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ORIGINAL ARTICLE – MELANOMA

Squamous Cell Carcinoma with Regional Metastasis to Axilla or Groin Lymph Nodes: a Multicenter Outcome Analysis

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ABSTRACT

Background. Cutaneous squamous cell carcinoma (cSCC) of the trunk/extremities with nodal metastasis represents a rare but significant clinical challenge. Treatment patterns and outcomes are poorly described.

Patients and Methods. Patients with cSCC who developed axilla/groin lymph node metastasis and underwent curative-intent surgery between 2005 and 2015 were identified at four Canadian academic centers. Demographics, tumor characteristics, treatment patterns, recurrence rates, and mortality were described. Overall survival (OS) and disease-free survival (DFS) were calculated using Kaplan–Meier analysis. Predictors of survival and any recurrence were explored using Cox regression and logistic regression models, respectively.

Results. Of 43 patients, 70% were male (median age 74 years). Median follow-up was 38 months. Median time to nodal metastasis was 11.3 months. Thirty-one and 12 patients had nodal metastasis to the axilla and groin, respectively. A total of 72% and 7% received adjuvant and neoadjuvant radiation, respectively, while 5% received adjuvant chemotherapy. Following surgery, 26% patients developed nodal and/or distant disease recurrence. Crude mortality rate was 39.5%. Mean OS was 5.3 years [95% confidence interval (CI) 3.9–6.8 years], and 5-year OS was 55.1%. Mean DFS was 4.8 years (95% CI 3.3–6.2 years), and five-year DFS was 49.3%. Any recurrence was the only independent predictor of death [$p = 0.036$, odds ratio (OR) = 29.5], and extracapsular extension ($p = 0.028$, OR = 189) and age ($p = 0.017$, OR = 0.823) were independent predictors of recurrence.

Conclusions. This represents the largest contemporary series to date of outcomes for patients with axilla/groin nodal metastases from cSCC. Despite aggressive treatment, outcomes remain modest, indicating the need for a continued multidisciplinary approach and integration of new systemic agents.

Nonmelanoma skin cancer (NMSC) is the most common cancer in the world. Cutaneous squamous cell carcinoma (cSCC) accounts for 20% of all NMSC but is responsible for the majority of NMSC mortality due to its higher metastatic potential.[1] The incidence of cSCC is increasing in the Americas, Australia, and Europe.[2] In Canada, 78,300 individuals were diagnosed with NMSC in 2015.[3] In the USA, an estimated 419,000–700,000 cases of cSCC are diagnosed each year.[4,5] Contemporary data demonstrate an overall cSCC disease-related mortality of 2.1%.[6,7] In a US study, estimated death from cSCC may be as common as death from renal, oropharyngeal carcinoma, and melanoma, highlighting cSCC as a significant health burden.[4]

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Generally, patients with cSCC have excellent prognosis. The mainstay of treatment for locally isolated disease includes surgical excision followed by careful dermatologic surveillance for recurrence. Radical procedures are rarely necessary when disease is detected early. Even in the setting of local recurrence or primary lesion progression, indolent growth rate offers the ability for localized treatment with good prognosis.[8] However, a small subset of cSCC patients will progress to nodal or distant metastatic disease. Regional lymph nodes are the most common site of metastasis, reportedly occurring in 2.0–12.5%.[4,9,10]

Most cases of cSCC occur in the sun-exposed head and neck region, where the corresponding treatment of nodal metastases is well documented.[11] cSCC originating in the trunk and extremities with metastases to the axilla/groin lymph nodes has received less attention. Few studies describe outcomes for this patient group, with most being small single-center case series,[4,6,7,12,13] and 5-year overall survival (OS) rates vary from 34.4% to 48.0%.[8,14]

Multimodality treatment has been used inconsistently with varying efficacy. While SCCs are often thought to be radiation sensitive, widespread application to cSCC with lymph node metastases remains a topic of investigation.

The aim of this study is to retrospectively examine clinical outcomes of patients with cSCC of the trunk/extremity with documented regional metastases to the axilla/groin nodal basins treated at four Canadian tertiary cancer centers.

