For low- and middle-income settings, portable AI-assisted devices such as smartphone colposcopes with embedded deep learning have demonstrated CIN2+ sensitivities above 90%, exceeding expert readers, and deep learning pipelines trained on large multi-institutional cervical image datasets (9,462 women, 17,013 images) reached an AUC of 0.89 when combined with HPV type, with an extreme misclassification rate of 3.4% on held-aside test sets.[34,38] These developments are directly relevant to SEM-, AFM-, and OCT-based screening because the computational infrastructure, feature extraction methods, and validation frameworks developed for cytology and colposcopy images are transferable to nanoscale imaging modalities.[6,15] Conversely, the challenges identified for AI in cervical screening, including algorithmic bias from non-representative training data, limited interpretability, regulatory uncertainty, and the need for large, diverse datasets and prospective validation,[6,34] apply equally to machine learning applied to SEM, AFM, and OCT data.[17,15,26]

COMPARATIVE EVALUATION AND CLINICAL TRANSLATION

Table 1 summarizes the diagnostic performance of the modalities reviewed, and Figure 1 compares their reported classification performance. Three observations follow. First, the reported accuracies of SEM-AFM, spectroscopic, and OCT pipelines (approximately 93–99%) are higher than those typically reported for cytology or HPV testing alone, but they derive from small, single-center, and frequently retrospective cohorts, and no head-to-head comparison of SEM-AFM or AFM with HPV testing within a single screening population has been published; by contrast, OCT has now been compared directly against combined HPV-cytology screening in a multicenter cohort and outperformed it.[15–17,20,21,24] Second, the mechanistic rationale is strong and convergent: malignant transformation alters surface ultrastructure, adhesion, mechanical compliance, metabolic state, and stromal collagen organization, and each modality captures a different aspect of these changes.[16,18,22,20,28] Third, multimodal designs consistently outperform single-modality analysis, whether SEM with AFM,[15] Raman with AFM and SEM,[22] widefield colposcopy with endomicroscopy,[33] or HPV genotyping with OCT,[25] supporting a multimodal architecture for future clinical studies (Fig. 2).

The practical barriers to clinical translation are consistent across modalities: the need for prospective validation in diverse populations,[6,37] standardization of sample preparation and imaging protocols,[5,18] the cost and infrastructure requirements of SEM and AFM instrumentation in screening settings,[15,16] and the interpretability and regulatory questions that apply to any machine learning-based diagnostic.[6,34] OCT, by contrast, is already *in vivo*, real-time, and comparatively low-cost, and its multicenter performance data position it closest to clinical adoption.[24,25] A realistic near-term pathway is therefore not replacement of HPV-based screening but targeted integration: Nanoscale and spectroscopic modalities are best positioned as triage tools for HPV-positive women or as adjuncts in specific scenarios, such as premenopausal women with atrophic epithelium where conventional cytology loses sensi-

Table 1 Diagnostic performance of emerging label-free, nanoscale, and AI-assisted modalities for early detection of cervical cancer

Modality	Sample	Classifier/analysis	Reported performance	Key evidence
Multimodal SEM-AFM	540 SEM+540 AFM cervical cell images	DWT features; triangle divergence; exponential graph regulation	Accuracy 95.9% (combined)	[15]
SEM (single modality)	SEM cervical cell images	16 DWT families; divergence-based classifiers	Classification rate 97.10%	[16]
AFM (single modality)	AFM cervical cell images	16 DWT families; divergence-based classifiers	Classification rate 98.29%	[16]
AFM adhesion maps	Precancerous and cancerous primary cervical cell lines	Random forest on high-resolution adhesion maps	AUC 0.93; accuracy 83%; sensitivity 92%; specificity 78%	[17]
Adaptive harmonic AFM	3,600 cervical epithelial and cancer cells	Adaptive harmonic probe; cellular classification	Classification accuracy improved by 7.97% (normal vs. cancer); 12.73% (HeLa/SiHa)	[19]
Single-cell Raman spectroscopy	128 cervical exfoliated cell samples	Stacking ensemble of 7 machine learning algorithms	AUC 0.987; accuracy 99.2%; sensitivity 98.9%; specificity 99.3%	[21]
FLIM of exfoliated cells	71 participants	Unsupervised machine learning on NAD(P)H lifetime	Sensitivity 90.9%; specificity 100%	[20]
In vivo OCT (multicenter)	1,214 patients with cervical lesions	Image interpretation versus histopathology	HSIL+: accuracy 93.4%; sensitivity 88.5%; specificity 95.0%; NPV 96.2%	[24]
OCT versus HPV+TCT screening	Same multicenter cohort	OCT versus combined HPV-cytology screening	Accuracy 83.7% versus 64.9%; specificity 91.8% versus 65.4%	[24]
OCT triage after HPV genotyping	883 women referred for colposcopy	OCT combined with HPV genotyping	AUC 0.921 (CIN2+); 0.920 (CIN3+); specificity gain over HPV+cytology	[25]
OCT deep learning (contrastive)	733 patients; external validation 118 patients	Contrastive self-supervised texture learning	AUC 0.98; external sensitivity 91.5%; specificity 97.4%	[26]
OCT deep learning (FPN)	Two clinical datasets	Feature pyramid network with texture encoding	F1 81.6% and 84.3%; outperformed 5 of 5 and matched best expert	[27]
AI-assisted digital cytology	NHS cervical screening program workflow	Decision-tree model of AI-assisted digital cytology	31,842 versus 103,151 staff hours; potential 69% productivity increase	[35]
AI-assisted cytology (clinical)	1,231 LBC slides, high-risk Chinese population	AI-assisted cytological system	Best Youden index at LSIL and HSIL+ thresholds; AUC 0.621 at HSIL+	[36]
Deep learning on cytology-cotest	337 women, temporal validation cohort	ResNet50 ensemble on digitized ThinPrep slides	Patch-level AUC 96% in temporal validation	[37]
Deep learning cervix images+HPV	9,462 women; 17,013 images	Multi-institutional deep learning pipeline	AUC 0.89; extreme misclassification 3.4%	[38]
Smartphone colposcope AI	Low-resource settings	Embedded deep learning on smartphone colposcopy	CIN2+ sensitivity >90%, exceeding expert readers	[34]

