Outcomes following surgery and post-operative radiotherapy for perineural spread of head and neck cutaneous squamous cell carcinoma.

Running title: Cutaneous SCC with perineural spread

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Keywords: perineural invasion; head and neck; skin cancer; squamous cell carcinoma; skull base surgery.

Totals: Pages: 16; Figures: 6; Tables: 6

There are no financial disclosures. This work is supported by a grant from the Princess Alexandra Hospital Research Foundation and a National Health and Medical Research Council post-graduate scholarship for Dr Timothy Warren.

Abstract

Background

Queensland, Australia has the highest rates of cutaneous squamous cell carcinoma (SCC). Perineural invasion (PNI) is associated with reduced local control and survival.

Methods

A retrospective review of a prospective database of patients with clinical PNI from cutaneous SCC of the head and neck (CSCCHN) treated with surgery and post-operative radiotherapy between 2000-2011 and a minimum of 24 months follow-up. Patients were excluded if immunosuppressed, had non-SCC histology or treated palliatively.

Results

50 patients (mean age 60 years) with median follow-up of 50 months were included. 54.8% of known primary tumors had incidental PNI. 10% had nodal disease at presentation. MR neurogram was positive in 95.8%. Recurrence-free survival at 5-years was 62%. 5-year disease-specific survival and overall survival were 75% and 64%, respectively. There were no peri-operative deaths.

Conclusion

This report demonstrates that long-term survival is achievable in patients with clinical PNI from CSCCHN following surgery and post-operative radiotherapy.

Introduction

Cutaneous squamous cell carcinoma of the head and neck (CSCCHN) occurs at epidemic rates in Australia.[1] Perineural invasion (PNI) is defined as the presence of tumor cells in the perineural space of a peripheral nerve and is estimated to occur in less than 5% of CSCCHN cases. When PNI is asymptomatic and only detected on histology, it is known as incidental PNI. When there is spread of tumor along the perineural space of a nerve, this is termed clinical PNI or perineural spread (PNS). This may manifest radiologically, histologically or clinically with progressive symptoms and signs of nerve dysfunction in the distribution of the affected nerve (i.e. dysaesthesia, facial palsy). The presence of perineural spread and its extent is best assessed by magnetic resonance (MR) neurography, preferably using a 3.0 Tesla (3T) platform.[2]

Clinical PNI is associated with higher rates of local recurrence and reduced overall survival when compared to incidental PNI.[3,4] The nerves most commonly affected are the trigeminal (V_1 ophthalmic, V_2 maxillary and V_3 mandibular divisions) and facial (VII) cranial nerves. PNS along a peripheral nerve is contiguous, and is primarily retrograde (towards the brainstem) yet can be antegrade (towards the skin). Skip lesions (if seen) are likely the result of technical processing artifact and not tumor emboli.[5,6] In addition, perineural invasion with concomitant intraneural invasion is seen in the majority of cranial nerve pathological specimens.[6] The natural history of PNS is typically slow retrograde tumor spread toward the brainstem with poor prognosis (i.e. central failure).

The American Joint Committee on Cancer (AJCC; 2010 7th edition) classifies all PNI into the skull base as T4 disease.[7] Currently, no consideration is given to the precise zonal extent of PNS, which has been shown to influence patient outcome.[8] Zonal extent of cranial nerve PNS is used at our institution for classification (see Table 1).[9] Generally, zone 1 or 2 disease is operable, whilst zone 3 disease is considered not, due to the perceived higher risk of iatrogenic spread of tumor via the cerebrospinal fluid (CSF) during surgery. However, surgery is considered on a case-by-case basis.

The management of clinical PNI varies between institutions yet surgical resection followed by post-operative radiotherapy (PORT) can lead to improved patient outcomes in selected patients.[10] Previously reported outcome data is restricted in its clinical application through the use of varying treatment approaches,[3,11] and pooling of either incidental PNI and clinical PNI cohorts[12] or different tumor types (i.e. SCC and basal cell carcinoma, BCC).[4] The purpose of this study is to describe the long-term survival of patients with perineural spread from CSCCHN treated with surgery and post-operative radiotherapy.