PATIENTS AND METHODS

In four Canadian tertiary centers (Toronto, Ottawa, Calgary, and Halifax), consecutive patients with cSCC of the trunk/extremities with axilla/groin nodal metastasis surgically treated from 1 January 2005 to 31 December 2015 were retrospectively identified from prospectively kept institutional databases. All patients had a confirmed clinical and pathological diagnosis of nodal metastasis and underwent curative-intent nodal dissection. Patients with primary mucosal cSCC (e.g., anogenital), cervical nodal metastases, head and neck primary lesions, and nodal metastases documented only on microscopic examination of sentinel lymph node biopsy were excluded. This study was approved by each institution's Research Ethics Board.

Descriptive statistics describe patient, disease, and treatment characteristics. Continuous variables are summarized using mean, median, and range, while categorical variables are reported as proportions and percentages. The primary outcome was 5-year OS, defined as time from nodal dissection to death from any cause. Secondary outcome was disease-free survival (DFS), defined as time from nodal dissection to occurrence of any local recurrence, regional/distant metastasis, or death, whichever occurred first. Chi squared and Fisher's exact tests were used to compare categorical variables, whereas Mann–Whitney *U* tests were applied to compare continuous variables. Survival analysis was performed using the Kaplan–Meier method. For OS, patients were censored at date of death or end of follow-up, whichever occurred first. Predictors of survival and any recurrence were explored using Cox regression and logistic regression models, respectively. Before variables were included in the Cox regression models, bivariate comparisons were completed using Chi square and log-rank (Mantel–Cox) tests. All *p*-values of 0.300 and lower were included in the Cox regression model. A similar stepwise approach was implemented to yield logistic regression model with high r^2 value. Analyses were conducted using SPSS 21.0 (IBM Corp., Armonk, NY).

RESULTS

Patient Characteristics

Table 1 presents patient, primary lesion, nodal disease, and treatment characteristics. Of 43 consecutive patients, median age was 74 years and 70% were male. Four patients had history of immunosuppression [fingolimod for multiple sclerosis (MS), prednisone for rheumatoid arthritis (RA), Crohn's disease, chronic lymphocytic leukemia (CLL) treatment]. Four patients had history of chronic lesions at the primary site (1 Marjolin's ulcer, 2 burn scars, 1 venous ulcer) prior to development of nodal cSCC. Median follow-up time was 38 months (3.2 years).

Primary Lesion Characteristics

A primary lesion was identified in 93% of patients. Six patients had multiple primary lesions. All known primary lesions were excised prior to nodal surgery, except for one patient who declined digital amputation. Of primary lesions with available pathology data, median diameter and depth were 3.0 and 1.1 cm, respectively. Perineural (PNI) and lymphovascular (LVI) invasion were present in two (5%) and four (9%) patients, respectively (Table 1).

Presentation and Treatment of Nodal Metastatic Disease

At time of diagnosis, 36 (84%) patients presented with clinically palpable nodes [median nodal size 5.5 cm with 42% having extracapsular extension (ECE)] and 42% required skin resection with the dissection. A total of 31 (72%) and 12 (28%) patients had axillary and groin

TABLE 1 Patient, primary lesion, nodal disease, nodal treatment, and recurrence characteristics (n = 43)

