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Cutaneous squamous cell carcinoma metastatic to the axilla and groin: Outcomes and prognostic factors

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Title Page

Manuscript Title

Cutaneous squamous cell carcinoma metastatic to the axilla and groin: outcomes and prognostic factors

Running Head

Nodal Metastatic Cutaneous SCC: Survival

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Abstract

Purpose

This study examined the clinical outcomes and prognostic factors of patients with metastatic cutaneous SCC metastatic to the axilla and groin when managed with curative-intent lymphadenectomy and received (neo)adjuvant treatment.

Methods and Materials

We conducted a single institution retrospective review. Patients had nodal disease without distant spread, were 18 years or older with no non-cutaneous primary identified.

Results

From January 2000 to July 2015, 78 patients were treated for axilla (64,82%) or inguinal (14,18%) involvement with cSCC. The median age was 75.5 years (range:29-95) and 8 patients (11%) were immunosuppressed. The median size of the largest node was 45mm (range:8-135) and extracapsular extension was found in 63 (81%) cases. A majority of patients were treated with surgery alone (21,26.9%) and surgery with adjuvant radiation therapy (54,69%). The 2-year OS and PFS were 50% (95% CI:40-63%) and 43% (95% CI:33-56%) and 5-year OS and PFS were 33% (95% CI:23-47%) and 32% (95% CI:22-46%) respectively in the entire cohort. On univariable analysis factors associated with longer OS were: younger age (HR 1.1, 95% CI: 0.9-1.3 p =0.021), improved performance status (HR 1.5, 95% CI:1.0-2.3 p =0.026), lack of immunosuppression (HR 3.3, 95% CI: 1.5-7.3 p = 0.001), lower lymph node ratio (HR 1.2, 95% CI:1.0-1.3 p =0.007), lower number of positive nodes (HR 1.1, 95% CI:1.0-1.2 p=0.004) and the use of radiation therapy (HR 0.5, 95% CI:0.3-0.9 p =0.012).

Conclusion

Metastasis to the axilla and groin with cSCC has poor outcomes with standard treatment. The addition of immunotherapy warrants investigation.

Main text

Introduction

Cutaneous squamous cell carcinoma (cSCC) represents 20-30% of non-melanoma skin cancers (1). Despite being such a common malignancy, nodal metastasis is an uncommon event and occurs in only 2-3% of diagnosed cancers (2).

Because the majority of cSCC occur in the head and neck, the outcomes and prognostic factors are better described in this region compared with the rest of the body (3). Studies in the head and neck region include reported outcomes for parotid and cervical metastasis (4-6), and a recently completed randomised controlled trial describing the effects of concurrent adjuvant chemo-radiation therapy compared with radiation therapy alone (7). Important adverse prognostic factors that have been identified from these studies include immunosuppression, extra-nodal extension (ENE) and the harvested number of positive lymph nodes as a fraction of the total number of lymph nodes removed (the lymph-node ratio) (4). Comparatively, literature on cSCC in the trunk or limbs which spread to the axilla and groin is sparse.(8-10) A recent multi-institutional series of 43 patients found a 5 year overall survival of 55.1% with regional recurrence the only predictor of survival and presence of ENE and age predictors of regional recurrence (10). A similar recent multi-institutional series of 74 patients found a 5 year overall survival of 51% with presence of multiple lymph nodes predictive of worse survival (11). This series also found higher regional recurrence in patients with lymph nodes larger than 6cm and those treated with surgery alone (11).

The American Joint Cancer Committee has opted not to include cSCC metastatic to the axilla and groin in their latest staging system, with staging only provided for cSCC involving the head and neck (3). In contrast, the Union for International Cancer Control (UICC) have included staging for non-head and neck cSCC sites, taking into account nodal size and count (12).

Curative management of nodal metastasis from cSCC has generally involved complete regional lymphadenectomy followed by adjuvant radiation therapy (4, 6, 9). Concurrent chemotherapy with radiation therapy has also been used but without strong evidence. Whether adjuvant radiation therapy can be safely omitted for those with a small disease burden is unclear. Radiation therapy when used alone, reserved for those with unresectable disease or high operative risk, has generally been for palliation, often without durable disease control.

With this lack of data for metastatic cSCC to the axilla and groin, we sought to examine the outcomes and prognostic factors for this population managed with radical intent.

Methods

This was a single institution retrospective review of patients who underwent curative intent lymphadenectomy for lymph node positive cutaneous SCC between January 2000 and July 2015. Ethics board review was performed and approved for this study. We searched through our electronic medical records for patients with axilla and groin/inguinal squamous cell carcinoma and included/excluded patients based on criteria below.

Inclusion and exclusion criteria

Included patients had histologically proven SCC located in in the axilla and groin lymph node basins. Patients had to be 18 years or older and treated with curative intent. During this study period our radical management of these patients included surgical clearance of the axilla (routinely to include level I-III) or groin (superficial inguinal lymphadenectomy), with or without (neo)adjuvant (chemo)radiation therapy. Radiation therapy of the nodal basin in included coverage of the involved nodal basin and a proximal nodal echelon with anterior and posterior conformal field however variation of coverage was noted between treating radiation oncologists. Coverage of the putative primary site was at the discretion of the radiation oncologist. Chemotherapy, when given, was used concurrently.

We excluded patients who had a history of a non-cutaneous primary (such as prior squamous cell carcinoma of the vulva, penis and perianal region) and those with evidence of distant metastatic disease at diagnosis. Patients treated with chemotherapy or radiation alone were also excluded.

