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In non-melanoma skin cancer, prognostic factors and the role of adjuvant radiation therapy: Retrospective, a single-center experience

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Abstract

Aim: Non-melanoma skin cancer (NMSC) is the most prevalent malignancy worldwide, with basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) representing the most common types of NMSC. In this retrospective analysis, patients with NMSC who had adjuvant radiotherapy (RT) had their treatment results and prognostic variables evaluated.

Materials and Methods: A total of 115 patients with NMSC who had adjuvant RT in our clinic during January 2006 and September 2021 were assessed. The average age was 74 years, and the male to female ratio was 1.95:1. (range: 25–95). The most often diagnosed kind of NMSC was SCC (93%, n=107), preceded by BCC (7%, n=8). The extremities (17.4%, n=20), the trunk (1.7%, n=2), and the head and neck area (80.9%, n=93) were where the bulk of NMSC lesions were discovered.

Results: The mean follow-up period was 60.7 months (the range was 4.2–194.7); metastases were found in six patients (5.2%), and locoregional recurrence was identified in 24 patients (20.8%). The 3- and 5-year total survival percentages were 71.2% and 59.3%, respectively, and the median overall survival (OS) time was 87.1 months. Tumor size and surgical margin status were linked to a worse OS in multivariate analysis of prognostic variables (hazard rate [HR]=3.0, 95% confidence interval [CI]: 1.8-5.2; p=0.001 and HR=2.4, 95% CI: 1.4-4.1; p=0.002, respectively).

Conclusion: Postoperative RT is an efficient, acceptable therapeutic option for NMSC in high-risk individuals. Our results suggest that surgical margin and tumor size were independent predictors of OS in NMSC patients; nevertheless, future studies including more patients are required to corroborate these results.

Introduction

The skin, the largest organ in the body, serves as the body's initial external defense against viruses and stresses such UV radiation, which is the main cause of non-melanoma skin cancer (NMSC) [1-3]. The most frequent kinds of NMSC are basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), which are the most often diagnosed malignant tumors globally. The head and neck region is the most often afflicted location (80%), and BCC is more prevalent than SCC by a ratio of about 4:1 [4,5]. Moreover, NMSC incidence rates rise annually [6]. Furthermore, due to projected changes in sunlight-related behavior, aging populations, and greater sun exposure, the incidence of NMSC is predicted to grow even more in the upcoming years, resulting in higher morbidity [1,2].

Surgical excision, cryotherapy, radiotherapy (RT), and topical medicines are some of the therapeutic options for NMSC [7]. Age, tumor volume, and functional and aesthetic results are only a few of the variables that influence the treatment technique selection. Large prospective randomized controlled investigations comparing various NMSC therapies do not yet exist. Avril et al. reported the first randomized trial comparing surgery with only RT for face BCCs 26 years ago [8], with outcomes favoring surgery both cosmetically and oncologically. Notwithstanding these results, there is a good chance that there were biases due to the numerous complicated surgical operations (reconstructions and re-excisions) in the surgical arm and the varied, dated methods and dosages employed in the RT arm. Recent research suggests that while surgical excision is still the preferred method of care for the curative cure of BCC and SCC, RT can be an essential component in both adjuvant and definitive situations [9].

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With the aim of finding predictive markers that affect locoregional control (LRC) and overall survival (OS) following RT, we retrospectively analyzed clinical features and results in a cohort of NMSC individuals operated with adjuvant RT. Our findings further support the need for bigger prospective studies to better understand the prognostic variables that influence health results in NMSC individuals following adjuvant RT.