	n (%)
Patient characteristics	
History of transplant, predisposing congenital disease[a]	0
Previous or concurrent malignancy	15 (35%)
Primary lesion(s)	
Location of primary cutaneous lesion	
Hand, arm	17 (39%)
Foot, leg	9 (21%)
Back, chest, abdomen	12 (28%)
Pelvis/buttock, genitalia (nonmucosal)	2 (4%)
No primary identified	3 (7%)
Laterality	
Left	23 (53%)
Right	19 (44%)
Bilateral	1 (2%)
Diameter of primary lesion (cm)	Median 3.0 (range 1.1–19.5)
Unknown	14 (33%)
Depth of primary lesion (cm)	Median 1.1 (range 0.2–6.5)
Unknown	20 (47%)
Anatomic depth, Clark	
I–III	0
IV	6 (14%)
V	8 (19%)[b]
Grade of primary lesion	
G1, well differentiated	6 (14%)
G2, moderately differentiated	14 (33%)
G3, poorly differentiated	7 (16%)
G4, undifferentiated	1 (2%)
Peripheral margin	
Clear	22 (51%)
Involved	6 (14%)
Deep margin	
Clear	22 (51%)
Involved	7 (16%)
Perineural invasion	
Yes	2 (5%)
No	18 (42%)
Lymphovascular invasion	
Yes	4 (9%)
No	20 (47%)
Nodal disease at presentation	
Mode of initial nodal diagnosis	
Palpable	36 (84%)
Radiologically detected	7 (16%)
Pathologic nodal diagnosis	
Core biopsy	15 (35%)
Fine-needle aspirate (FNA)	18 (42%)
Excisional biopsy	9 (21%)
Location of nodal disease	
Axilla	31 (72%)
Groin	12 (28%)
Treatment of nodal disease	
Surgery	
Lymph nodes resected[c]	
Total number of lymph nodes in axillary dissection	Median 17 (range 0–41)
Positive lymph nodes in axillary dissection	Median 2 (range 0–18)
Total number of lymph nodes in groin dissection	Median 10.5 (range 3–19)
Positive lymph nodes in groin dissection	Median 1 (range 0–13)
Largest diameter axillary dissection (cm)	Median 5.5 (range 0–9.5)
Largest diameter groin dissection (cm)	Median 3.95 (range 1.1–12)
Extracapsular extension	
Yes	18 (42%)
No	15 (35%)
Radiation	
Neoadjuvant	3 (7%)
Adjuvant	31 (72%)
Total radiation dose (cGy)	Median 5000 (range 3000–6600)
Number of fractions	Median 25 (range 5–33)
Death	17 (40%)
Time to death, days (months)	Median 403 (13); range 54–2703
Recurrent disease	
Any recurrence	
No	32 (74%)
Local and nodal and distant	1 (2%)
Nodal alone	5 (12%)
Nodal and distant	3 (7%)
Distant alone	2 (5%)
First recurrence	
Local	1 (9%)
Nodal	6 (55%)
Distant	2 (18%)
More than one site	2 (18%)
Treatment of recurrence	
Surgery and radiation	2 (5%)
Surgery, chemotherapy, and radiation	1 (2%)
Chemotherapy and radiation	2 (5%)
Radiation	1 (2%)
Palliative care	5 (12%)

TABLE 1 continued

	n (%)
Time to nodal recurrence, days (months)	*n* = 8
	Median 268.5 (9.0)
	Mean 436.9 (14.6)
	Range 105–1392
Time to distant metastasis, days (months)	*n* = 6
	Median 162 (5.4)
	Mean 322 (10.7)
	Range 105–1092

[a]E.g., xeroderma pigmentosum, albinism

[b]Where % does not add up to 100%, the remaining percentage represent unavailable data

[c]All patients had biopsy-proven nodal disease preoperatively. Post nodal dissection, lymph nodes for multiple patients were difficult to identify (e.g., "uncertain lesion could represent nodal obliteration, extensive extranodal extension")

disease, respectively. No patient had concurrent groin and axillary disease at presentation. Median time from primary lesion presentation to nodal metastasis (defined as primary lesion biopsy date to nodal disease biopsy date) was 11.3 months.

Twenty-five and six patients underwent axillary lymph node dissection of levels I/II/III and levels I/II, respectively. Seven and five patients underwent superficial groin and superficial/deep groin dissection, respectively. The decision to pursue level 3 dissection or add pelvic node dissection was based on preoperative imaging, intraoperative findings of the extent of tumor burden, as well as patient characteristics with regards to risk and morbidity; For example, if there was no obvious disease along the iliacs on imaging, then superficial groin dissection alone was performed. Twenty-five (58%) patients experienced surgical complications, the most common being lymphedema in 16 (37%) patients, followed by poor range of motion, infection, and wound dehiscence. Three (7%) and 31 (72%) patients received neoadjuvant and adjuvant nodal radiation, respectively. Adjuvant radiation was offered based on high-risk tumor characteristics such as a poorly differentiated primary with LVI/PNI as well as nodes with ECE. The majority of patients were offered radiation, but due to comorbidity, some may have declined or felt to be inappropriate for treatment. In general, 5000 cGy divided into 25 fractions was given to the nodal basins. The optimal fields covered were where there were positive nodes, thus level 3 and the pelvis were included when indicated in a case-by-case fashion. Two patients received adjuvant chemotherapy (Table 1).