Materials and Methods

50 consecutive patients with clinical PNI from CSCCHN treated with curative intent surgery between 2000-2011 with a minimum 24 months follow-up for alive patients identified from a prospective database were included. Immuno-suppressed patients (n = 2) and patients with PNI of other tumor types (melanoma {n = 2} and BCC {n = 6}) were excluded. Informed patient consent and ethics approval from the Metro South Human Research Ethics Committee was obtained (2003/197). Details of primary tumors were obtained from pathology archives. Primary tumors and perineural spread was classified according to AJCC 2010 TNM criteria (see Tables 2 and 3).[7] An 'r' notation was applied to the staging if a patient presented with PNS from recurrence of a previously treated primary skin cancer.

All patients underwent pre-operative diagnostic imaging with MR neurography evaluated by a skull base radiologist, or computed tomography (CT) when MRI was contraindicated. All management plans were discussed in specialized multidisciplinary head and neck and/or skull base tumor boards. Surgical resection was planned with imaging findings and all tumors were resected en bloc with frozen section margin control via a skull base or sub-cranial approach as described in Table 4 and in our previous reports.[6,10,13] Surgery was of curative intent in all patients. Neck dissection was performed if: (i) nodal disease was evident or suspected on pre-operative assessment; or (ii) surgical access to the neck was required to enable reconstruction.

PORT was offered to all eligible patients. Treatment was individualized depending on each patient's suitability and disease extent (skin, nerve, nodal involvement). In the later half of the 2000's, prescribed volumes were typically dependent on the zonal extent of disease on imaging and pathology: zone 1 up to ganglion; zone 2 to the pre-pontine aspect of the nerve; and zone 3 up to brainstem.[9] Fields encompassed the peripheral branches of involved nerves, and the regional nodes were addressed only if pathologically involved. Bolus was generally considered over the skin corresponding with the nerve distribution. Post-operative concurrent chemo-radiotherapy was only used if extra-capsular nodal extension was present.

Post-operative follow-up consisted of regular outpatient review (quarterly until 3 years, then biannually until at least 5 years post-treatment) in conjunction with baseline and serial MR neurography for surveillance (biannually until 3 years, then annually to 5 years). Follow-up was taken from the date of surgery until date of last follow-up or date of death. Recurrence was classified as local (further sub-classified as peripheral at skin or central at meninges/ brain/brainstem), regional (nodal) or distant metastasis. Local recurrence was defined as either an in-field, or out-field of radiotherapy.

The primary outcomes measured were loco-regional control (LRC), recurrence-free survival (RFS, any recurrence), disease-specific survival (DSS, death from disease) and overall survival (OS, death from all causes). Variables assessed included age, gender, nodal involvement, nerve(s) involved, single/multiple nerves involved, disease zone, margin status, PORT, salvage versus definitive intent and tumor differentiation. Since there were only two patients with zone 3 disease, zone 2 and 3 were combined for analysis. Crude survival probabilities were estimated and plotted using the Kaplan-Meier technique and analysis undertaken to assess for significant associations with the variables detailed above. A p value of ≤ 0.05 was deemed statistically significant. Analyses were conducted using SAS software Version 9.2 (SAS Institute Inc. Cary, NC).

Results

Patient and primary tumor characteristics

Patient and primary tumor characteristics are described in Table 2. Mean age at the start of treatment for clinical PNI was 60 years (range 34-91 years), and the overall male-to-female ratio was approximately 4:1. Median follow-up period following surgery was 50 months (range 9-151 months).

