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Metastatic cutaneous squamous cell carcinoma to the parotid: Adjuvant radiotherapy and treatment outcomes

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Abstract

Introduction: Adjuvant radiotherapy is an established component in the management of metastatic cutaneous squamous cell carcinoma (SCC) involving the parotid gland. Radiotherapy technique, dose and volumes are seldom described sufficiently to allow close examination. We report our treatment outcomes and focus on treatment-related factors that affect outcomes in this cohort. **Methods:** We performed a retrospective review of patients with metastatic cutaneous SCCs who underwent parotidectomy with or without ipsilateral neck dissection. All patients received adjuvant radiotherapy. Demographics, clinical data and treatment details were collected from an intuitional electronic database. Individual patient-level radiotherapy technique, volumes and doses were reviewed. **Results:** Between July 2008 and July 2018, 60 patients met our inclusion criteria. Median follow-up duration was 32.7 months. The mean age was 66.4 years. The majority of patients (49 patients) received full neck irradiation. The 2-year and 5-year loco-regional failure-free survival was 87% (95% confidence interval (CI): 0.74–0.93) and 71% (95% CI: 0.52, 0.83), respectively. The 2-year and 5-year overall survival was 76% (95% CI: 0.62, 0.85) and 60% (95% CI: 0.45, 0.72), respectively. There were 15 cases of loco-regional failures, with 6 cases with dermal involvement. Lymphovascular invasion (LVI) was associated with higher loco-regional failure (hazard ratio: 8.43, 95% CI: 1.85–38.39, $P = 0.005$) and cancer-specific mortality (hazard ratio: 5.40, 95% CI: 1.40–20.87, $P = 0.015$). Treatment technique, intensity-modulated radiation therapy (IMRT) vs 3D conformal radiotherapy (3D CRT), bolus use, perineural invasion (PNI) and surgical margins were not significantly associated with loco-regional failure. **Conclusion:** We demonstrated high loco-regional control rates with routine use of comprehensive adjuvant radiotherapy. The presence of LVI was identified as a strong predictor for recurrence. Further analysis will help to define optimal radiation dose and techniques.

Introduction

Non-melanomatous skin cancer is the most commonly diagnosed cancer in Australia each year.[1] Approximately two in three Australians will be diagnosed with skin cancer by age 70.[2] Squamous cell carcinoma (SCC) is the second most common cutaneous malignancy, and a rise in incidence of SCCs have been noted. The sun-exposed head and neck region is a common site for the development of cutaneous SCC. Whilst the majority of

patients achieve good outcomes following complete excision, approximately 5% of patients would have metastases to the regional lymph nodes at diagnosis.[3]

The patterns of lymph node spread of cutaneous SCC from the head and neck have been extensively examined by several investigators.[4–6] The parotid gland contains lymph nodes draining the scalp, posterior head, ears, cheek and temple.[7] Studies of lymphatic drainage patterns have illustrated significant intercommunication between the nodes in the deep cervical chain.[7]

Patients who develop metastases to the parotid gland often present with a parotid mass, which warrants further evaluation for a cutaneous primary or index lesion. It is not uncommon that the index lesion is not ascertained even following a thorough history and clinical review.[8]

The use of adjuvant radiotherapy following parotidectomy and neck dissection is supported by multiple retrospective study data and has become an accepted standard of care in patients with metastatic parotid cutaneous SCC.[9–11] However, data regarding radiotherapy technique, dose and delivery is often insufficiently described in surgical studies, which impedes improvements to clinical practice. Meanwhile, significant technological advancements in both patient set-up, imaging and treatment delivery have been made, allowing for improved treatment accuracy, higher dose conformity and ability to spare critical organs at risk.

This paper analyses a cohort of patients following surgery and adjuvant radiotherapy treatment for metastatic parotid SCC at Townsville Cancer Centre (TCC). We report on clinical and treatment-related factors that affect outcomes in this cohort.

Methods

The study was conducted following approval by the Townsville Hospital and Health Service Human Research Ethics Committee. We performed a single institution retrospective study in patients treated with adjuvant radiotherapy between July 2008 and July 2018. An electronic database (MOSAIQ) was used to identify the patients with nodal cutaneous SCC based on International Classification of Diseases (ICD) codes. Patient charts were individually reviewed. Patients were included in our study if they underwent curative intent parotidectomy, with or without neck dissection, followed by adjuvant radiotherapy. We included patients whose primary site was either confirmed or suspected to be of cutaneous head and neck origin. Patients who presented with direct invasion of the parotid gland from a primary cutaneous SCC were excluded. Patients with other histology such as mucosal SCC, Merkel cell carcinoma, melanoma and primary salivary gland tumours were also excluded. Relevant medical records, operative reports, pathology reports, radiotherapy planning and treatment documents were reviewed for each patient. The treatment factors examined include extent of parotidectomy, extent of neck dissection, surgical margins, radiotherapy technique, concurrent chemotherapy use, bolus use, full or partial neck irradiation.