Data collection

Data collected included demographic details, treatment modalities and various clinicopathological prognostic factors. Specifically, we defined immunosuppression as an active haematological malignancy or taking active immunosuppressive medications (for organ transplantation or auto-immune disease). We used the UICC staging as a framework to group patients into nodal stages (13). This included two patients with presumed synchronous primary bilateral axillary metastasis treated radically with surgery followed by radiation therapy. Information on primary tumours was missing or poorly collected or difficult to define as some patients had multiple primaries and hence we were unable to accurately provide a stage. Local failure was recorded if there was documented failure at the skin primary site. Regional failure was recorded if there was documented failure at the treated nodal basin (axilla or groin) or the next echelon of lymph nodes. Lymph node ratio (the ratio of number of positive lymph nodes divided by the total number of removed lymph nodes) was an important prognostic factor found in another study and we included this data in our current study (4). We also collected data on the number of lymph nodes removed in both the axilla and groin dissections. This has been shown in patients with melanoma to be a surrogate marker of the quality of surgery as surgical quality was not able to be directly evaluated(14).

Statistical analysis

Overall survival (OS) was defined as the time from the start of treatment to the date of death from any cause. Progression free survival (PFS) was the time from the start of treatment to the nodal disease to the date of progression at any site or death from any cause, whichever occurred first. OS and PFS were described using Kaplan-Meier methods, with yearly estimates and 95% confidence intervals. Cumulative incidence of first failure was defined as the time from start of treatment to the date of first failure (local, nodal or distant progression) or date of death and was assessed considering each failure and death as competing events. Cumulative incidence confidence intervals were calculated using the Kalbfleisch-Prentice Method. Univariable Cox proportional hazard models were used to assess the impact of candidate prognostic factor on OS and freedom from regional failure (FFRF). As the timing of commencement of radiation therapy varied between patients, the HR and p-value for radiation therapy was calculated considering RT as a time-varying covariate. A detailed multivariable analysis was not possible due to the small sample size. All statistical analyses were performed in R 3.4.2 (R Core Team (2015)).

Results

Study Group

There were 78 patients with squamous cell carcinoma in the axilla and groin who met inclusion criteria. The median age of the population was 75.5 years (range, 29-95 years) and 53 (68%) were male. Forty-five percent of patients had a documented prior (28 patients) or synchronous (7 patients) primary site associated with the lymph node basin, and the remainder assumed to have a cSCC based on a prior history of cSCC or had no evidence of a primary tumour in other sites. Pre-treatment staging was performed with either CT (n=75, 96%) and/or FDG-PET (n=38, 49%). Sixty-four (82%) patients had axillary disease while 14 (18%) had inguinal disease. Eight (10%) patients had immunosuppression (reasons included chronic lymphocytic leukaemia or requiring active immunosuppressant therapy due to organ transplantation or auto-immune disease). Pathology assessment demonstrated a median number of lymph nodes involved of 2 (range: 1-22) and the median size of the largest involved lymph node was 45mm (range: 8-135mm). There was extra-nodal extension in 63 (81%) patients. Table 1 summarises the demographics of the study population along with details of both the primary and nodal disease.

Treatment

Patients were treated with surgery alone (n=21, 26.9%), surgery with adjuvant radiation therapy (n=54, 69.2%), surgery with adjuvant chemo-radiation therapy (n=1, 1.3%) and neoadjuvant radiation therapy followed by surgery (n=2, 2.6%). Of the 21 patients who did not have radiotherapy, 9 had progressed prior to radiotherapy being commenced within 12 weeks of their operation. The remainder of the patients were not referred for radiotherapy for unknown reasons (n=6, 28.6%), a lack of perceived benefit (n=4, 19.0%) and contra-indications to radiotherapy with connective tissue disease/prior radiotherapy (n=2, 9.5%).

The median nodal yield at axillary lymphadenectomy was 14 with a median of 2 positive nodes. For patients undergoing inguinal lymphadenectomy, the median nodal yield was 11 with a median of 2 positive nodes.

The median radiation therapy dose was 50 Gy (range: 24 – 66) and in 78.9% the dose was less than 60Gy. The most common dose fractionation schedule used in this cohort was 50Gy in 25 fractions over 5 weeks. Chemotherapy was used in one patient who was treated with concurrent weekly carboplatin.

Outcomes

After a median follow-up of 5.3 years, 41 patients 52.6% relapsed. The median PFS was 17 months (95% CI: 10 – 29). In the non-immunosuppressed cohort 5-year OS and PFS were 38% (95% CI: 26-51%) and 37% (95% CI: 24-51%) respectively. In the entire cohort the 2-year OS and PFS were 50% (95% CI:40-63%) and 43% (95% CI:33-56%). The 5-year OS and PFS were 33% (95% CI: 22-45%) and 32% (95% CI: 22-44%) respectively (Figure 1 and 2).

Figure 3 shows the cumulative incidence of site of first relapse in the whole cohort. Of these relapses, there were only 3 local failures and these occurred along with regional and/or distant disease, representing 7.3% of relapses. Regional relapse alone as a site of first failure was 25% (95% CI: 16-36%) and regional with distant failure was 16% (95% CI: 9-25%) at 5 years. The majority of regional relapses occurred in the first year of following completion of treatment. Metastatic disease alone as site of first failure occurred in 13% (95% CI: 6-22%) at 5 years.

The cumulative incidence of cSCC deaths at 5 years was 51% (95% CI: 39-62%), while 12% (95% CI: 5-22%) had an unrelated cause of death and in 4% (95% CI: 1-11%) the cause was unknown.

Prognostic factors

Factors associated with worse OS were: older age (HR 1.1 per 5 years increase, 95% CI: 1.0-1.3 p = 0.021), worse performance status (HR 1.5, 95% CI: 1.1-2.3 p = 0.026), presence of immunosuppression (HR 3.3, 95% CI: 1.5-7.3 p = 0.001), higher lymph node ratio (HR 1.2 per 10% increase, 95% CI: 1.0-1.3 p = 0.007), increased number of positive nodes (HR 1.1, 95% CI: 1.0-1.2 p = 0.004). Factors associated with improved OS were the use of radiation therapy (HR 0.5, 95% CI: 0.3-0.9 p = 0.012). The results were similar when the immunocompromised patients were excluded (Table 2). Figure 4 illustrates the difference in overall survival between the immunosuppressed and non-immunosuppressed patients.