Recurrence and Survival

Following curative-intent nodal dissection, 11 patients (26%) developed recurrence (5 nodal, 2 distant, 3 nodal and distant, and 1 local, nodal, and distant) (Table 1). Nodal recurrence occurred in the irradiated field. However, the exact site of recurrence was not consistently documented. Median time to nodal and distant recurrence was 15 and 11 months, respectively. Table 2 details treatment patterns for first recurrence. Of note, four patients in the recurrence group did not undergo adjuvant radiation following their initial surgery. Active treatment for recurrence was completed for six patients, and the remaining five elected palliative care. Overall mortality was 73% in the recurrence group.

In the 43 patients examined, mean OS was 5.3 years (95% CI 3.9–6.8 years) and 5-year OS was 55.1%. Mean DFS was 4.8 years (95% CI 3.3–6.2 years), and 5-year DFS survival was 49.3% (Fig. 1). Overall crude mortality was 39.5%.

Predictors of Recurrence and Survival

Based on a stepwise approach, any recurrence was a significant predictor of overall death ($p = 0.036$, OR = 29.5) (Table 3a). ECE ($p = 0.028$, OR = 189) and age ($p = 0.017$, OR = 0.823) were significant predictors of any recurrence ($R^2 = 0.673$) (Table 3b).

DISCUSSION

This study is the largest modern North American and first Canadian series documenting treatment patterns and outcomes for patients with operable cSCC with nodal disease in the axilla/groin. Although all patients were treated initially with aggressive intent, 5-year OS and DFS remained modest at 55% and 49%, respectively. Recurrence patterns suggest that, even after nodal disease treatment, the patient remains at high risk for locoregional and distant metastases.

Few studies report isolated outcomes for patients with known axilla/groin nodal metastases following cSCC of the trunk or extremities (Table 4). In an American series (1944–1976) by Ames et al., in 91 patients with extremity cSCC and resectable regional nodal metastases treated with aggressive dissection but without adjuvant chemoradiation, regional failure rates were 47% and 23% with and without ECE, respectively.[15] Correspondingly, the 5-year overall actuarial survival was 39%, reducing to 25% in those with ECE. Successful retreatment following regional recurrence after nodal dissection was seldom possible, as persistent disease on the chest or trunk was uncontrolled by multimodal efforts with radiation and/or chemotherapy. This is

TABLE 2 Treatment for patients with recurrence after treatment of nodal metastases

"+" Margin for primary lesion	Initial nodal treatment	ECE	Time to first recurrence (months)	First recurrence	All recurrence(s)	Treatment of recurrence	Overall survival (months)	Status at follow-up
No	Axillary dissection levels I/II	Yes	6.6	Nodal	Nodal	Chemotherapy + radiation	22.0	Dead
Yes	Superficial groin dissection	Yes	16.8	Local	Local, nodal, distant	Re-excision of nodal recurrence + radiation	61.3	Alive
?	Superficial and deep groin dissection + radiation[a]	Yes	8.3	Distant	Distant	Chemotherapy	31.0	Dead
No	Axillary dissection I/II/III + radiation[a]	Yes	20.1	Nodal	Nodal	Repeat radiation	29.5	Alive
?	Axillary dissection I/II/III + radiation[a]	?	6.4	Nodal	Nodal	Chemotherapy + repeat radiation	16.6	Alive
Yes	Axillary dissection levels I/II/III	No	7.5	Nodal	Nodal	Nodal reexcision + repeat radiation	11.9	Dead
No	Axillary dissection I/II/III + radiation[a]	Yes	2.0	Nodal + distant	Nodal + distant	Palliative	2.9	Dead
No	Axillary dissection I/II/III + radiation[a]	No	3.6	Nodal	Nodal	Palliative	12.7	Dead
?	Superficial and deep groin dissection	Yes	0.7	Nodal	Nodal + distant	Palliative	1.7	Dead
No	Axillary dissection I/II/III + radiation[a]	Yes	4.5	Distant	Distant	Palliative	6.3	Dead
No	Axillary dissection levels I/II/III + radiation[a]	Yes	3.2	Distant	Distant	Palliative	4.7	Dead