The primary endpoint was loco-regional failure-free survival (LRFFS). The LRFFS was defined as disease recurrence above the clavicles related to previously treated parotid SCC. The secondary endpoints were cancer-specific survival (CSS) and overall survival (OS). Duration to these endpoints were taken from the date of histological diagnosis confirming metastatic SCC.

Treatment

All patients were discussed at the Townsville Hospital head and neck multidisciplinary meeting (MDM). Each patient was staged according to the American Joint Committee on Cancer's staging manual, with the most current edition at the time. All patients obtained histological diagnosis by fine needle aspiration (FNA). Pre-operative imaging consisting of CT, MRI and PET were used in 35 (58.33%), 11 (18.33%) and 36 (60%) patients, respectively.

At our institution, standard practice is to perform a superficial parotidectomy, unless there was radiological or clinical suspicion for disease involving the deep part of parotid or facial nerve, in which case a total parotidectomy was required. In cases where tumour involved adjacent structures such as temporal bone or mandible, a radical extended parotidectomy was undertaken, with the aim of obtaining an en bloc excision of the tumour mass with clear margins. Patients with clinically involved neck nodes underwent therapeutic neck dissection as well. Given the reported rate of occult metastasis in the neck reported in the literature is as high as 35%,[4] patients with parotid disease and a clinically negative neck were also considered for an ipsilateral neck dissection. This was generally influenced by assessment of patient fitness, expected surgical outcome and complication risk, and risk of occult metastasis and determined in the MDM. Where primary site involves occipital or posterior scalp, a posterolateral neck dissection is typically recommended by our MDM.

In our department, patients with any parotid nodal disease were referred for consideration for adjuvant radiotherapy, following MDM consensus. The radiotherapy volume covered the parotid bed, including the deep lobe, and all surgically perturbed regions that may harbour microscopic disease. Elective neck irradiation was offered to all patients with a neck

dissection and included the lower unperturbed neck in instances where the risk of further relapse below surgical bed was considered to be significant.

The preferred dose fractionation in our department was 60 Grey (Gy) in 30 fractions. All dose fractionation schedules were included in this study. A boost dose was considered in cases of positive margin or significant extracapsular extension. The radiotherapy technique was designated by the treating radiation oncologist. Patients are immobilised with a S-framed thermoplastic mask. In the three-dimensional conformal radiation therapy (3D-CRT) era, a wedged pair field arrangement was commonly adopted, in some cases with a lightly weighted direct lateral beam (Fig. 1). When the lower neck required treatment, then a junction technique would be employed. This technique utilised a mono-isocentre in the neck region (Fig. 1). The superior aspect of the PTV (parotid/parotid bed) would be treated with the technique outlined above. The inferior aspect of the PTV would be treated with an anterior and posterior beam that would be angled accordingly to spare the spinal cord. In some instances, a partial junction could be utilised depending on the size and shape of the PTV. In these instances, one or more of the 3D CRT beams could treat the length of the PTV therefore allowing a partial junction, in turn reducing the uncertainty of the dose in the junction area by eliminating the need for a junction for that field (Fig. 2). Step and shoot intensity modulated radiation therapy (IMRT) was available in our department since 2012 and was increasingly utilised over time. In the earlier phase, this most commonly consisted of 5 fields, separated by 40° (Fig. 2). Imaging for positional verification has improved immensely. Earlier treatments relied on weekly kilovoltage (KV) imaging with a tolerance of <5 mm. In conjunction with IMRT, daily cone-beam computed tomography (CBCT) became standardly used. Hexapod couch capabilities allowing 6° of correction also became available and allowed for enhanced target alignment and reduced setup error.

The placement of tissue-equivalent bolus (generally between 0.5 and 1 cm thickness) was used at the discretion of the treating radiation oncologist and not institutionally defined. When used, bolus was placed on the area of the parotid/parotid bed region where the PTV extended out to skin edge. Packing with wet gauze was commonly used for ear canal and deficits from surgery to ensure prescription dose was achieved to PTV. Concurrent chemotherapy, cisplatin or cetuximab was considered at the discretion of the MDM. Every attempt was made for radiotherapy to begin within 6 weeks of their surgery. Patients were followed up by both the radiation oncologist and treating surgeon on an alternating basis, every 3 months for the first 2 years, then less frequently until 5 years after completion of treatment.