Factors associated with risk of regional relapse were: increased UICC N-stage (HR 1.9, 95% CI: 1.1-3.5 p = 0.031), the presence of ECE (HR 8.9, 95% CI: 1.2-65 p = 0.009), higher lymph node ratio (HR 1.4, 95% CI: 1.2-1.7 p = <0.001), higher number of positive nodes (HR

1.3, 95% CI: 1.2-1.4 p = <0.001). These results were similar in the non-immunosuppressed subset (Table 3).

Overall, the presence of immunosuppression was found to be a significant prognostic factor for worse overall survival with presence of immunosuppression associated with a HR 3.35, 95% CI 1.54-7.28 p=0.001.

Discussion

This study shows that patients with cutaneous squamous cell carcinoma with metastasis to the axilla and groin have a poor prognosis with an overall survival of only 33% at 5 years and progression free survival of 32%. Regional control appeared to be suboptimal with a substantial percentage of this cohort having regional relapse, with (16%) or without (25%) distant metastasis. Of note, our population was elderly with a median age of 75.5 years and death from comorbidities occurred in 14% of the population.

Similar to our study, other published series on this disease had small numbers: 43 and 24 patients in more recent publications and 106 patients in a study from the 1980's (8-10). Pang *et al.,* after a median follow up of 38 months, reported that 26% developed either regional and metastatic recurrence, and 5-year OS was 55.1% (10). Prognostic factors for OS was the development of recurrence and for any recurrence were presence of ENE and age (10). Nodal recurrences occurred at a median time of 15 months and distant at 11 months (10). This is similar to our data showing that majority of recurrences occurred within the first 12 months. Yang *el al.*, in a similar sized and contemporaneous cohort demonstrated a 5-year OS of 51%(11). They did find a similar number of regional relapses, in total 26 representing 54% of the study population (11). In our cohort 51% of patients relapsed however there was a higher rate of regional failure (68.3%). This may be explained by the larger group of patients with extra-nodal extension in our cohort (80%) compared with 72% and 50% in the surgery + RT and surgery alone groups respectively (11). In this series, both nodal size (>6cm) and treatment with surgery alone were associated with higher rates of regional recurrence (11). In our series, treatment with surgery alone did not have reach statistical significance for lower rates of regional control however was associated with overall survival. This difference may be due to missed regional recurrences due to the retrospective nature of the series or a limited small sample size. Prospective data collection and larger sample sizes are needed to further assess this finding. All relapses occurred within 2 years and this was consistent with our findings (11). Goh *et al.*, after a median follow up of 18.5 months, reported that 27% developed regional and metastatic recurrence and 73% were alive. Because of their small numbers, they were unable to find any prognostic markers.

Ames *et al.* reported a 5 year survival similar to our series (39%) and only identified extra-nodal extension to be important. In our study, we found a number of prognostic markers worthy of further exploration.

Immunosuppression, extra-nodal extension, age and the lymph node burden (measured by the lymph node ratio and number of nodes involved) were associated with regional control and/or overall survival on univariable analysis (a larger study is required to perform a multivariable analysis to assess the adjusted effects and independent value of those variables). This is concordant with cutaneous squamous cell carcinomas in the head and neck region (4-6). Controversially we included patients with bilateral disease. While the TNM staging system specifies that patients with bilateral disease should be classified as having metastatic disease (13), we treated these patients radically. One of our patients with bilateral disease was disease free at 5 years while the other succumbed to metastatic disease. We included them according to the highest stage of their ipsilateral disease and it is unclear how they should be staged. Larger combined series with other institutions may be required in the future to validate the staging system. Of note, factors such as immunosuppression and nodal burden should be considered in future attempts at defining the stage of tumour.

Most of our patients (69%) were managed with surgery followed by adjuvant radiation therapy. However, the effectiveness of radiation therapy is unclear. The confidence intervals were very wide, ranging from no effect to large effect sizes. The RT doses were also quite variable and 9 of the 21 patients not receiving radiation therapy relapsed within 12 weeks of surgery, suggesting selection bias. Therefore this study is unable to answer the questions of how effective is radiation therapy in this patient population and when is the right timing to give radiation therapy

The poor regional control in this cohort, however, suggests that attempting to optimise regional control with radiation therapy is probably warranted. This may include reducing the treatment package time (TPT) as has been demonstrated in the head and neck cohort where TPT greater than 14 weeks was associated with both inferior OS and PFS in patients with primary cutaneous SCC (15). Unlike the head and neck where a population can be defined for the safe omission of radiation therapy, this is not defined from our data (16). Factors such as presence of ENE, high lymph node ratio and high number of positive nodes were associated with regional failure and so these adverse factors should be considered in the decision to recommend adjuvant radiation therapy.

Compared with the outcomes for cSCC of the head and neck, this population did worse with a 5-year OS of 33% in this series compared with 50% in the head and neck series published from the same institution(4). We believe there may be a number of reasons for this. Firstly, it may be that this population has worse nodal involvement at presentation. The median node size in our series was 45mm (range: 8 – 135) compared with 15 mm (range: 2-65) in a similar analysis performed with metastases to the head and neck. This may be due to a difficulty in detecting abnormally enlarged lymph nodes in the axilla and groin leading to a later presentation compared with a more visible area in the head and neck. Secondly, the adjuvant radiation therapy dose was also relatively less compared with the head and neck region. The National Comprehensive Cancer Network guidelines recommend an adjuvant dose of 60 Gy or more for involved areas for cSCC with nodal involvement in the head and neck region (17). However, in this study of those patients who did receive radiation therapy, 78% had less than 60Gy. This may be due to a reluctance of radiation oncologists to prescribe high doses for potential toxicity, including limb oedema, risk of bowel, lung toxicity and the use of hypo-fractionated treatment in those with advanced age or poor performance status. Our results also appeared poorer compared with the series published on axilla and groin cSCC from Canadian Institutions (10) but similar compared with the other published Australian series (9). The Canadian series used similar radiation doses (median dose 50Gy) but had far fewer cases with extra-nodal extension (42% versus 80.8%). There may be some geographic differences in the aggressiveness of disease.

