

Surgery and Hypofractionated Radiotherapy Improve Local Control in High-Risk Head and Neck Non-Melanoma Skin Cancer

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ABSTRACT

Non-melanoma skin cancers (NMSCs) are the most common malignancies worldwide. This study aimed to evaluate the clinical outcomes of radiotherapy (RT) alone versus surgery followed by RT in patients with high-risk head and neck (HN) NMSCs. Patients diagnosed with HN-NMSCs and treated with RT at three institutions between June 2010 and September 2022 were retrospectively analyzed. The primary endpoint was local recurrence-free survival (LRFS). A total of 73 patients were included. The median follow-up was 50 months (range: 18-164). Fifty patients (68.5%) underwent surgery prior to RT, while 23 patients (31.5%) received definitive RT. Nine patients (12.3%) experienced in-field recurrence. The 2-year LRFS was 90.2%, and the 5-year LRFS was 86.3%. LRFS was significantly better in patients who received surgery plus RT compared to those treated with definitive RT alone ($p=0.014$; HR: 0.20; 95% CI: 0.05-0.83). Hypofractionated RT regimens were associated with improved LRFS compared to conventional RT ($p=0.040$; HR: 4.4; 95% CI: 0.91-21.3). In high-risk HN-NMSC patients, the combination of surgery and RT, as well as hypofractionated RT regimens, provided superior local control compared to definitive RT alone and conventional fractionation schedules.

Keywords: Basal cell carcinoma, Non-melanoma skin cancer, Radiotherapy, Head and neck cancer, Local control

INTRODUCTION

Non-melanoma skin cancers (NMSCs), primarily comprising basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), are the most common malignancies worldwide. BCC typically exhibits indolent behavior with a low metastatic potential, whereas SCC carries a higher risk of nodal and distant spread. The incidence of both entities continues to increase, particularly in chronically sun-exposed areas such as the head and neck (HN) region.^{1,2}

Surgical excision remains the standard first-line treatment for most NMSCs, aiming to achieve oncologic control while preserving function and cosmesis.³ Radiotherapy (RT), either as a definitive

modality or in the adjuvant setting, plays an essential role in the management of high-risk tumors especially in patients with perineural invasion (PNI), positive surgical margins, or contraindications to surgery.^{1,3,4} In the adjuvant context, RT is well established, but its role as a sole treatment modality remains less clearly defined, with limited prospective comparative data available.⁴

In addition to treatment modality, fractionation schedule and RT delivery technique may influence outcomes in this population. Hypofractionated regimens and modern RT platforms such as IMRT are increasingly used in clinical practice, particularly in elderly or frail patients, due to convenience and improved dose conformity.

However, their oncologic efficacy relative to conventional approaches remains under investigation. Given the lack of high-level evidence guiding the use of definitive versus adjuvant RT strategies, particularly by histologic subtype, our study aimed to compare local control outcomes in patients with high-risk HN-NMSC treated with either definitive RT or surgery followed by adjuvant RT. We further assessed the impact of RT fractionation, technique, and histologic subtype (BCC vs SCC) on local recurrence-free survival (LRFS), with exploratory subgroup analyses.

PATIENTS AND METHODS

Study Design and Patient Selection

This retrospective, multicenter study included patients diagnosed with histologically confirmed non-melanoma skin cancer (NMSC) of the head and neck who received RT at Ankara Atatürk Research and Training Hospital, Ankara Numune Research and Training Hospital, and Ankara Bilkent City Hospital between June 2010 and September 2022. Eligible patients were ≥ 18 years old and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0-4. Patients were included if they had a diagnosis of BCC or SCC located in the head and neck region and were treated with RT, either as definitive or adjuvant therapy. Exclusion criteria were: 1) absence of pathological confirmation, and 2) tumors located outside the head and neck region.

Data Collection

Patient data were retrieved from hospital records, radiology and pathology reports, radiotherapy dose-volume histograms, and electronic medical systems. Variables collected included demographic characteristics, tumor histology, T and N stage, PNI status, surgical details (if applicable), radiotherapy technique and dose, use of chemotherapy, and follow-up outcomes. Staging was performed according to the 8th edition of the American Joint Committee on Cancer (AJCC) classification.

Radiotherapy Protocol

Patients received either conventional or hypofractionated radiotherapy using electron and photon beam techniques.

Electron therapy was delivered using 6 MeV electron beams with a source-to-skin distance (SSD) of 100 cm, utilizing Varian Trilogy and Varian Millennium linear accelerators. It was primarily used for superficial lesions in the head and neck region. In these cases, isodose prescription depth was determined based on clinician preference and anatomical depth. Bolus material (0.5–1 cm) was applied to optimize surface dose delivery, and field shaping was achieved using custom lead blocks.

Photon-based treatments were administered via helical intensity-modulated radiotherapy (IMRT) platforms, including Tomotherapy and Radixact systems. For these patients, the planning target volume (PTV) was defined directly at the skin surface, and no bolus was applied due to favorable surface dose characteristics of helical IMRT. All patients were immobilized with thermoplastic masks to ensure reproducible setup.