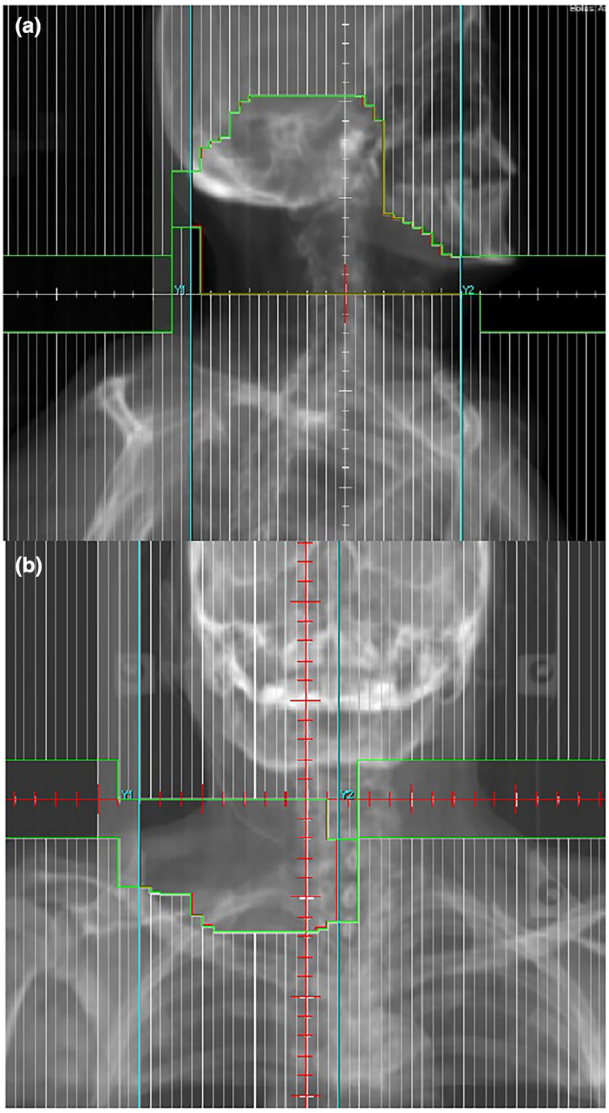

Figure 1. (a) Digitally reconstructed radiograph (DRR) illustrating one beam treating parotid bed and upper neck nodes in a representative 3D-CRT plan. (b) Digitally reconstructed radiographs (DRRs) illustrating one beam treating lower neck nodes below the junction in a representative 3D-CRT plan.

Statistics

Data analysis

Data analysis was performed in STATA (StataCorp LLC. 2017. Stata Statistical Software: Release 16.1 College Station, TX, USA). Descriptive statistics was used to describe the demographic and clinico-pathological