ECE extracapsular extension

[a]Adjuvant radiation

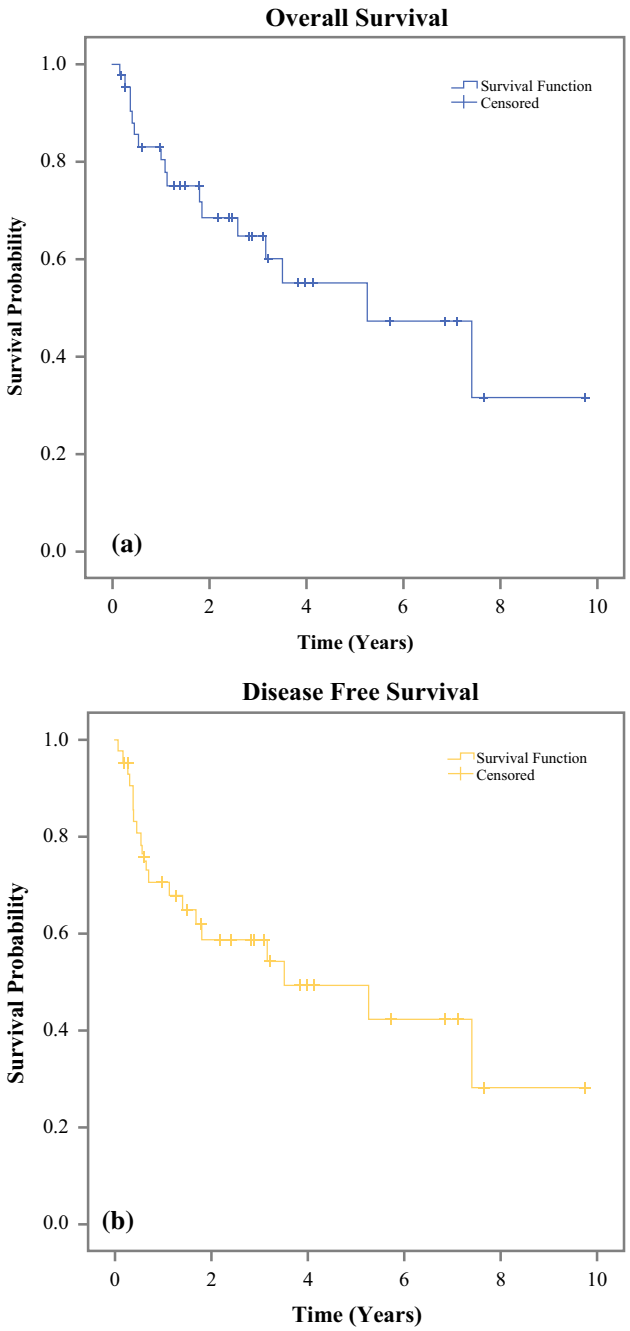

FIG. 1 Kaplan–Meier curves of (**a**) OS and **b** DFS for cutaneous squamous cell carcinoma patients with axilla/groin metastasis

in line with our study showing that ECE and advanced age were predictors of recurrence and that having any type of recurrence was a predictor of death.