Materials and Methods

Patient selection

From January 1, 2006, to September 30, 2021, patients with NMSC who had treatment at the Department of Radiation Oncology, Faculty of Medicine, Karadeniz Technical University, Trabzon, Turkey, were included in this retrospective analysis. Because of to the retrospective nature of the de-identified data gathering and the institutional ethics board of Karadeniz Technical University's approval of the study on 06/03/2023 (Protocol number: 2023/16), informed consent was waived. The study was carried out in accordance with the Declaration of Helsinki's ethical principles. Patient files and phone or in-person discussions with individuals or their family were used to gather information about the patients. Individuals who were included in the research had been histopathologically determined to have NMSC (BCC or SCC), and staging was carried out in line with the 2017 Tumor Node Metastasis (TNM) staging method developed by the American Joint Committee on Cancer. Age, sex, tumor kind, stage, and localization data were all examined. The research excluded individuals with additional skin lesions, initial malignancies in any other tissue, metastasis, or chronic autoimmune disease.

Treatment

In accordance with institutional norms based on illness location, predicted functional results, and patient variables, all patients were assessed and handled in a multidisciplinary environment. From June 2011, RT was carried out using a linear accelerator and a 3D treatment planning system. Before to that, RT was carried out in a two-dimensional (2D) treatment planning system using a Co60 and/or linear accelerator. For immobilization and simulation of all therapeutic stages, a head and neck mask was employed. RT was carried out using 6, 9 or 12 MeV electron beams due to the disease's shallow penetration. As a reference depth, an isodose depth of 85% was used. Although this wasn't always practicable, depending on how close the initial tumor was to organs at risk, the ideal minimum clinical target volume (CTV) margin was 0.5–1.0 cm. BCC and SCC for negative and positive microscopic surgical bed margins, the adjuvant RT dosage was given at 60 and 66 Gy, respectively.

Follow-up visits

The first month following the completion of RT, a preliminary follow-up appointment was scheduled as a control. Once every three months after that, follow-up appointments were arranged at intervals of six months. Physical examination, a complete blood count, and liver function tests were performed at each visit. In suspected cases, neck MRI was preferred for imaging especially for head and neck cancers.

Endpoints

The end points were OS and LRC. OS was defined as the duration from diagnosis to the last follow-up or date of death. Between the conclusion of adjuvant RT and the incidence of local and/or distant recurrence, LRC was assessed. Co-primary outcome measures were surgical margin and tumor size, and others (see Table 2).

Statistical analysis

Using SPSS v. 22 software, data assessment and statistical analysis were carried out. It was examined how patient and tumor parameters, such as tumor volume, gender, positive surgical margins, perineural invasion (PNI), and lymphovascular invasion (LVI), correlated with the clinical outcome. The range of survival times was evaluated using the Kaplan-Meier survival analysis. To examine the difference in survival between groups, the log-rank test was used, and the Bonferroni correction was used to make comparisons among groups. For multivariate analysis, independent factors predicting survival were analyzed using Cox regression analysis. Type-1 error levels under 5% were deemed significant. We conducted a post hoc calculations of statistical power using an online tool (ClinCalc: www.clincalc.com, accessed on 13 April 2023) to determine impact of primary outcome on clinical outcome (overall survival). The primary outcome (overall survival) was examined in the following prespecified factors: by age (<65, >65 y), gender, tumor size, depth of invasion, PNI, LVI, tumor grade, surgical margin, N and T category (Table 2). Based on an overall cumulative impact on the primary outcome), the study had >95% power.

Results

Patient characteristics

In all, 115 patients with NMSC participated in this research, including 39 (33.9%) women and 76 (66.1%) males. Male:female ratio was 1.95:1 and median patient age was 74 years (range: 25-95 years). The most common type of NMSC was SCC (93%, n =107), followed by BCC (7%,