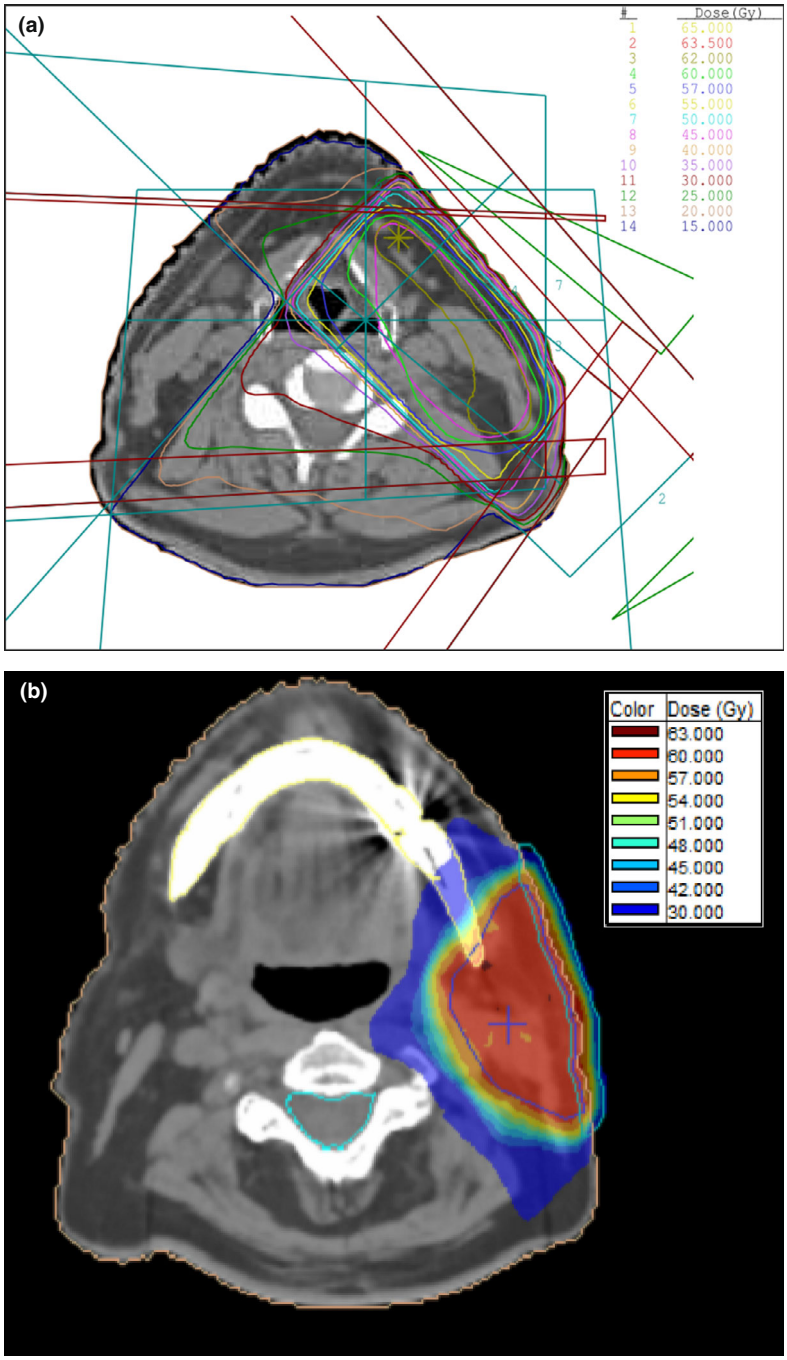

Figure 2. (a) Treatment planning dose distribution of same patient as Figure 1, using wedged pair configuration. (b) Treatment planning dose distribution for a representative 5-field step-and-shoot intensity modulated radiation therapy (IMRT).

features of the patients. Survival analyses were calculated using either Kaplan–Meier method or Cox Proportional Hazards Regression model, as appropriate.

The survival time was defined as the period between the diagnosis date and the occurrence of the event of interest (loco-regional failure, cancer-specific death or any death). The outcome variable was dichotomised and equal to 1 when the event of interest occurred and equal to 0 for censured (event of interest did not occur during the study period).

Kaplan–Meier curves characterised all time-to-event variables, including overall survival and time to event of

interest. Two- and five-year overall survival estimates, and 95% confidence intervals (CI) were computed for each event of interest. Overall, inference was based on a 5% level of significance.

The potential effect of age, lymphovascular invasion (LVI), perineural invasion (PNI), N stage, extranodal extension, margin status, type of parotidectomy, extent of neck dissection, concurrent chemotherapy and use of bolus were tested on LRFFS using univariable Cox regression model (Supporting information).

Results

Patient and treatment details

Patient demographics and tumour characteristics are summarised in Table 1. A total of 60 patients were included in the study period based on our inclusion criteria. The mean age was 66 years (range 37–88 years). There were seven patients who were classified as immunocompromised, with five patients having a concurrent haematological malignancy, one patient with a diagnosis of HIV, and another one patient immunosuppressed secondary to cyclosporine for membranous nephropathy. In 40 patients (67%), the location of index lesion (primary site) was able to be determined. The most common primary site involved was the face with 10 (16%) patients, followed by peri-auricular area with 7 (11%) patients.

The median interval between management of the index site and the presentation for metastatic disease was 7.9 months (range 0–120 months). In 4 cases, patients presented with synchronous primary and metastatic parotid nodal disease.

Surgical and radiotherapy details are shown in Table 2. The majority of patients (38 patients) had a superficial parotidectomy performed. 59 patients underwent a neck dissection, with supra-omohyoid neck dissection being the most commonly performed (34 patients). The mean size of the parotid lesion was 27.5 mm (range 7-80 mm) which contained the mean number of intra-parotid nodes of 2.0 (range 0–11). The mean number of involved nodes in the neck were 4.6 (range 0–73) with the mean number of dissected nodes as 26.9 (range 0–83). Surgical margins were involved in 20 patients (33%) whereas 30 patients (50%) were found to have close margins (<2 mm). Extracapsular extension was present in 38 patients (71.7%). Twenty-four patients had perineural invasion (PNI), of which nine patients (15%) had clinical signs of facial nerve palsy suggesting perineural involvement of the facial nerve.