In an Australian series (1977–1987) examining 21 patients with operable nodal metastatic disease, mean OS was 53.8 months.[16] Among the 11 patients who died, 4 and 7 had regional and widespread distant metastatic recurrences, respectively. The overall mortality rate for those with nodal metastases was 70.6% with mean follow-up of 4 years from diagnosis of primary lesion. In a more recent Australian series from 2010 exploring the outcomes of 26 patients with axilla/groin metastases treated with surgery ± radiation and chemotherapy, the crude overall mortality rate and recurrence rate were both 27%, with median follow-up time of 18.5 months.[17] Interestingly, 57% of the patients who recurred had their first recurrence in the lungs at a median time of 2.2 months. This short time interval is in stark contrast to what is seen in our study, where the median time was 14.6 and 10.7 months for regional and distant recurrence, respectively. Although four patients in the Australian study underwent salvage therapy (two surgery, one chemoradiation, and one chemotherapy alone), five of the seven patients with recurrent disease ultimately had cSCC-related death. Poor survival was seen for patients with any recurrence, as in our study, with 8 of 11 (73%) patients ultimately having cSCC-related death. Interestingly, these two Australian studies demonstrate patterns of predominantly distant metastasis early after nodal dissection, in contrast to our study and the American study, suggesting that there may be different environmental factors and disease patterns in these different parts of the world.

Once biologically aggressive cSCC manifests as nodal metastases, disease control is often challenging and corresponding treatment efficacy is poor. Several efforts have been made to alter outcomes for these patients, with marginal success to date. One strategy is to identify high-risk biologically deleterious features of the primary lesion, with the goal of optimizing local therapy and surveillance to prevent recurrences or detect them early. Several studies have reported prognostic features of the primary cSCC tumor associated with recurrence and death. These include diameter > 2 cm, depth of invasion > 2 mm, poor differentiation, PNI/LVI, anatomic location, and predisposing wound or immunosuppression.[8,16,18] Other strategies include consideration of sentinel lymph node biopsy (SLNB) for stratification, use of adjuvant radiation therapy (RT), and Moh's micrographic surgery for optimal local control of the primary lesion and prevention of nodal metastases. SLNB demonstrates an acceptable 4.6% false-negative rate in clinically node-negative cSCC, but its prognostic significance remains uncertain due to variable indications for testing and inability to critically define a "high-risk" group in which SLNB would be most useful.[19]

The National Comprehensive Cancer Network (NCCN) and American Joint Committee on Cancer, as well as other centers, have suggested high-risk identification algorithms.[20–22] The Brigham and Women's Hospital (BWH) Tumor Staging for cSCC has been proposed and subsequently validated, offering superior prognostication of localized cSCC over existing systems.[20,23,24] Nevertheless, the BWH system does not address nodal and distant

TABLE 3 (a) Cox Regression model with dependent variable being death. (b) Logistic regression model with dependent variable being any recurrence

Variable	*B*	SE	Wald	df	Sig.	Odds ratio	95.0% CI for Exp (*B*)	
							Lower	Upper
(a)								
Any recurrence	3.386	1.617	4.386	1	0.036[a]	29.548	1.243	702.622
Tumor grade[a]	1.038	1.463	0.503	1	0.478	2.822	0.160	49.636
Presence of LVI	1.687	1.564	1.164	1	0.281	5.404	0.252	115.767
Received radiation	− 1.528	1.250	1.495	1	0.221	0.217	0.019	2.513
Received chemotherapy	− 9.826	1755.429	0.000	1	0.996	0.000	0.000	
Age	0.040	0.047	0.714	1	0.398	1.040	0.949	1.140
(b)								
Extracapsular extension	5.240	2.390	4.807	1	0.028	188.589	1.743	20,402.177
Radiation	0.447	1.433	0.097	1	0.755	1.564	0.094	25.927
Immunosuppression	4.333	2.681	2.612	1	0.106	76.204	0.398	14,593.253
Number of positive nodes	0.079	0.121	0.424	1	0.515	1.082	0.854	1.370
Age	− 0.195	0.082	5.663	1	0.017	0.823	0.701	0.966
Survival time (in days)	− 0.003	0.002	3.645	1	0.056	0.997	0.994	1.000

[a]Dichotomized for Cox regression into 1 = G1 and G2, 2 = G3 and G4

TABLE 4 Previous studies of cutaneous squamous cell carcinoma of the trunk or extremities with axilla/groin nodal metastasis