SEM: Scanning electron microscopy; AFM: Atomic force microscopy; DWT: Discrete wavelet transform; AUC: Area under the curve; FLIM: Fluorescence lifetime imaging microscopy; NAD(P)H: Reduced nicotinamide adenine dinucleotide (phosphate); LBC: Liquid-based cytology; LSIL: Low-grade squamous intraepithelial lesion; HSIL: High-grade squamous intraepithelial lesion; CIN2+/CIN3+: Cervical intraepithelial neoplasia grade 2/3 or worse; HPV: Human papillomavirus; TCT: ThinPrep cytologic test; NPV: Negative predictive value; PPV: Positive predictive value; NHS: National Health Service.

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Table 2 Diagnostic performance of *in vivo* OCT in a multicenter study of 1,214 patients (pathology as gold standard)

Metric	OCT, HSIL+ (%)	OCT, LSIL (%)	HPV+TCT combined screening (%)
Accuracy	93.4	84.7	64.9
Sensitivity	88.5	61.7	64.5
Specificity	95.0	96.3	65.4
Positive predictive value	85.0	89.3	-
Negative predictive value	96.2	83.2	-

HPV+TCT values from the same multicenter comparison; PPV and NPV not reported for the combined screening arm. PPV: Positive predictive value; NPV: Negative predictive value; HPV: Human papillomavirus; OCT: Optical coherence tomography; HSIL: High-grade squamous intraepithelial lesion; LSIL: Low-grade squamous intraepithelial lesion.

tivity [5] and post-treatment follow-up where metabolic imaging showed early recurrence detection.[20] Self-sampling evidence suggests a further integration point: coupling self-collected specimens to label-free cell analysis could extend triage capacity to under-screened populations[7–9,11] (Table 2, 3, Fig. 5).

Limitations and Future Directions

The evidence base for SEM- and AFM-based early detection of cervical cancer remains preliminary. Sample sizes are small, most studies are retrospective, and external validation is lacking.[5,15–17] Reported accuracies may be inflated by dataset-specific feature engineering and by the absence of blinded, consecutive, screening-population sampling.[15,16] Standardization of cell preparation, fixation, imaging parameters, and feature extraction is not established, which impedes comparison across studies.[5,18] For OCT, multicenter evidence is stronger but remains confined to referral populations, and OCT performance for low-grade lesions is modest (sensitivity 61.7%), limiting its standalone use.[24] The regulatory pathway for machine learning-based diagnostics using nanoscale imaging data is not defined.[6,34] Finally, the cost and throughput of SEM and AFM are not yet compatible with population-scale screening, and the technology may realistically enter clinical practice first in research and specialized diagnostic settings.[15,19]

Future studies should prioritize: (1) Prospective, multicenter, blinded validation of SEM-AFM and spectroscopic pipelines against histopathological endpoints in consecutive screening populations; (2) head-to-head comparison with HPV testing and cytology within the same cohort, mirroring the multicenter OCT design;[24] (3) development of standardized operating procedures for sample preparation and imaging, including for self-collected specimens;[10,11,18]; (4) integration of nanoscale imaging data with HPV status and cytology in multimodal machine learning models;[25,37,38] and (5) exploration of cost-effective AFM, Raman, and OCT configurations suitable for point-of-care or low-resource deployment, building on the portable colposcopy-endomicroscopy experience.[33,34] If these steps are taken, nanoscale and spectroscopic modalities could mature from promising research tools into complementary components of risk-based cervical screening programs.