All patients received adjuvant radiotherapy. The respective median and mean dose were 60 Gy and 60.6 Gy (Standard Deviation (SD): 4.8, range 44–69 Gy) to the parotid bed and 60 Gy and 56.6 Gy (SD: 4.8, range 40–64.5 Gy) to the ipsilateral neck. The dose and fractionation schedules are summarised in Table 3. The most commonly dose fractionation was 60 Gy in 30

Table 1. Patient and tumour characteristics.

N	60
Mean age (years)	66.4
Age range (years)	37–88
Gender	
Male	56 (93.3%)
Female	4 (6.7%)
Immunosuppression	
Immunocompromised	7 (12%)
Non-immunocompromised	53 (88%)
Smoking status	
Current smoker	14 (23.3%)
Ex-smoker	25 (41.7%)
Non-smoker	13 (21.7%)
Unknown	8 (13.3%)
Index site	
Scalp	5 (8.3%)
Face	10 (16.7%)
Forehead	4 (6.7%)
Nose	2 (3.3%)
Ear	6 (10%)
Peri-auricular	7 (11.7%)
Temple	6 (10%)
Unknown	20 (33.3%)
Pathological T stage	
Tx	40 (66.7%)
T1	8 (13.3%)
T2	11 (18.3%)
T3	0
T4	1 (1.7%)
Pathological N stage	
N1	21 (35%)
N2a	2 (3.3%)
N2b	30 (50%)
N2c	3 (5.0%)
N3	3 (5.0%)
Unknown	1 (1.7%)
Histological grade	
Well differentiated	7 (11.7%)
Moderately differentiated	19 (31.7%)
Poorly differentiated	22 (36.7)
Grade unknown	12 (20%)
Lymphovascular invasion	
Present	15 (25%)
Absent	35 (58.3%)
Unknown	10 (16.7%)
Perineural invasion	
Clinical PNI	9 (15%)
Pathological PNI	15 (25%)
PNI absent	36 (60%)
Extracapsular extension	
Present	38 (63.3%)
Absent	22 (36.7%)

Table 2. Surgical and radiotherapy details.

	n (%)
Extent of parotidectomy	
Superficial	39 (65%)
Total	17 (28.8%)
Extended/radical	4 (6.8%)
Extent of neck dissection	
Supra-omohyoid	34 (56.7%)
Radical	8 (13.3%)
Modified radical	10 (16.7%)
No neck dissection	8 (13.3%)
Surgical margins	
Positive	20 (33.3%)
Negative	10 (16.7)
Close[1]	30 (50%)
Radiotherapy technique	
3D CRT	34 (56.7%)
IMRT	26 (43.3%)
Concurrent chemotherapy	
Yes	12 (20%)
No	48 (80%)
Bolus	
Yes	38 (63.3%)
No	17 (28.3%)
Unknown	5 (8.3%)

3D CRT, three-dimensional conformal radiation therapy; IMRT, intensity-modulated radiation therapy.
[1]Defined as margin <2 mm.

Table 3. Prescription dose and fractionation for parotid bed.

Number of patients	Total dose to parotid bed (grey)	Total number of fractions	Sequential boost (seq), simultaneous integrated boost (sib), no boost (nil)
1	44	22	nil
2	50	25	nil
2	50	20	nil
2	52	20	nil
1	54	24	nil
1	56	28	nil
1	58.86	27	nil
1	59.4	33	nil
30	60	30	nil
2	63.6	32	seq
3	63.9	30	sib
2	64.5	30	sib
1	64.8	33	seq
1	65	50	seq
3	65.1	30	sib
5	66	33	seq
1	69	36	seq
1	70	35	seq

fractions, which was used in 30 patients. Only 1 patient did not complete their prescribed dose, this patient declined treatment after 44 Gy of a prescribed dose due to unrelated patient factors. 3D-CRT was used in 34 patients, and step-and-shoot IMRT in 26 patients. The radiotherapy field was limited to include only parotid bed and partial neck (inferior border covering level 3) in 11 patients, and the entire neck to level 4 or 5 in 49 patients. Thirty-eight (63.3%) patients received bolus over the parotid bed. Bolus thickness was not recorded. Twelve patients received concurrent chemotherapy. Of these, cisplatin was the chemotherapy agent in nine patients, carboplatin in one patient and cetuximab in two patients.