The choice of fractionation scheme and radiotherapy technique was individualized based on tumor location, depth of invasion, patient comorbidities, and institutional resources. Biologically effective dose (BED) values were calculated using the linear-quadratic model with an α/β ratio of 10, appropriate for tumor tissue.

Study Endpoints

The primary endpoint was local recurrence-free survival (LRFS), defined as the time from the start of RT to the date of in-field recurrence or last follow-up. In-field recurrence was defined as recurrence within the radiation treatment field.

Ethical Approval: The study was approved by the Clinical Research Ethics Committee of Ankara Bilkent City Hospital (Date: March, 08, 2023, Decision No: E1-23-3279). Informed consent was not required due to the retrospective nature of the study.

Statistical Analysis

Statistical analysis was performed using SPSS software version 26.0 (IBM Corp., Armonk, NY). The Shapiro–Wilk test was used to assess normality. As the data were not normally distributed, non-parametric tests were employed. Subgroup analyses were conducted for BCC and SCC patients to bet-

Table 1. Comparative clinicopathologic and treatment characteristics

Characteristic	BCC (n= 23)	SCC (n= 50)
Mean age (years)	66.5	72.0
Male sex	12 (52.2%)	32 (64.0%)
T1-T2 stage	19 (82.6%)	30 (60.0%)
Nodal involvement (cN+)	2 (8.7%)	13 (26.0%)
Distant metastasis (cM1)	0 (0%)	3 (6.0%)
PNI	17 (73.9%)	35 (70.0%)
Surgery performed	15 (65.2%)	35 (70.0%)
Hypofractionated RT	17 (73.9%)	24 (48.0%)
IMRT technique used	16 (69.6%)	38 (76.0%)
Electron treatment	7 (30.4%)	12 (24.0%)
In-field recurrence	1 (4.3%)	8 (16.0%)

ter understand histology-specific patterns in local control outcomes. These analyses were exploratory in nature and not pre-specified in the study design. LRFS was estimated using the Kaplan–Meier method, and comparisons between groups were performed using the log-rank test. Cox proportional hazards regression was used for multivariate analysis. Hazard ratios (HRs) with 95% confidence intervals (CIs) were reported. A p-value < 0.05 was considered statistically significant.

RESULTS

A total of 73 patients diagnosed with high-risk non-melanoma skin cancer (NMSC) of the head and neck were included in the final analysis. All patients received curative-intent radiotherapy between June 2010 and September 2022 across three tertiary centers. The cohort comprised both BCC and SCC cases, with varying clinical presentations including primary and recurrent tumors. The median follow-up time was 50 months (range: 18–164). Clinical, pathological, and treatment-related factors were analyzed in relation to local recurrence-free survival (LRFS), with subgroup analyses performed by histologic subtype (Table 1).

Basal Cell Carcinoma (BCC)

A total of 23 patients (31.5%) had BCC. The mean age was 66.5 years, and 52.2% (n= 12) were male. Among BCC patients, 65.2% (n= 15) underwent surgery followed by adjuvant RT, while 34.8% (n=

8) received definitive RT alone. Most tumors were T1-T2 stage (82.6%, n= 19). No distant metastases were observed. PNI was noted in 73.9% (n= 17) of cases. Hypofractionated RT was used in 73.9% (n= 17), and IMRT in 69.6% (n= 16). Electron therapy was administered in 30.4% (n= 7).

Only one in-field recurrence (4.3%) was observed. Patients who underwent surgery had significantly longer LRFS than those who did not (median LRFS: 42.6 vs. 11.5 months, $p= 0.031$). Hypofractionated RT was associated with improved LRFS (median: not reached vs. 12.9 months, $p= 0.069$), though not statistically significant. Similarly, electron therapy showed a favorable trend (no recurrences in the electron group vs. median LRFS of 11.4 months in the non-electron group, $p= 0.055$). Hypofractionated radiotherapy was associated with a longer median LRFS (not reached) compared to conventional RT (12.9 months), although the difference was not statistically significant ($p= 0.069$).

Patients who underwent surgery had significantly longer LRFS than those who did not (median LRFS: 42.6 vs. 11.5 months, $p= 0.031$ by log-rank test). Consistent with this finding, univariate Cox regression demonstrated a strong protective effect of surgery (HR: 0.119; 95% CI: 0.012–1.175), although statistical significance was borderline ($p= 0.068$) due to the small sample size and low event rate. In contrast, electron therapy was not statistically significant (HR: 0.024, 95% CI: 0.000–17.707, $p= 0.269$), likely due to low event count and censoring.

Squamous Cell Carcinoma (SCC)

A total of 50 patients (68.5%) had SCC. The median age was 74 years (range: 40-93), and 64.0% (n= 32) were male. Surgery followed by adjuvant RT was performed in 70.0% (n= 35), while 30.0% (n=15) received definitive RT. Most tumors were T1-T2 (60.0%, n= 30), with nodal involvement in 26.0% (n= 13) and distant metastases in 6.0% (n= 3). PNI was present in 70.0% (n= 35). Hypofractionated RT was used in 48.0% (n= 24), and IMRT in 76.0% (n= 38). Electron therapy was administered in 24.0% (n= 12). In the SCC group, six patients (12.0%) received concurrent chemoradiotherapy.