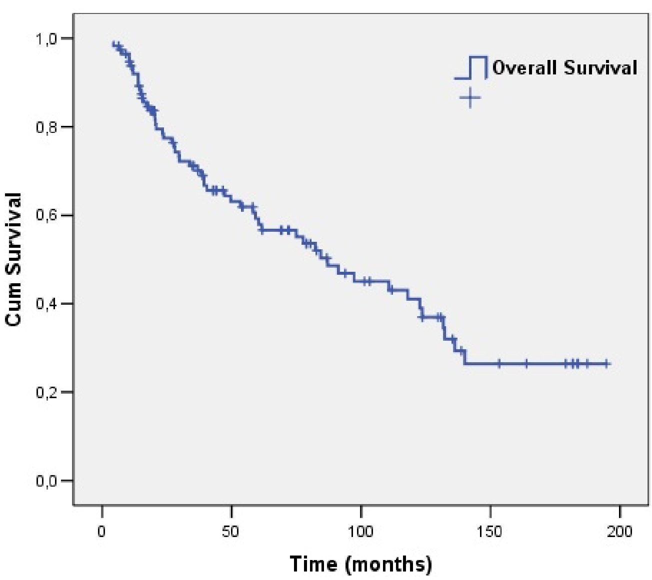

Figure 1. Overall survival (months).

Table 1. Patient and tumor characteristics.

Variable	n (%)
Age, median (range) (y)	74 (25-95)
Gender	
Male	76 (66.1)
Female	39 (33.9)
Histopathologic type	
BCC	8 (7)
SCC	107 (93)
Tumor size (cm)	
≤2 cm	63 (54.8)
>2 cm	52 (45.2)
Depth of invasion	
<2 mm	38 (33)
≥2 mm	77 (67)
Ulceration	
Absent	8 (7)
Present	43 (37.4)
Unknown	64 (55.7)
PNI	
Negative	100 (87)
Positive	15 (13)
LVI	
Negative	110 (95.7)
Positive	5 (4.3)
Grade	
G1	83 (72.2)
G2	28 (24.3)
G3	4 (3.5)
T category	
T1	36 (31.3)
T2	21 (18.3)
T3	45 (39.1)
T4	13 (11.3)
N category	
N0	100 (87)
N1	7 (6.1)
N2	3 (2.6)
N3	5 (4.3)
Surgical margin	
Negative -Close	73 (63.5)
Positive	42 (36.5)
Tumor status	
Primary	103 (89.6)
Recurrence	12 (10.4)
Immunosuppression	
Absent	113 (98.3)
Present	2 (1.7)

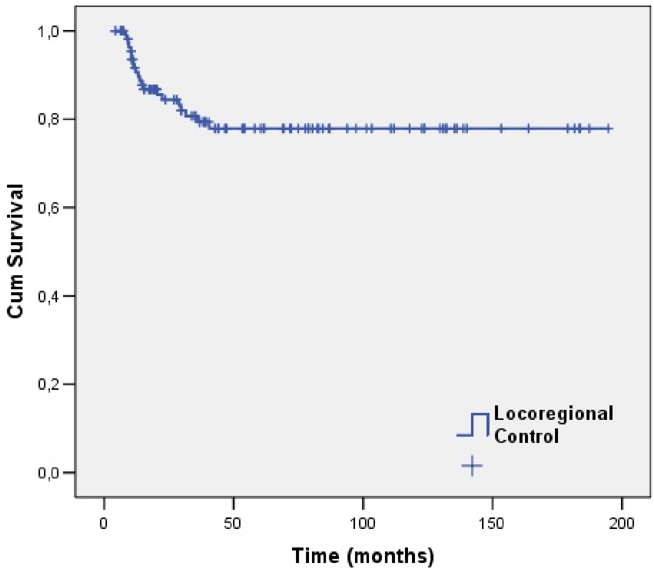

Figure 2. Locoregional control (months).

n=8). The extremities (17.4%, n=20), the trunk (1.7%, n=2), and the head and neck (80.9%, n=93) were the primary tumor locations. In 42 cases (36.5%), the surgical margin was positive, and in 73 (63.5%), it was negative or near. Table 1 lists the patient features in summary.

Locoregional recurrence and distant metastasis

As of September 30, 2022, with a median follow-up of 60.7 months (range: 4.2–194.7 months), 72 (62.6%) patients were alive, and 43 (37.4%) patients died; 14 patients died of disseminated disease, and 29 died of underlying medical illnesses. 19 patients (16.5%) experienced local recurrence, five experienced locoregional recurrence, and six patients (5.2%) experienced distant metastases.