We explored the impact of lymph node ratio, found to be significant in studies on nodal cSCC metastasis in the head and neck (4, 18). The lymph node ratio is likely a surrogate marker for the burden of disease with a greater number of nodes involved connoting a higher stage of disease. It may also reflect the quality of surgery. In our study, it was significant for both overall survival and regional control. With other metastatic diseases affecting the axilla and groin, such as melanoma, it has been suggested that this quality may also be measured by the number of nodes excised (19). Suggested numbers for minimum number of nodes were 12, 6 and 13 for the axillary and inguinal and ilioinguinal lymphadenectomies respectively. In our study, the median number of nodes removed from the axilla (14, range: 3-30) and groin (10.5, range: 7-14) regions were comparable. We were however unable to be conclusive as to whether the quality of surgery may have had an impact on the outcome of these patients in a retrospective study with relatively small numbers.

Lastly, in keeping with the experience from other series of cSCC, we found that immunosuppression had a very strong association with poor outcomes. In our population, not a single patient who was immunosuppressed survived beyond 4 years.
Enhancing the immune environment has shown promise in patients with metastatic cSCC. Based on promising results in the metastatic/unresectable settings (20), trials are exploring the role of anti-PD1 therapy in resectable loco-regionally advanced disease in phase 3 adjuvant trials (NCT03969004, NCT03833167) . In addition, a preliminary study has shown very encouraging results with neo-adjuvant cemiplimab with a high pathologic response rate.(21) This latter approach may yield better results in the group destined to develop early recurrence post surgery before post-operative RT can be started. Incorporation of immunotherapy into trials for regionally advanced cSCC in immunocompromised patients will need to first await evidence that anti-PD1 therapies are also active in these patients in the metastatic/unresectable setting.

Conclusion

Our series has identified a population with cutaneous squamous cell carcinoma with a poor prognosis. Suggestive factors associated with regional control and/or overall survival were immunosuppression, performance status, extra-nodal extension, age and the lymph node burden. While most patients were managed with lymphadenectomy followed by adjuvant radiation therapy, regional relapse was still common. Immunotherapy may be an important avenue for management of this disease in the future.

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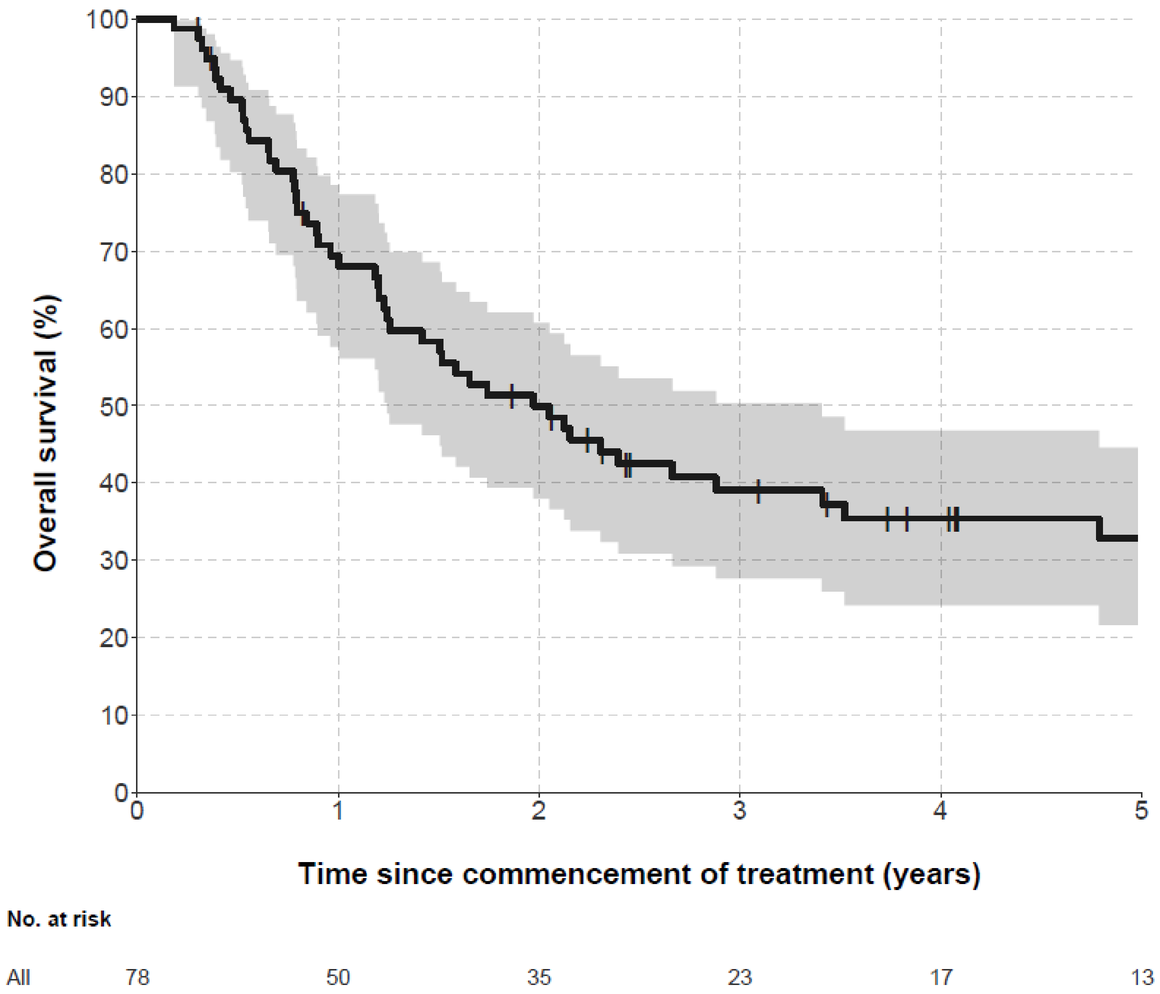
Figures and Figure Legends

Figure 1.