In-field recurrence occurred in 8 patients (16.0%). Surgery was significantly associated with improved LRFS (median not reached vs. 21.6 months, $p= 0.002$). Hypofractionation showed no survival benefit ($p= 0.751$). Electron therapy did not significantly influence outcomes ($p= 0.460$).

Univariate Cox regression revealed that surgery significantly reduced recurrence risk (HR: 0.137, 95% CI: 0.032–0.577; $p= 0.007$). Electron therapy was not significant (HR: 0.463, $p= 0.471$).

DISCUSSION

This retrospective, multicenter study evaluated local control outcomes in patients with high-risk non-melanoma skin cancer (NMSC) of the head and neck, stratified by histologic subtype (BCC vs SCC). Our subgroup analyses demonstrated that combining surgery with radiotherapy (RT) was associated with significantly superior local recurrence-free survival (LRFS) in both BCC and SCC patients. Additionally, hypofractionated RT regimens showed a trend toward improved outcomes in BCC cases, while no such benefit was observed in SCC. Electron beam therapy appeared favorable in BCC but did not achieve statistical significance.

Surgical excision remains the standard first-line treatment for both low- and high-risk NMSC, aiming to achieve clear margins with acceptable cosmetic outcomes.⁵ RT is typically reserved for patients who are medically inoperable, poor surgical candidates, or for tumors located in cosmetically sensitive areas.^{3,5} Historically, surgery has been

considered superior to RT in terms of local control and cosmesis. For instance, in the randomized trial by Avril et al., the 4-year actuarial local failure rate was significantly lower in the surgery group (0.7%) compared to the RT group (7.5%).⁷ However, recent data using modern RT techniques have shown comparable local control and, in some cases, even better cosmetic outcomes for RT.⁸⁻¹⁰

In our study, the 5-year LRFS rate was 95.7% in BCC and 84.0% in SCC. Subgroup analysis revealed that surgery significantly improved LRFS in both histologies. In BCC, surgery was associated with a marked reduction in recurrence ($p= 0.031$), and a similar trend was confirmed by Cox regression analysis (HR: 0.119, $p= 0.068$). In SCC, the benefit of surgery was even more pronounced ($p= 0.002$; HR: 0.137; $p= 0.007$). These findings reinforce the role of surgery as a key component of curative treatment in high-risk NMSC.

Patients with recurrent tumors had significantly lower LRFS compared to those with primary tumors ($p= 0.029$), supporting clinical expectations that recurrent disease poses greater therapeutic challenges. These results emphasize the importance of initial comprehensive management to reduce relapse risk and suggest the need for intensified RT strategies in recurrent settings.

Adjuvant RT is well-established for patients with high-risk features such as gross PNI, positive or close margins, T3-T4 tumors, or recurrence after prior surgery.¹ In our cohort, patients treated with adjuvant RT after R0 or R1 resection had significantly better 5-year LRFS (92.2%) compared to those treated with definitive RT (73.1%). Interestingly, no significant difference was observed between R0 and R1 resections ($p= 0.397$), suggesting that RT may compensate for microscopic residual disease in R1 settings, as shown in other multimodal series.¹¹

Although our analysis did not demonstrate a statistically significant difference in LRFS between BCC and SCC ($p= 0.075$), prior literature supports a more favorable prognosis for BCC.^{12,13} The trend observed in our study is consistent with these findings, despite the limited event count in the BCC group.

Hypofractionated RT is increasingly adopted in elderly or frail patients due to convenience and comparable efficacy.^{5,8,16} In our BCC subgroup, hypofractionated RT was associated with improved LRFS (mean: 88.2 vs. 23.4 months; $p=0.069$), although the log-rank test fell short of significance. In contrast, no such benefit was observed in SCC ($p=0.751$). These results suggest that hypofractionation may be particularly suitable for select BCC patients.

Electron beam therapy also showed a favorable trend in BCC, with no recurrences among patients who received electrons. However, the Cox model did not reach statistical significance due to limited event count (HR: 0.024, $p=0.269$). In SCC, electron use did not impact outcomes.

Limitations: This study has several limitations. Due to its retrospective design, data on toxicity and cosmetic outcomes were not systematically recorded. Disease-specific survival could not be assessed due to incomplete cause-of-death documentation. The relatively small BCC subgroup and limited number of recurrences constrain multivariable analysis and generalizability. Variability in RT technique (2D, 3D, IMRT) may have introduced treatment heterogeneity, although subgroup comparisons did not identify significant differences.

Conclusion Our findings suggest that the combination of surgery and radiotherapy improves local control in patients with high-risk head and neck NMSC, with stronger evidence for SCC. Hypofractionated RT may be beneficial in BCC and selected patient groups. These results support a tailored, multimodal approach to optimizing outcomes in head and neck skin cancers.

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