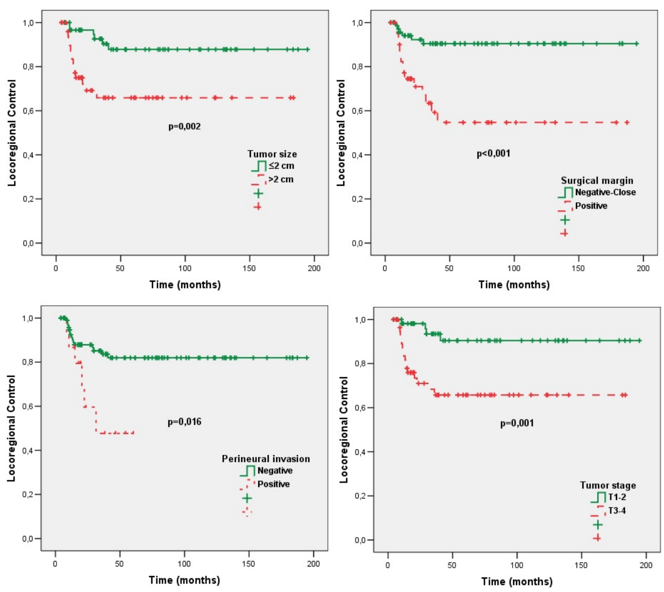

Figure 3. Univariate analysis of the locoregional control.

Table 2. Results of log-rank univariate analysis for overall survival and locoregional control.

Patient and tumor characteristics	n (%)	OS (5-y) (%) (±SE)	p value	LRC (5-y) (%) (±SE)	p value
Age (y)			0.056		0.615
≤65	32 (27.8)	76 (±0.09)		76.3 (±0.08)	
>65	83 (72.2)	53.2 (±0.06)		78.1 (±0.05)	
Gender			0.564		0.171
Male	76 (66.1)	65 (±0.06)		82.6 (±0.05)	
Female	39 (33.9)	49.6 (±0.09)		69.4 (±0.08)	
Histopathologic type			0.390		
BCC	8 (7)	53.6 (±0.2)		83.3 (±0.15)	0.718
SCC	107 (93)	59.6 (±0.05)		77.7 (±0.05)	
Tumor size (cm)			**0.00001**		**0.002**
≤2 cm	63 (54.8)	72.1 (±0.06)		87.8 (±0.05)	
>2 cm	52 (45.2)	44 (±0.08)		65.9 (±0.07	
Depth of invasion			**0.033**		0.276
<2 mm	38 (33)	75.2 (±0.08)		84.4 (±0.07)	
≥2 mm	77 (67)	51 (±0.06)		74.2 (±0.06)	
PNI			**0.001**		**0.016**
Negative	100 (87)	65.1 (±0.05)		82.0 (±0.04)	
Positive	15 (13)	21.3 (±0.12)		47.7 (±0.16)	
LVI			0.141		0.707
Negative	110 (95.7)	60.1 (±0.05)		78.0 (±0.04)	
Positive	5 (4.3)	40 (±0.22)		75.0 (±0.22)	
Grade			0.571		0.071
G1-2	111 (96.5)	59.9 (±.05)		79.0 (±0.04)	
G3	4 (3.5)	50 (±0.25)		50.0 (±0.25)	
T category			**0.002**		**0.001**
T1-2	57 (49.6)	69.8 (±0.07)		90.4 (±0.05)	
T3-4	58 (50.4)	49.3 (±0.07)		65.7 (±0.07)	
N category			0.442		0.770
N0	100 (87)	60.1 (±0.06)		77.2 (±0.05)	
N1-2-3	15 (13)	51.9 (±0.13)		83.9 (±0.10)	
Surgical margin			**0.00001**		**0.00001**
Negative -Close	73 (63.5)	74 (±0.06)		90.4 (±0.04)	
Positive	42 (36.5)	36.2 (±0.08)		54.7 (±0.09)	
Tumor status			**0.039**		0.213
Primary	103 (89.6)	62.4 (±0.05)		80.0 (±0.04)	
Recurrence	12 (10.4)	34.3 (±0.15)		63.5 (±0.15)	

