Published in final edited form as:

Br J Dermatol. 2019 February ; 180(2): 417–418. doi:10.1111/bjd.17244.

Local recurrence and quality of life after adjuvant radiation therapy in high-risk squamous cell carcinoma

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Dear Editor, Cutaneous squamous cell carcinoma (cSCC) is a keratinocyte cancer typically treated by surgery, recurring in <5% of all-comers after initial margin-negative excision. However, a subgroup of patients at higher risk for local recurrence (LR) after surgery exists.¹ Retrospective and poorly controlled studies have inadequately defined this subgroup. This is exemplified by a recent analysis showing that among a single cohort of patients, 87% of tumours were categorized as high-risk cSCC using the National Comprehensive Cancer Center (NCCN) guidelines, compared with 18% using the American Joint Committee on Cancer criteria.² Nevertheless, a landmark prospective study of 653 patients comprehensively evaluated all putative risk factors for LR of cSCC.² On multivariate analysis, two factors were independently associated with LR after margin-negative-excision: depth of invasion (DOI) > 6 mm and desmoplasia [including perivascular or perineural invasion (PNI)]. The LR risk with either factor was 12% at 2 years and 25% at 6 years.³ In the present study, we assessed the LR risk after surgery and adjuvant radiotherapy (ART) in high-risk cSCC, defined by DOI > 6 mm or desmoplasia. Additionally, we studied changes in quality of life (QoL) after ART.

With institutional review board approval (#16–934), we identified patients treated with ART after surgery for high-risk cSCC at our centre between 2004 and 2018. We defined high-risk cSCC strictly as those exhibiting desmoplasia (including PNI ≥ 0.1 mm) or DOI > 6 mm. Patients with gross residual tumour post-surgery and those receiving ART for regional nodal metastases were excluded. Primary outcomes examined included LR, defined as recurrence within 2 cm of the surgical site, and Skindex-16 scores. Time to LR was defined from ART to recurrence. Patients were censored at last follow-up. QoL was assessed using the validated Skindex-16 instrument before and after ART. Statistical analyses were performed using Prism version 7.0d (GraphPad Software, Inc., La Jolla, CA, U.S.A.) and R version 3.4.3 (R Project, Vienna, Austria).

Fifty-two patients met the inclusion criteria (Table 1). The median ART dose was 60.0 Gy (range 8.0–74.0). The median follow-up time after ART was 15.5 months (range 0.7–100.2).

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Conflicts of interest

None declared.

Two patients (4%) experienced LR at 1.9 and 2.5 months after microscopically positive margin excision and ART doses of 55.9 and 53.0 Gy, respectively. LR-free survival was estimated to be 95.8% [95% confidence interval (CI), 90.3–100%] at 2 years. Univariate analysis revealed an association between LR and ART doses of < 60 Gy ($P = 0.03$) and microscopically positive margins ($P = 0.04$). Skindex-16 scores were available for 26 (50%) patients before and 24 (46%) after ART. The composite score improved by 11.2 points (95% CI 2.0–20.4, $P = 0.02$) after ART. Scores improved by 3.9 (95% CI -7.8 to 15.5, $P = 0.51$), 15.0 (2.3–27.8, $P = 0.02$) and 11.7 (2.1–21.3, $P = 0.02$) in the Symptoms, Emotions and Functioning domains after ART.

Until now, no studies have investigated LR after surgery and ART using the strict high-risk cSCC criteria.³ Current NCCN guidelines recommend ART for PNI or positive margins.⁴ A systematic review found LR rates for high-risk cSCC treated with surgery alone were 7–18%, compared with 12–19% after ART.⁵ Highlighting limitations of the existing data on this topic, the review noted the variable definitions of high-risk, follow-up, and endpoint assessments, which precluded robust analyses and limited interpretation of the findings. Our results suggest that surgery followed by ART is associated with a LR rate considerably lower than expected in a well-defined high-risk cohort. Univariate analysis demonstrating associations between LR and margin-positive excision and ART doses < 60 Gy support the NCCN guidelines, which encourage margin-negative excisions when possible and ART doses of ≥ 60 Gy.⁴

For the first time, data are presented indicating that surgery and ART is not associated with a decrease in QoL. The effects of skin conditions on QoL are commonly measured using the validated Skindex-16 instrument. In a previous study, mean improvements of 9.6, 23.8 and 5.3 were found in the Symptoms, Emotions and Functioning subscores after Mohs surgery, compared with 8.5, 16.9 and 4.2 after surgical excision.⁶ Comparatively, we found mean improvements of 3.9, 15.0 and 11.7 among the same domains after ART.

In conclusion, surgery and ART for high-risk cSCC is associated with a low LR risk and no deleterious effect on QoL. Randomized controlled trials are necessary to demonstrate if ART is the cause of these observations.

Acknowledgement

This study was supported by a Cancer Center Support Grant to Memorial Sloan Kettering Cancer Center, P30-CA008748 (PI: Craig Thompson). The funding body was not involved in the design of the study, data collection or analysis, interpretation of the data, or writing of the manuscript.

Funding sources

Cancer Center Support Grant to Memorial Sloan Kettering Cancer Center.

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Figure 1. Local recurrence rates of high-risk cSCC after treatment with surgery and adjuvant radiotherapy.

Time-to-event curve was estimated using Kaplan-Meier survival analysis.

Figure 2. Skindex-16 scores before adjuvant radiotherapy and after adjuvant radiotherapy. Plots displaying patient Skindex-16 scores before adjuvant radiotherapy and after adjuvant radiotherapy, with the average and standard deviation delineated by the lines, along the domains of Symptoms (a), Emotions (b), and Functioning (c). Two-tailed t-tests comparing the difference between the means was performed, with * indicating statistical significance as defined by $p < 0.05$.

Table 1.

Patient, tumour and treatment characteristics with univariate analysis of variables and local recurrence

Characteristics	Patients, <i>n</i> = 52 (%)	HR (95% CI) ^a	<i>P</i> -value ^b
Age			
73 years	26 (50)	1	0.97
> 73 years	26 (50)	0.94 (0.06–15.03)	
Sex			
Male	39 (75)	1	0.39
Female	13 (25)	0	
Primary tumour location			
Scalp	9 (17)	1	0.60
Face and ear	35 (67)	0.23 (0.005–10.8)	
Neck and shoulder	4 (8)	0	
Trunk	4 (8)	0	
Tumour diameter			
2 cm	16 (31)	1	0.39
> 2 cm	26 (50)	0	
Unknown	10 (19)	0	
Perineural invasion	46 (88)	1	0.59
Desmoplasia	1 (2)	0	0.84
Depth of invasion			
6 mm	8 (15)	1	0.13
> 6 mm	16 (31)	0.39 (0.003–48.08)	
Unknown	28 (54)	0	
Surgical technique			
Mohs micrographic surgery	22 (42)	0	0.42
Wide local excision under anaesthesia	28 (54)	1	
Local excision in clinic	2 (4)	0	
Microscopically positive margin			
Yes	16 (31)	1	0.04 *
No	36 (69)	0	
ART dose			
< 60 Gy	15 (29)	1	0.03 *
60 Gy	37 (71)	0	

^aHR = 0, local recurrence events did not occur in the specified subgroup^bKaplan–Meier analysis with log-rank test performed, with* *P* < 0.05 indicating statistically significant association

ART, adjuvant radiation therapy; CI, confidence interval; HR, hazard ratio