Legend

The overall survival including and excluding immunocompromised patients, treated curatively with cutaneous squamous cell carcinoma metastasizing to the axilla and groin, calculated using the Kaplan-Meir methods.

A Overall survival: All patients



B: Overall survival: Non-immunosupressed patients

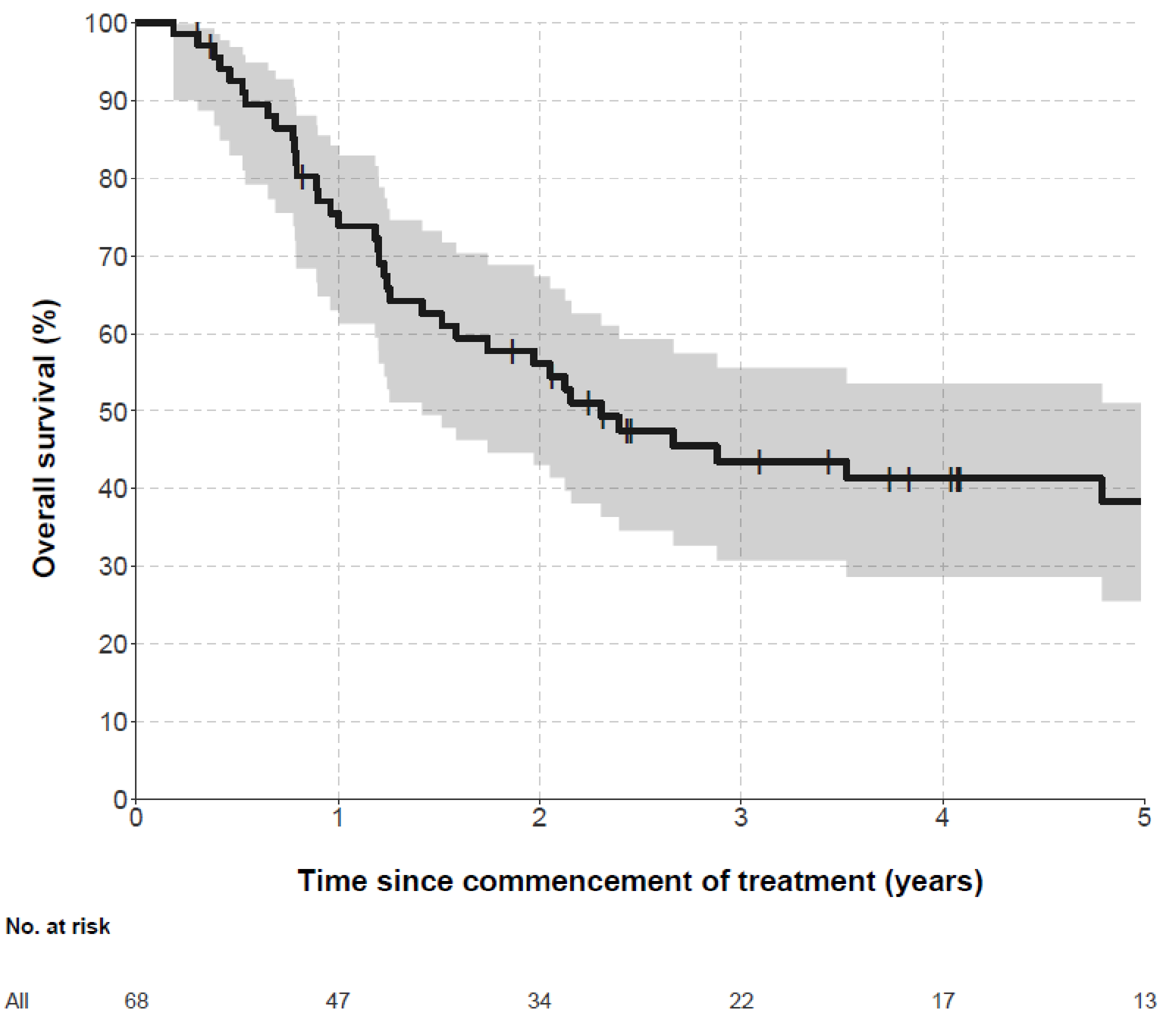
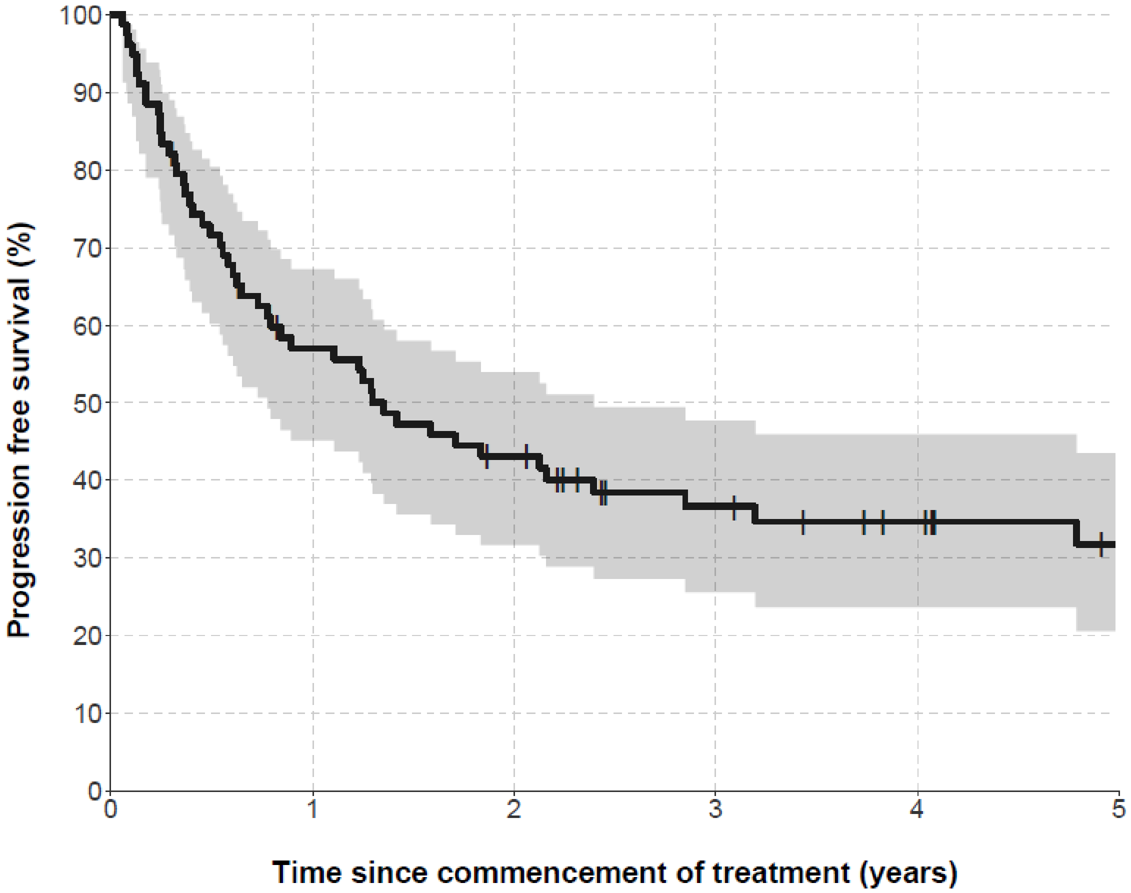