Study	Patients with nodal metastasis	Treatment	Overall survival (OS) (months)	5-Year OS (%)	5-Year DFS	Mortality
Ames et al.[15]	106	Surgery	–	39	–	86% (follow-up minimum 48 months)
Joseph et al.[16]	34	Surgery (21) chemo/radiation (13)	Mean 53.8	–	–	70.6% (mean follow-up 48 months)
North et al.[14]	21	± Surgery	Median 25	48	–	–
Mullen et al.[18]	24	Surgery ± chemo/radiation	–	42	29%	–
DeLima et al.[8]	22	Surgery ± radiation	–	34	–	–
Goh et al.[17]	26	Surgery ± chemo/radiation	Median 18.5	–	–	25% (median follow-up 18.5 months)

metastasis, and does not offer practical clinical guidance as offered by NCCN guidelines.[25] Overall, no universally accepted staging system exists, making management challenging. Once nodal disease has been diagnosed, larger nodal size, increasing numbers of affected nodes, and ECE have been recognized as factors contributing to worse outcomes.[16,26] In our study, at least 18 patients (42%) had ECE, and 64% of patients with disease recurrence after nodal dissection surgery had ECE, which we showed was a predictor of worse survival.

Radiation as an adjuvant therapy for cSCC has been proposed for patients, with two specific purposes: treating patients perceived at high risk of recurrence postsurgery at the primary site, or to consolidate therapy following nodal dissection for metastatic disease.[27] Adjuvant RT, together with surgery, demonstrates improved outcomes in patients with regional metastases compared with treatment with either modality alone,[28,29] although most data are from patients with lesions in the head and neck. In our study, patients who had postoperative adjuvant radiation had recurrence rates of 17.6% (6/34) compared with 55.6% (5/9) in those treated without radiation. Of three patients who received preoperative neoadjuvant radiation for their nodal disease and subsequently underwent surgical resection, no patients developed recurrence.

More effective systemic treatment for advanced and recurrent cSCC is clearly required. Chemotherapy for cSCC has typically been reserved for patients with unresectable local or regional disease, or for those with widespread distant metastases. Regimens are often

cisplatin based ± 5-fluorouracil, but their preponderance for significant side effects makes them suboptimal.[27] In a prospective phase II study of locally advanced head and neck cSCC treated with definitive radiotherapy and platinum-based chemotherapy alone, 10 patients achieved complete response in 19 evaluable patients.[30] As most cSCCs overexpress epidermal growth factor receptors (EGFRs), drugs have been targeted against the extracellular receptor as well as the intracellular signal components.[31–33] These oral drugs are relatively easy to administer and tolerate, but none are currently approved for first-line use in trunk and extremity cSCC in Canada. Clinical trials show promise with 28% response rate and 69% disease control with cetuximab (an EGFR inhibitor) in patients with unresectable cSCC.[34] Combination studies with human epidermal growth factor receptor 2 (HER2), insulin growth-like factor blockades, and S100 targeting are also underway to tackle the issue of progressive drug resistance.[35–37] More recently, programmed cell death protein (PD)-1 inhibitors have been of great interest.[38,39] A 2018 phase 2 trial showed cemiplimab-induced response in 50% of patients, with response duration exceeded 6 months in 57% of patients.[40] This high efficacy may pave the way for PD-1 inhibitors to become the standard of care for advanced cSCC.

This study has several limitations. In particular, the small numbers of patients result in challenges regarding the ability to conduct complete modeling for predictors of recurrence, namely missing data about the primary tumors, which consequently could not be entered into the multivariable model.

CONCLUSIONS

Axillary and groin nodal metastases from cSCC are uncommon and are associated with poor 5-year OS of 55%. Even with aggressive multimodality treatment, regional recurrences are common (26% in this study) and contribute to significant morbidity and mortality. Checkpoint inhibitors (PD-1 inhibitor) and EGFR inhibitors show great promise for treatment of advanced disease. We advocate for a multiinstitutional registry to standardize collection of relevant clinical parameters and optimize accrual to clinical trials.

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