All tumors with PNS to the skull base are staged as T4 however as most cases present some time after the primary has been excised we assessed the primary cutaneous SCC. Of these, 60% had an obvious primary and the majority were staged as T2 (40%, 20/50). 12% of patients presented with PNS having had no cutaneous primary tumor (6/50, T0). In 28% of patients the primary tumor was unassessable (TX) due to either: (i) incomplete/missing pathology reports or cutaneous malignancies treated externally without formal histological diagnosis (i.e. cryotherapy, laser or shave excision through primary care provider); or (ii) the exact primary index lesion was uncertain as multiple cutaneous malignancies were present in the region of interest.

The frequencies of all known primary sites are detailed in Table 2. The cheek was the most common location of a cutaneous primary (20%). In 28% of patients, the location of the primary was unknown yet the approximate location of certain TX primary tumors was known and therefore included. Of the patients treated with surgery for the primary tumor (34 patients), 12 had involved margins, 8 had close margins, 11 had clear margins and 3 had unclear margin status. Of the patients with a known primary tumor, 63.3% had incidental PNI reported. From the histopathology reports of primary tumors that included a measurement of involved nerve diameter (n = 12), the maximal diameter ranged from 0.03 mm – 0.9 mm (median 0.2 mm).

Assessment

The features of perineural spread are described in Table 3. MR neurogram was performed in 96% (48/50) and was positive for PNS in 95.8% (46/48). Two patients were assessed with computed tomography only (CT) due to MRI contra-indications, and this was positive in one patient. All patients with clinically evident PNS of the trigeminal nerve at presentation had

disease evident on MR neurography (43/43). The extent of PNS was zone 1 in 32% (16/50), zone 2 in 60% (30/50) and zone 3 in 4% (2/50). Spinal nerve involvement is rare and not currently represented in the zonal classification system. Two patients with great auricular nerve involvement are included in this series.

There were two patients with negative MR neurography. One patient, who had a pre-auricular SCC with incidental PNI previously treated with surgery and post-operative radiotherapy, presented with a partial facial nerve palsy and no detectable PNS on MR neurography. The facial nerve branch was 0.5 mm diameter on histopathology. The second patient presented with a parotid mass and local dysaesthesia, and a past history of a cheek SCC. Great auricular nerve PNS was detected intra-operatively and confirmed on histopathology (nerve diameter 1 mm), yet disease was not detectable on MR neurography.

94% of patients were clinically staged as N0 at presentation. 4% (2/50) were staged N1 and 2% (1/50) staged N2 pathologically. All patients were classified as M0. Eighteen patients (36%) presented with a subcutaneous tumor mass overlying or adjacent to the involved cranial nerve exit foramina. The majority of these were in the V_1 or V_2 distribution yet masses were also detected under the pre-auricular skin.

Treatment

All patients underwent en-bloc surgical resection of involved nerve(s) with curative intent (for approaches see Table 4).[6,10,13] 28% received prior treatment for perineural spread (surgery and/or radiotherapy) and were treated as salvage intent in this series. 5 patients (10%) underwent a neck dissection: 3 for apparent clinical N1 disease or greater (confirmed pathologically); 1 to permit access for reconstruction (N0); and 1 due to clinical suspicion (clinical N0, pathological N2b). 32% (16/50) of patients required an orbital exenteration for V_1 involvement.

There were no peri-operative deaths. Surgical complications included: free-flap failure requiring return to theatre (*n* = 1), deep-vein thrombosis (*n* = 1), extradural hemorrhage

requiring evacuation in theatre (*n* = 1), CSF leak treated with lumbar drain (*n* = 1), and wound infection (*n* = 1) treated with washout and antibiotics. In addition, one patient sustained an intra-operative myocardial infarction necessitating a change in reconstruction plan (undertaken with local flap instead of free flap). This patient developed peri-operative pneumocephalus and a CSF leak with poor neurological recovery requiring rehabilitation, and subsequently died from pneumonia 9 months post-treatment. Also, one patient developed an oro-antral fistula after a sub-labial approach to V_2 and PORT, and had successful local flap repair.