Abbreviations:, BCC: basal cell carcinoma; SCC: Squamous cell carcinoma; LVI: lymphovascular invasion; PNI: perineural invasion, LRC: locoregional control; OS, overall survival, n = number of patients.

Survival analysis

Median OS 87.1 months and (95% confidence interval [CI]: 54.6-119.5); 3- and 5- year OS are respectively, 71.2% (standard error [SE] ±0.05) and 59.3 % (SE±0.05) (Figure 1). The rates for the 3- and 5-year LRC were, respectively, 79.4% (S.E. 0.04) and 77.9% (S.E. 0.04) (Figure 2).

In univariate analyses, the following variables were looked at as potential prognostic factors for OS: age (65 and >65), gender (male and female), histopathological type (SCC and BCC), tumor diameter (2 cm and >2 cm), depth of invasion (2 mm and 2 mm), PNI (positive and negative), LVI (positive and negative), grade (1 and 2/3), T stage (1/2, 3/4), and surgical margin status (negative/close and positive). The statistical significance of these variables were tumor diameter (P=0.001), depth of invasion (P=0.033), PNI (P=0.001), T stage (P=0.002), and surgical margin status (P=0.001). Tumor diameter (P=0.02), PNI (P=0.016), T stage (P=0.001), and surgical margin status (P=0.001) were all statistically significant predictive variables for LRC, according to a univariate analysis (Figure 3). Table 2 summarizes the outcomes of the OS and LRC univariate analyses.

As potential predictors of OS, multivariate analyses looked at age (65 and >65), tumor diameter (2 cm and >2 cm), depth of invasion (2 mm and 2 mm), PNI (positive and negative), T stage (1/2, 3/4), and surgical margin sta-

Table 3. Results of multivariate analysis for overall survival, and locoregional control by Cox proportional hazard model.

Variable	Overall Survival		LRC	
	Hazard Ratio (95%CI)	p value	Hazard Ratio (95%CI)	p value
Age (y) ≤65 vs >65	2.2 (1.1-4.3)	**0.029**	0.8 (0.3-2.0)	0.610
Tumor size (cm) ≤2 vs 2<	3.0 (1.8-5.2)	**0.0001**	1.9 (0.6-6.5)	0.317
Depth of invasion (mm) <2 vs 2≤	1.6 (0.9-2.9)	0.137	0.7 (0.2-2.3)	0.560
PNI Negative vs Positive	1.4 (0.6-3.1)	0.385	1.5 (0.5-4.4)	0.489
T category T1-2 vs T3-4	0.8 (0.3-1.7)	0.523	3.4 (1.1-10.6)	**0.032**
Surgical margin Negative -Close vs Positive	2.4 (1.4-4.1)	**0.002**	3.8 (1.4-10.0)	**0.008**
Tumor status Primary vs recurrence	1.2 (0.5-2.8)	0.745	1.0 (0.3-3.7)	0.980

Abbreviations: BCC: basal cell carcinoma; SCC: squamous cell carcinoma; LVI: lymphovascular invasion; PNI: perineural invasion, LRC: locoregional control; n = Number of patients.

tus (negative/close and positive). The tumor diameter and surgical margin status were shown to be statistically significant among these factors (hazard ratio [HR]=3.0, 95% CI: 1.8-5.2, p=0.001 and HR=2.4, 95% CI: 1.4-4.1, p=0.002, respectively). T stage and surgical margin status were strongly correlated with LRC in multivariate analyses (HR=3.4, 95%CI: 1.1-10.6; p=0.032 and HR=3.8, 95%CI: 1.4-10.0; p=0.008, respectively). The outcomes of the multivariate analysis are presented in Table 3.