Figure 2.

Legend

The progression free survival including and excluding immunocompromised patients, treated curatively with cutaneous squamous cell carcinoma metastasizing to the axilla and groin, calculated using the Kaplan-Meir methods.

A Progression free survival: All patients



No. at risk

	0	1	2	3	4	5
All	78	41	30	20	15	10

B: Progression free survival: Non-immunosupressed patients

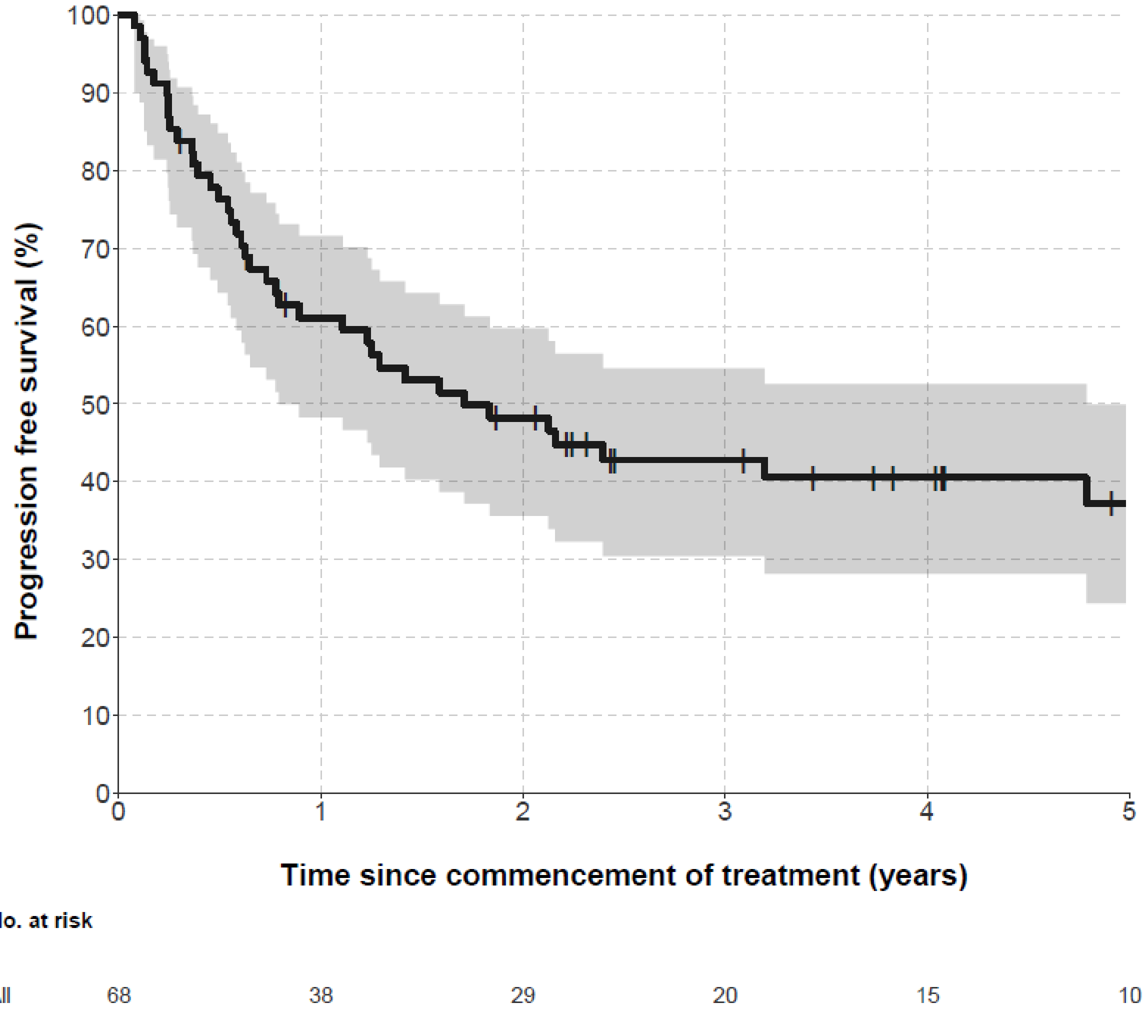


Figure 3.

Legend

Cumulative incidence curves of the site of first failure of patients of patients treated curatively with cutaneous squamous cell carcinoma metastasizing to the axilla and groin.