The median follow-up duration was 32.7 months (range 4.6–149.4 months). The 2-year and 5-year LRFFS was 87% (95% CI: 0.74–0.93) and 71% (95% CI: 0.52–0.83), respectively (Fig. 3). The 2-year and 5-year CSS was 89% (95% CI: 0.76–0.95) and 83% (95% CI: 0.68–0.91). The 2-year and 5-year OS was 76% (95% CI: 0.62–0.85) and 60% (95% CI: 0.45–0.72), respectively (Fig. 3).

Patterns of failure

Overall, there were 15 cases of loco-regional failure. In five cases, recurrent disease was identified within the parotid bed. Ten cases were found to have cutaneous or subcutaneous disease, which included two cases involving the graft or scar sites. Of these 10 cases, there was only one case (graft site recurrence) in which bolus was omitted. The ipsilateral neck nodes were involved in three cases, there were two cases of isolated contralateral neck node recurrence, and one case of bilateral nodal recurrence.

When the dosimetry plan was reviewed, 10 cases were identified to have in-field recurrence within a high-dose region. The contralateral recurrences were all out of field. There was one marginal recurrence and two in field recurrence involving the ipsilateral neck. All patients with loco-regional failure were considered for salvage therapy. Seven patients underwent salvage curative-intent surgical resection. Four patients received further adjuvant radiotherapy.

Sites of loco-regional failure are summarised in Table 4. There was a total of four loco-regional failures with IMRT compared to 11 with 3D-CRT, though this was not statistically significant when tested (95% CI 0.25–2.8; $P = 0.771$). All 4 IMRT recurrences had at least a component of dermal involvement, as compared to five of the 11 treated with 3D CRT.

There was a total of 14 distant failures recorded in our cohort. Five of these had concurrent loco-regional failures which were included in the description of loco-regional failure above. Eleven of these died subsequently during our follow-up period with eight of these attributed to this

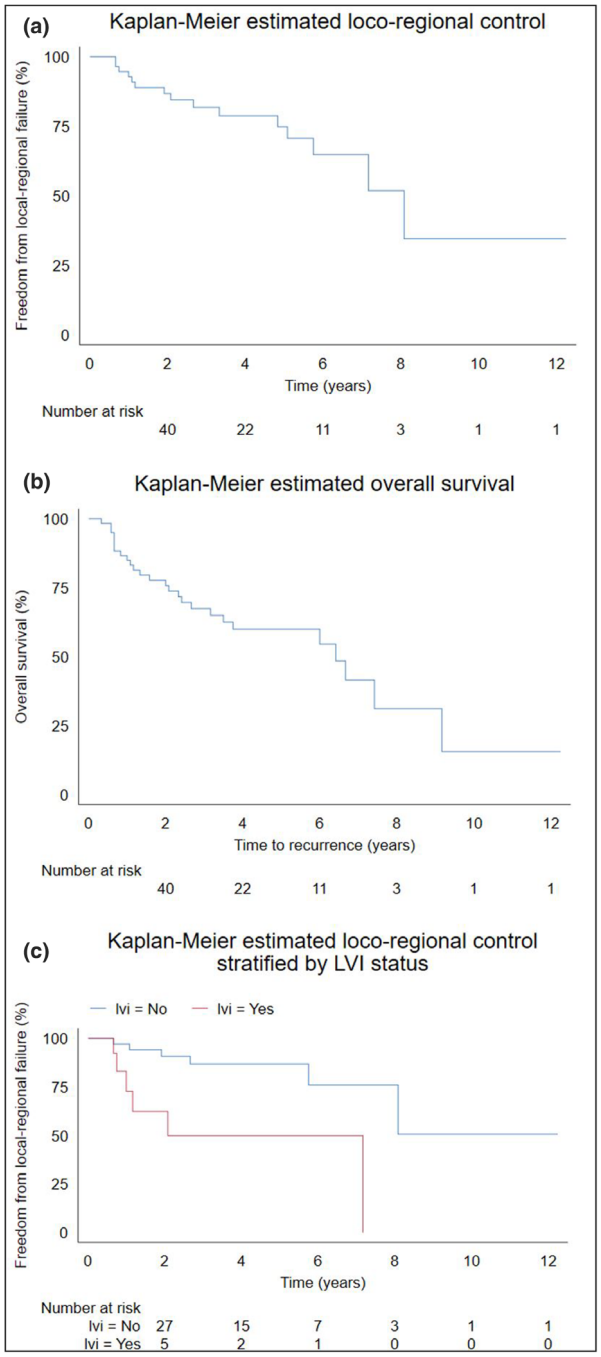

Figure 3. (a) Kaplan–Meier graph showing loco-regional control for entire treatment cohort. (b) Kaplan–Meier graph showing overall survival for entire treatment cohort. (c) Kaplan–Meier graph showing loco-regional control for entire treatment cohort stratified by lymphovascular (LVI) status.