Discussion

With annual increases in incidence, skin malignancies have become one of the most prevalent cancers in the world. The two most significant etiologic factors for the development of skin cancer are exposure to sunshine and radiation, while geographic location and elderly age are also risk factors. Australia, New Zealand, and the US are the countries with the highest incidence and fatality percentages of skin cancer worldwide [10,11]. The most common form of skin cancer to be identified is NMSC, and among the several subtypes of NMSC, BCC is much more prevalent and typically has a far good prognosis than SCC because of its local development pattern and low risk of metastasis. Individuals with BCC had a superior 5-year LRC than those with SCC (97% vs. 84%; p=0.02) [12] even when PNI is present. In our research, we discovered that individuals with BCC and SCC had similar 5-year LRCs (83.3% vs. 77.8%, correspondingly; p=0.718).

Our demographic results largely match with information from earlier research. The head and neck regions are often where NMSCs are most prevalent, while different studies have shown varying percentages of NMSC lesions in various sites. Here, we observed the greatest number of overall excisions in the head and neck region, consistent with results from several American and European studies [13-15]. The American Cancer Society reports that NMSC is twice as prevalent in men as it is in women, and SCC is three times more common in men than in women [3,16]. Epidemiology studies have also shown that the burden of disease of NMSC is much higher in men than in women. However while prevalence is rising in all age groups, regardless of sex, over 80% of NMSC diagnoses are made in patients over the age of 55 [17,18]. Consequently, the male/female proportion of 1.95:1 and the average age of 74 years (interquartile range: 25–95) for the participants in our investigation are in line with previous research.

RT is capable of being utilized in a definitive, adjuvant, or combined context and is essential in the cure of cutaneous BCC and SCC [19]. Important decisions about diagnostic testing for RT should be taken as part of interdisciplinary treatment. The purpose of postoperative RT is to sterilize microscopic cancer cells that remain after extensive excision of BCC and SCC in order to lower the risk of local recurrence. When there are other high-risk variables present, such as PNI, penetration of the bone or nerves, or recurrent disease, adjuvant RT is frequently advised [20]. Nevertheless, it should be noted that in our examination of the literature, we were unable to locate any randomized controlled trials contrasting adjuvant RT to surgery on its own for BCC or SCC, with the existing studies being constrained by retrospective designs and possible selection bias. Adjuvant RT was linked to a better OS (HR=0.59, 95%CI: 0.38-0.90) in one retrospective study of individuals with progressed head and neck SCC by Harris et al. [21] compared to surgery alone. They found that individuals with PNI and regional disease who received adjuvant radiation had increased disease-free survival and OS. Similar to this, in an analysis of 67 individuals with locoregional recurring, 30% of whom received adjuvant RT, Strassen et al. [22] discovered advantages when employing adjuvant radiation beyond surgery alone. Adjuvant RT enhanced the 5-year recurrence-free interval (78% vs. 30%; p=0.02) and OS (79% vs. 46%; p<0.05) in this population. In addition, Kim et al. [23] found that patients treated with adjuvant RT as opposed to final RT had increased 3-year disease-specific survival (38.3%; 95%CI: 22.2-54.4 vs. 92.9%; 95%CI: 77.9-95.5). Even though having a median OS of 87.1 months in our analysis of NMSC patients who had adjuvant RT, the 3- and 5-year OS percentages were reported to be 71.2% and 59.3%, respectively. These numbers are broadly similar with rates in previous studies.