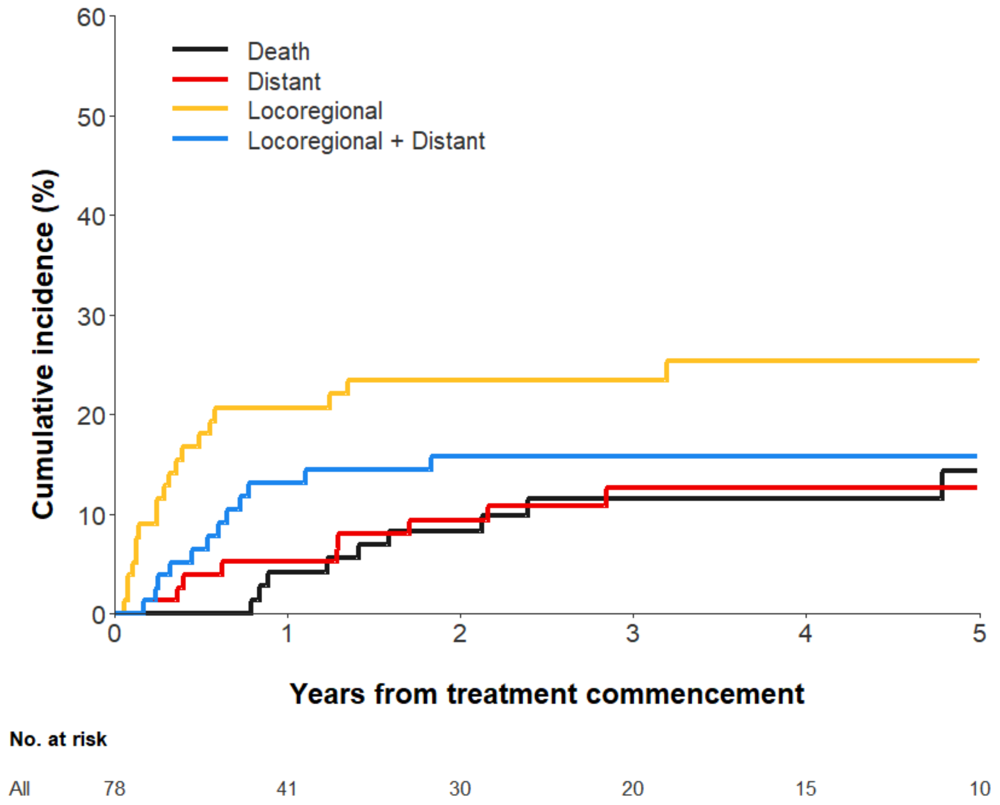
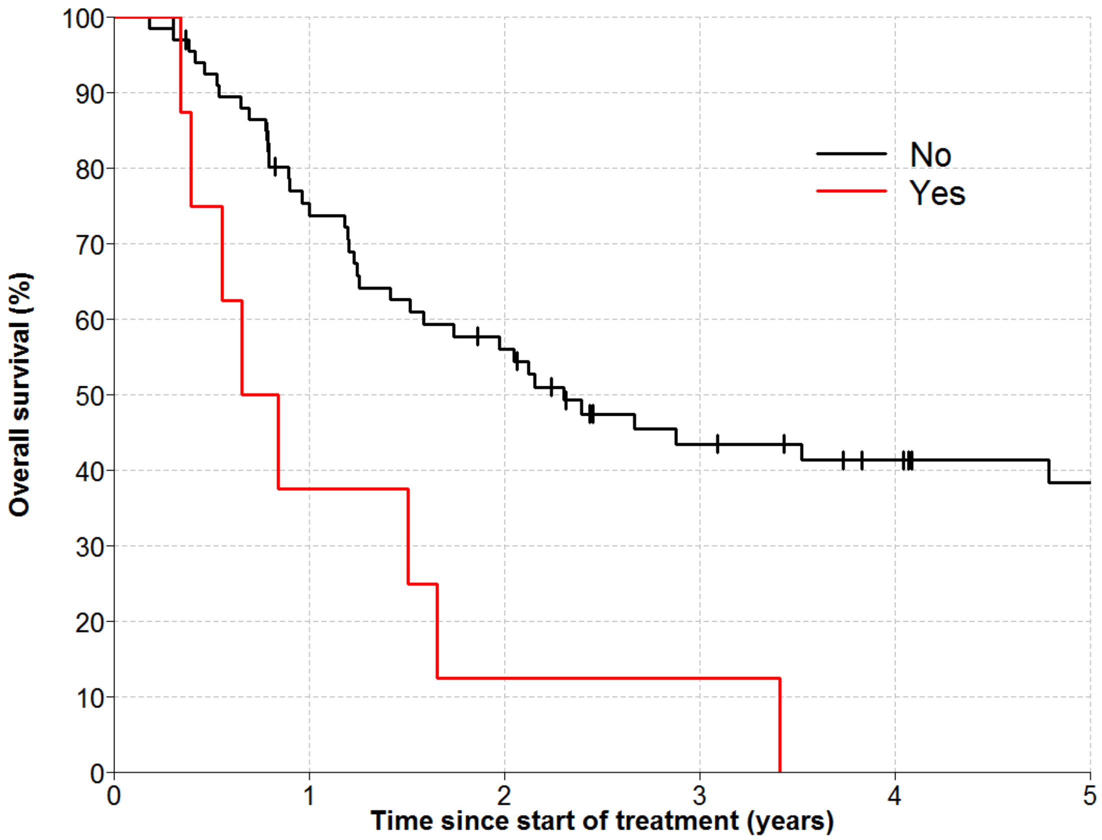


Figure 4.

Overall survival by immunosuppression status



Number at risk

	0	1	2	3	4	5
No	68	47	34	22	17	13
Yes	8	3	1	1	0	0

Table 1. Characteristics of 78 patients with axilla and groin nodal metastasis.