Clear central nerve margin was obtained in 35 patients (70%), and 5 patients (10%) had close margins (i.e. < 5 mm clearance). Two patients required a two-stage operation to clear a nerve margin, whilst one patient required a three-stage operation. Clearance of potential peripheral nerve margin in skin was not pursued due to the risk of disfigurement, and PORT was relied upon for treatment of potential peripheral nerve distribution spread.

The detail of nerves involved is included in Table 3. V_2 was the most common nerve (42%), followed by V_1 (36%) and VII (36%). The majority of patients had single nerve involvement (68%). Multiple nerve involvement occurred in 32%, with the most common scenario being VII and V_3 co-involvement. The great auricular nerve (C2 spinal nerve) was involved in 2 patients, with disease peripheral to the dorsal root ganglion.

94% (47/50) received PORT with dose range of 50-63 Gray in 25-30 fractions daily 5 days/week. Five patients received nodal irradiation for regional nodal disease present on histopathology, and five patients elective nodal irradiation. Two patients who failed previous definitive RT were treated with salvage surgery and not offered further PORT. One died from disease after local recurrence 53 months post-treatment, and the other remains disease free 75 months post-treatment. One further patient with zone 1 disease initially not offered PORT due to age (91 years), subsequently developed subcutaneous peripheral recurrence 7 months later which was treated with salvage surgery and local PORT. This patient remains disease free 30 months since last treatment. Complications following PORT included wound

breakdown (*n* = 2), radionecrosis (*n* = 4; 3 affecting bone, 1 affecting anterior temporal lobe), corneal irritation necessitating orbital exenteration (*n* = 2) and visual impairment (radiation microangiopathy, *n* = 2) treated conservatively. One patient received chemotherapy (cisplatin) for nodal disease with extra-capsular extension.

Outcomes

OS at 5-years was 64% with 14 deaths in this series (see Figure 1). 10 patients died from disease, with DSS at 5-years of 75% (see Figure 2). Mean time to death from disease was 39 months (range 10-90 months; median 30 months). The ultimate cause of death was predominantly central failure (12%), none being in the brainstem, with composite peripheral failure in 4% and distant metastasis in 4% (see Table 5).

Patterns of recurrence are described in Table 5. RFS at 5-years was 62% (see Figure 3). There were 18 patients with recurrence of disease, and 6 patients had a second recurrence. Mean time to any recurrence was 24 months (range 4-75 months; median 21 months), with 81% occurring within 4 years and 95% within 5 years post-treatment. Recurrence was significantly associated with worse OS (p = 0.002). Local recurrence was the most common pattern, particularly peripheral in-field (14%). Three patients had central recurrence of disease (two with simultaneous peripheral and central recurrence), and all died from disease. One patient recurred with regional nodal disease (on the outer edge of the treatment field) and one recurred with local, regional and distant disease.

LRC at 5-years was 62% (see Figure 4), and successful surgical salvage of loco-regional recurrence was achieved in 33% (6/18). Two patients had out-of-field local recurrence on the contralateral side with eventual central failure (one at 75 months post-treatment, possibly representing a second yet unknown primary). One patient developed out-of-field loco-regional recurrence at 20 months post-surgery in the distal branches of V_2 and V_3, and following salvage surgery remains alive and disease-free at 118 months since last treatment.

RFS at 5-years by zonal disease extent demonstrated a significant difference when zone 1 (88%) was compared to zone 2 and 3 combined (51%, p = 0.05, see Figure 5). DSS at 5-years by zonal disease extent was 93% for zone 1 disease and 73% for zone 2 and 3 combined (p = 0.17). OS at 5-years by zonal disease extent was 75% for zone 1 disease and 63% for zone 2 and 3 combined (p = 0.2). Age, gender, nodal involvement, nerve involved, single versus multiple nerves involved, PORT, salvage versus definitive intent, and tumor differentiation were not associated with recurrence or survival. Margin status did not demonstrate a significant association with recurrence or survival, yet a trend towards significantly better overall survival was evident when patients with clear/close margins were compared to those with involved margins (p = 0.13; see Figure 6).