It is accepted that approximately 30–40% of incompletely excised BCCs recur [3]. Re-excision is recommended by some in order to produce a negative margin [24]. Nevertheless, RT is an alternative if the implicated margin prevents straightforward re-excision (for example, the periosteum of the nose) [25]. The inclusion of adjuvant RT increased the 5-year local control from 61% to 91%, according to a notable Canadian experiment. [26]. Also, this study found that the 5-year local recurrence rate was 17% if the lateral margin was positive and 33% if both the lateral and deep margins were implicated. Among patients who had operation with positive surgical margins, the 5-year LRC was 54.7%, compared to 90.4% in patients who had negative surgical margins. Here, consistent with these findings, our univariate and multivariate analyses uncovered a statistically significant relationship (P<0.05) between surgical margin and both LRC and OS.

PNI is characterized by the presence of cancerous cells in the nerves' perineural region. It occurs infrequently in SCC, with a reported incidence ranging from 2.4% to 14. PNI is also documented in BCC, but less frequently; however, because BCC is less aggressive and there is less data, making recommendations is challenging [27,28]. Although Leibovitch et al. [30,31] identified 283 incidences of PNI in 10,035 cases of BCC (2.74%), Mohs and Lathrop [29] recorded a 1% occurrence of PNI in a large-scale series of BCC. Here, consistent with the literature, we identified 15 cases of incidental PNI in 115 NMSC patients (13%). NMSCs with PNI had a worse prognosis and a greater rate of recurrence. Patients with PNI had a recurrence-free survival (RFS) rate of 26% and a 5-year overall survival (OS) rate of 45%, according to Kygirdis et al. [32], as opposed to 82% and 76%, respectively, in patients without PNI. In our analysis, we found that patients with PNI had a 5-year OS of 21.3% and a 5-LRC rate of 47.7% (as opposed to 65.1% and 82%, respectively, in patients without PNI). Moreover, univariate analysis showed that PNI and LRC and OS were substantially related (p< 0.05).

An key prognostic marker is tumor size, with SCC tumors with a diameter bigger than 2 cm having a doubled probability of recurrence and a tripled chance of metastasis [33]. The risk factor most strongly linked to disease-specific death, according to a comprehensive study by Thompson et al. [34], is tumor diameter >2 cm, which results in a 19-fold increased risk of death from SCC in comparison to tumors 2 cm. Nodular BCCs larger than 1 cm in size that are located in high-risk areas are likewise given a bad prognosis since they have a high probability of recurring. Univariate analysis revealed a statistically significant connection (p<0.001) among tumor grade and both OS and LRC in our study of NMSC patients.

Depth of invasion (or thickness) is another important predictor of metastases. Individuals with tumors that are less than 2 millimeters thick have a low chance of metastasis, but a depth of invasion greater than 4 millimeters is linked to a higher risk [35]. Just 17% of patients with a lesion 4 mm metastasized in a study involving individuals with metastatic SCC of the head and neck, compared to 83% of patients with lesions >4 mm [36]. According to Clayman et al. [37], SCC with a greater depth of invasion was linked to a decreased disease-specific survival rate (p=0.009). Similarly, Jackson et al. found that patients presenting with cutaneous SCC showing muscle invasion had a worse 5-year RFS than patients with tumors limited to the dermis (66% vs. 87%; p=0.0135). We observed a statistically significant correlation among depth of invasion and lifespan (P=0.033), which is consistent with our findings.

We note that this study had several limitations; these include missing data due to its retrospective nature, which required the review of patient medical records over a long period of time. Further, given its single-center design, this study may not represent the general population. Lastly, the small number of cases in this study is another limitation.

Conclusion

Individuals with close or positive margins, larger tumors, or tumors with perineural dissemination, deep penetration, or nodal metastases might consider combining surgery with adjuvant RT. Adjuvant RT can prolong survival and decrease recurrence in patients with resected NMSC. Large tumor size and the surgical margin were unfavorable prognostic variables in NMSC in multivariate analysis. Choosing who is an acceptable target for adjuvant RT still depends on clinical judgment because there is no conclusive proof of benefit.

Ethical approval

This research was approved by the institutional ethic board of Karadeniz Technical University (Protocol number: 2023/16) at 06/03/2023 and conducted according to the ethical principles of the declaration of Helsinki.

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