Variable	No. (%)
Age, y	
Median (range)	75.5 [29-95]
Sex	
Female	25 (32.1)
Male	53 (67.9)
Performance status*	
0	23 (32.9)
1	33 (47.1)
2	11 (15.7)
3	3 (4.3)
Unknown	8
Immune suppression	
None	68 (89.5)
Organ transplant recipient	1 (1.3)

Auto-immune disease	1 (1.3)
Chronic lymphocytic/myeloid leukemia	6 (7.9)
Unknown	2
Size of primary, mm	
Median (range)	25 (7-134)
Unknown	45
Location of primary site	
Hand	11 (31.4)
Upper arm	5 (14.3)
Trunk	12 (34.3)
Upper leg	1 (2.9)
Lower leg	3 (8.6)
Foot	3 (8.6)
Unknown	43
Location of nodal metastasis	
Axilla	64 (82.1)
Groin	14 (17.9)
Size of largest involved node, mm	
Median (range)	45 (8-135)
Number of nodes involved	
Median (range)	2 (1-22)
Number of nodes removed	
Whole group, median (range)	13 (3-30)
Axilla, median (range)	14 (3-30)
Groin, median (range)	10.5 (3-14)
Lymph node ratio†	
Median (range)	0.21 (0.04-1)
Extracapsular extension	
Yes	63 (80.8)
No	15 (19.2)
Differentiation of involved node	
Well	6 (9.2)
Moderate	29 (44.6)
Poor/undifferentiated	30 (46.1)
Not reported	13
UICC N-stage	

N1	11 (14.1)
N2‡	46 (59)
N3	21 (26.9)

* Performance status as measured by the Eastern Cooperative Oncology Group, † Ratio of number of nodes involved to number of nodes removed, ‡ included two patients with bilateral axillary nodal metastasis, one of whom was disease free at 5 years and another who developed distant metastasis 1.1 years after the start of treatment.

Table 2. Univariate Cox regression analysis of factors associated with overall survival for patients with cSCC metastasis to the axilla and groin.

		All patients		Non-immunosupressed subset	
Variable	**Level**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
UICC N stage	Per stage increase	1.4 (0.9 - 2.3)	0.109	1.4 (0.9 - 2.3)	0.156
Age (years)	Per 5 years increase	1.1 (1.0 - 1.3)	**0.021**	1.1 (1.0 - 1.3)	**0.030**
ECOG	Per unit increase	1.5 (1.1 - 2.3)	**0.026**	1.6 (1.1 - 2.5)	**0.023**
ECE	No	ref	0.232	ref	0.141
	Yes	1.6 (0.7 - 3.4)		2.0 (0.8 - 5.1)	
Immunosuppression	No	ref	**0.001**		
	Yes	3.3 (1.5 - 7.3)			
Histology	Undiff/poorly differentiated	ref	0.661	ref	0.318
	Mod/well differentiated	1.1 (0.6 - 2.1)		1.4 (0.7 - 2.7)	
Use of PET	No	ref	0.235	ref	0.430
	Yes	0.7 (0.4 - 1.2)		0.8 (0.4 - 1.4)	
Lymph node ratio (%)	Per 10% increase	1.2 (1.0 - 1.3)	**0.007**	1.2 (1.0 - 1.3)	**0.022**
Number of nodes excised	Per 1 node increase	1.0 (0.9 - 1.0)	0.597	1.0 (0.9 - 1.0)	0.390
Number of positive	Per 1 node increase	1.1 (1.0 - 1.2)	**0.004**	1.1 (1.0 - 1.2)	0.057

nodes

Maximal nodal diameter	Per 1cm increase	1.0 (0.9 - 1.1)	0.792	1.0 (0.9 - 1.1)	0.933
Nodal site	Inguinal	ref	0.406	ref	0.349
	Axilla	1.4 (0.6 - 3.1)		1.6 (0.6 - 4.0)	
RT	No	ref	**0.012**	ref	0.082
	Yes	0.5 (0.3 - 0.9)		0.5 (0.3 - 1.1)	

Table 3. Univariable Cox regression analysis of factors associated with regional control for patients with cSCC metastasis to the axilla and groin.

		All patients		**Non-immunosupressed subset**	
Variable	**Level**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
UICC N stage	Per stage increase	1.9 (1.1 - 3.5)	**0.031**	1.8 (0.9, 3.4)	0.073
Age (years)	Per 5 years increase	1.0 (0.9 - 1.2)	0.565	1.0 (0.9, 1.2)	0.619
ECOG	Per unit increase	1.2 (0.7 - 2.0)	0.442	1.1 (0.6, 2.0)	0.683
ECE	No	ref	**0.009**	ref	**0.008**
	Yes	8.9 (1.2 - 65)		Not estimable	
Immunosuppression	No	ref	0.078		
	Yes	2.3 (0.9 - 6.1)			
Histology	Undiff/poorly differentiated	ref	0.988	ref	0.659
	Mod/well differentiated	1.0 (0.5 - 2.2)		1.2 (0.5, 2.8)	
Use of PET	No	ref	0.126	ref	0.310
	Yes	0.6 (0.3 - 1.2)		0.7 (0.3, 1.5)	
Lymph node ratio (%)	Per 10% increase	1.4 (1.2 - 1.7)	**<0.001**	1.4 (1.2, 1.7)	**<0.001**
Number of nodes excised	Per 1 node increase	1.0 (0.9 - 1.0)	0.619	1.0 (0.9, 1.0)	0.560

Number of positive nodes	Per 1 node increase	1.3 (1.2 - 1.4)	**<0.001**	1.3 (1.1, 1.5)	**<0.001**
Maximal nodal diameter	Per 1cm increase	1.1 (1.0 - 1.3)	0.204	1.1 (0.9, 1.2)	0.362
Nodal site	Inguinal	ref	0.732	ref	0.577
	Axilla	0.9 (0.4 - 2.1)		0.8 (0.3, 2.0)	
RT	No	ref	0.126	ref	0.240
	Yes	0.5 (0.2 - 1.2)		0.6 (0.2 - 1.4)	