Table 3 Evidence for HPV self-sampling as the specimen pipeline for cell-based technologies

Study	Setting/population	Design	Key finding
Mekuria et al.[7]	LMICs; 6 trials, 29,018 participants	Systematic review and meta-analysis	Uptake RR 1.11 (95% CI 1.10–1.11); RR 1.82 (95% CI 1.67–1.99) in sensitivity analysis
Pretsch et al.[8]	Under-screened low-income women, USA	Phase 3 randomized controlled trial (MBMT-3)	Uptake 72% versus 37%; RR 1.93 (95% CI 1.62–2.31)
Li et al.[9]	13 provinces, China; 20,136 women	Internet-based self-sampling program	95.97% found self-sampling easy; reached remote and under-screened women
Munjoma et al.[10]	Zimbabwe; 609 self-versus 611 provider samples	Cross-sectional crossover trial	HPV positivity 26.9% versus 29.3%; statistically similar
Gomes et al.[11]	Global review across healthcare settings	Narrative review	Vaginal brush sensitivity 94.6%; cost reduction 32–48%; uptake 20–35%
Anand et al.[12]	Urban slum settings, India	Cross-sectional acceptability study	97% acceptance; 95.1% agreement with health-worker samples
Wang et al.[14]	Rural China; 172 invited women	Pre-implementation implementation science study	62.2% completed self-sampling; 99.1% samples met testing standards

HPV: Human papillomavirus; RR: Risk ratio; CI: Confidence interval; LMICs: Low- income countries.

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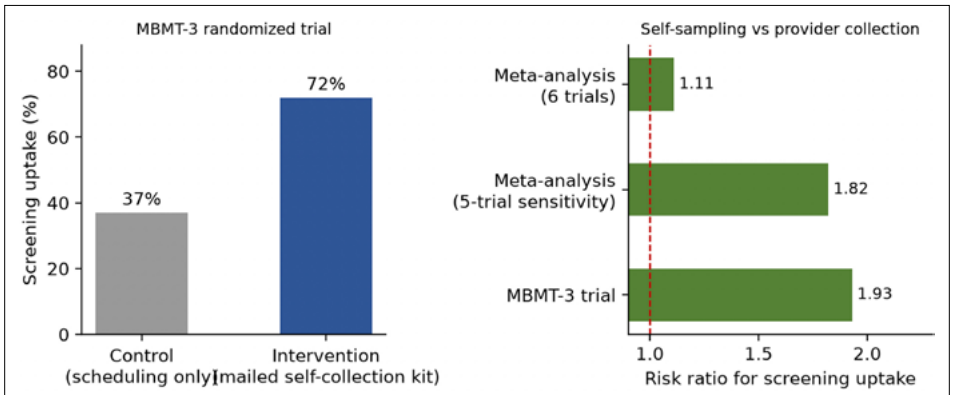

Fig. 5. Human papillomavirus self-sampling evidence: screening uptake in the MBMT-3 randomized trial (left) and risk ratios for uptake with self-sampling versus provider collection (right).

CONCLUSION

Emerging label-free modalities, SEM and AFM of exfoliated cervical cells, their multimodal and machine learning-assisted combinations, adjacent spectroscopic and metabolic imaging platforms, and *in vivo* OCT with its AI-assisted analysis, have reached sufficient diagnostic performance to justify rigorous clinical evaluation for early detection of cervical cancer. Multimodal SEM-AFM pipelines have achieved accuracies of approximately 96%; machine learning on AFM adhesion maps has distinguished precancerous from cancerous cells with an AUC of 0.93; single-cell Raman spectroscopy combined with machine learning has reached an AUC of 0.987; and *in vivo* OCT has reached 93.4% accuracy for high-grade lesions, with demonstrated superiority over combined HPV-cytology screening and an AUC of 0.921 as an HPV triage tool. The remaining barriers are not conceptual but logistical and regulatory: prospective validation, standardization, and cost-effective deployment. The most realistic path to clinical impact is targeted integration into existing HPV-based screening algorithms as a triage or adjunct tool, with self-sampling programs supplying the specimen pipeline, rather than replacement of established tests, and the framework proposed here, multicenter prospective validation, standardized protocols, and multimodal model development, is intended to guide the next phase of studies in this field.

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Peer-review: Externally peer-reviewed.

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CORRIGENDUM

Corrigendum to "The Relationship between the Care Burden, Anxiety, and Social Support Levels of Mothers of Children with Cancer"

In the published article entitled "The Relationship between the Care Burden, Anxiety, and Social Support Levels of Mothers of Children with Cancer" (DOI: 10.5505/tjo.2021.2607), in the Materials and Methods section of the article, the data collection period was inadvertently stated as follows:

Current statement:

"This descriptive study was carried out in a university hospital in Turkey, Pediatric Hematology-Oncology clinic between October 20, 2018, and January 20, 2019."

Corrected statement:

"This descriptive study was carried out in a university hospital in Turkey, Pediatric Hematology-Oncology clinic between December 20, 2018, and January 20, 2019."

The authors regret this error.

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