Table 4. Patterns of loco-regional failure.

	Site of failure			
Technique	Dermal	Parotid bed	Ipsilateral neck nodes	Contralateral neck nodes
3D CRT	6	4	2	3
IMRT	4	2	1	0

3D CRT, three-dimensional conformal radiation therapy; IMRT, intensity-modulated radiation therapy.

malignancy. The median duration from date of distant relapse to death was 2.3 months (range 1.5–69.4 months).

The presence of LVI was associated with a higher risk for loco-regional failure at all times of follow-up (hazard ratio: 2.41, 95% CI: 1.72–19.40, $P = 0.005$) (Fig. 3). There was a non-significant trend towards higher failure observed for PNI, close and positive margins, smokers, immunosuppressed, age > 70 years, no chemotherapy and bolus use. On multivariate analysis, LVI was associated with a higher risk of loco-regional failure (hazard ratio: 8.43, 95% CI: 1.85–38.39, $P = 0.006$). Smoking was not statistically significant risk factor, (hazard ratio: 9.82, 95% CI: 1.00–96.64, $P = 0.050$), and chemotherapy was associated with a trend to lower local failure although not significant (hazard ratio: 0.21, 95% CI: 0.02–1.85, $P = 0.159$).

LVI was also associated with significantly inferior cancer-specific mortality (hazard ratio: 5.40, 95% CI: 1.40–20.87, $P = 0.015$). In patients with LVI, there were 6 loco-regional failures, and 6 distant failures, resulting in a cumulative risk of 40% for loco-regional and distant failure. Five of the loco-regional failures were in-field, occurring in the parotid bed, scar or subcutaneous tissue. Three failures were classified as dermal relapses, and only 1 nodal failure in the ipsilateral neck. There were 2 cases of contralateral neck failure, of which one was an isolated contralateral recurrence.

Discussion

In our cohort, adjuvant radiotherapy was delivered in all patients with parotid SCC following parotidectomy and/or neck dissection. The loco-regional failure-free survival rates were 87% and 71% at 2 and 5 years respectively, which are comparable to other published data, with the loco-regional failure rate of 10–30% at 5 years.[6,12–14] Previous retrospective studies have identified positive surgical margins[4] and extranodal extension[9,15] as factors that predict higher rates of relapse. However, these studies included patients that received adjuvant radiotherapy as well as patients that did not. In our

study, all patients received adjuvant radiotherapy in a relatively uniform manner. This allowed us to assess whether previously identified treatment and prognostic factors retained significance.

Our multivariate analysis confirmed that LVI was associated with a significantly higher rate of loco-regional failure. Despite its absence in the American Joint Committee on Cancer (AJCC) staging system, multiple authors have reported LVI as a risk factor with high risk of developing nodal metastasis[16] and disease-specific mortality.[17] In our cohort, both in-field loco-regional and distant failures were common, with a majority being dermal recurrences. Six out of 15 loco-regional failures involved dermal recurrences, which could be accounted by the phenomenon of in-transit metastasis.[18] We also noted that, of the 6 loco-regional failures in the LVI group, there were 2 contralateral neck failures. The high incidence of failure associated with LVI is of concern and ways to reduce that include delivering higher dose to the parotid tumour bed and/or extending the cutaneous treatment field akin to that of treating Merkel cell carcinoma. Such approach needs to be balanced against potential toxicities. Whilst concurrent systemic therapy has not been shown to have clinical benefit in all comers with high-risk cutaneous SCCs,[12] it may have utility in this subgroup, though this remains to be definitively demonstrated.

The rate of close or incomplete excision after parotidectomy is high owing to the complex anatomy and propensity of the parotid disease for deep infiltration. Twenty patients (33.3%) in our cohort had positive margins, and 30 patients (50%) had close margins defined as <2 mm. This is despite maximal resection with total parotidectomy in 17 patients (28.8%) and extended parotidectomy in four patients, (6.8%). In such situations, it is common to consider dose escalation or a localised boost to the high-risk region when positive or close surgical margins are noted. Of the 20 patients with positive surgical margins, 14 received total doses higher than 60Gy (range: 63.6–69 Gy) to partial or entire parotid bed. Dose escalation has not been extensively studied for parotid metastasis, and particularly in the era of 3D-CRT was limited by toxicity to organs at risk. Chen et al[19] retrospectively analysed 36 patients with parotid metastatic SCC treated with PORT, finding significantly higher relapse with a dose <60 Gy. There was only 1 failure at a dose of 60 Gy or higher, thus limiting the ability to evaluate any benefit in dose escalation at this range. In the absence of prospective data, some radiation oncologists favour a dose of 66 Gy in 2 Gy per fraction in situations of microscopically positive margins or extranodal extension. Extrapolating from mucosal head and neck SCCs, dose escalation in the range of 63–68.4 Gy at 1.8 Gy per fraction did not improve tumour control.[20] In line with this, recently published consensus guidelines from Head and Neck Cancer International Group (HNCIG)[10] and American Society for Radiation Oncology (ASTRO) guidelines[21] recommend dose of 60–66 Gy. We suggest that the uniform application of adjuvant radiotherapy as well as selected use of dose escalation in this cohort nullified the significance of positive margins.

Furthermore, we did not identify a significant difference between those that received higher than 60 Gy to the parotid bed and those that received 60 Gy or less. However, it is worthwhile noting that margin status was not associated with a poorer outcome in our study. In a series with 66 patients all receiving adjuvant radiotherapy, Goh et al[22] reported a correlation between margin status and inferior disease-free survival. It is worth noting that the average dose to the parotid bed in their study was 53.9 Gy and to the lower neck was 43.6 Gy, compared with 60.6 and 56.6 Gy in our study, respectively.

We examined the influence of radiotherapy technique on locoregional failure. When comparing loco-regional failure for patients treated by IMRT technique to 3D-CRT, we found that there was no statistical significance between the two cohorts. In our department, IMRT was adopted between 2011 and 2012, based upon evidence largely from mucosal head and neck treatments. This has been accompanied by significant advances in technology, as well as improved understanding of normal tissue effects in the head and neck, an example being the significance of sparing salivary glands for quality of life. However, cutaneous malignancies exhibit notable differences in biology, have higher mutational burden and different patterns of relapse, with high rates of dermal involvement at relapse. This justifies the concern for geographic miss when employing steeper dose gradients with more conformal techniques. In our study, we found 4 loco-regional and 5 distant failures in our IMRT cohort, compared with 9 loco-regional and 9 distant failures in our 3D-CRT, which was not statistically significant in our univariate analysis. Furthermore, in-field recurrences comprised a majority of loco-regional failures in both IMRT and 3D-CRT, and there was also no major difference in the pattern of dermal involvement.

Bolus was used in the majority of cases, including 13 of the 15 cases of loco-regional recurrence. Furthermore, bolus was used in 9 of 10 cases of cutaneous or subcutaneous recurrence. Despite the substantial proportion of recurrences being cutaneous, we did not detect any reduction in loco-regional failure with the use of bolus. In an analysis of 75 patients, Pramana et al[17] found the use of bolus was associated with worse skin reactions without any significant benefit in loco-regional

control or cancer specific survival. This was despite a high rate of dermal recurrences of 87% in their cohort. At this time, there is no consensus in its use. Risk and benefit of bolus use should be further investigated in a prospective manner.

The limitations of our study include the inherent bias associated with a retrospective study and small sample size. Due to inconsistent documentation, we did not record acute and late toxicity. There was also a small proportion of missing patient and treatment factor data which further decreased statistical power. The effect of primary tumour stage on loco-regional control was not examined in detail, due to limited data collected. Furthermore, quality-of-life metrics were not collected.

Treatment for advanced cutaneous malignancies has evolved in recent times. Whilst the role of chemotherapy has diminished, there is significant enthusiasm to explore the role of immunotherapy. An Australian-led international randomised phase 3 trial is currently underway to test the role of adjuvant cemiplimab in high-risk cutaneous SCC.[23] Our results support current treatment techniques as used in our cohort, although optimal dose and fractionation remain unresolved. It is likely that risk-adapted approach of radiotherapy and systemic therapy will further improve treatment outcomes, and future well-designed prospective studies are required to explore this.

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Conflicts of interest

The authors of this paper have no conflicts of interest to disclose.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 Cox univariate analysis