Discussion

This case series details the outcomes of patients with perineural spread from CSCCHN treated with surgery and PORT. This treatment approach offers patients a reasonable survival benefit with a limited rate of complications. This is contingent on careful pre-operative planning, including appropriate imaging, and treatment within a specialized multidisciplinary unit.

The most common location of primary tumor was the cheek, and V_2 disease extending to zone 2 is the most common site and extent of clinical PNI. Almost 40% of known primary tumors did not demonstrate PNI, and this may reflect the inherent difficulties in detecting PNI in an asymptomatic patient.[14] Importantly, the absence of either PNI in a primary tumor or an obvious index lesion does not exclude a patient from having clinical PNI, and can lead to diagnostic delays as the symptoms and signs may be wrongly attributed to Bell's palsy or trigeminal neuralgia.[15]

The prognostic significance of nerve diameter in the primary tumour remains unclear, yet it has been proposed that a diameter ≥ 0.1 mm is associated with aggressive disease.[16,17] Standardized pathology reporting to include all high-risk features of cutaneous malignancies is important to permit accurate staging of each primary and to guide appropriate adjuvant

treatment. Only 12/30 pathology reports of primary tumours included an involved nerve diameter measurement (median 0.2 mm; range of 0.03 - 0.9 mm), and robust analysis in this study is therefore not possible.

MR neurography compliments all aspects of patient management from diagnosis and treatment planning through to follow-up and surveillance. MR neurography is useful for disease staging with the zonal classification system, which in turn guides surgical planning and resection extent and should be offered to all eligible patients. Of note, all patients in this series with V nerve involvement had positive MR neurography. The two cases in this series with MR-negative disease represented either rare disease (one patient with great auricular nerve involvement) or early disease (one patient with partial VII involvement in a previously irradiated parotid bed).

Some centers report imaging-negative PNS at rates of 22-47% and this may reflect the use of unfocussed whole-brain MRI or an absence of disease.[3,18] In our experience imaging-negative disease in a symptomatic patient is uncommon as evidenced by 94% of patients in this series being imaging-positive. This is enhanced with the use of 3T MRI with neurography protocol interpreted by a skull base radiologist, with 95.8% being positive. Imaging-positive disease in an asymptomatic patient is rare, and may warrant nerve biopsy prior to large-scale resection. CT or CT/PET imaging is recommended if MRI is contra-indicated but lacks sensitivity.

The rate of regional nodal involvement in patients with clinical PNI is estimated at approximately 9-16%.[4,11,19] The rate of regional nodal disease in this series was low at 10%, and only two patients had regional nodal recurrence (one as first recurrence, one as a second recurrence). This is consistent with the premise that PNS is likely a function of both tumor biology and proximity to nerve, and is a unique form of metastasis largely independent of lymphatic metastasis. Some centers advocate elective nodal irradiation due to a risk of subclinical disease.[20] Presently at our institution, nodal irradiation is generally only offered if nodal disease is evident clinically or pathologically. A neck dissection would be undertaken for the same reason, or if required for reconstruction.

Surgical resection for perineural spread is typically only undertaken with curative intent and the surgical approach to PNS is dictated by the nerve(s) involved as outlined in Table 4.[13] This is followed by PORT in all eligible patients. Surgery is offered to patients with zone 1 and zone 2 disease, whilst surgery for zone 3 disease is considered on a case-by-case basis. Resection of bulky zone 3 disease has the potential to cause tumor seeding and dissemination via the CSF and at our institution patients with zone 3 disease are generally offered radical or palliative radiotherapy.

Complications from surgery were limited and related to the large-scale nature of the surgery required for disease clearance. Importantly, there were no peri-operative deaths. Radiotherapy was also associated with limited treatment effects, however two patients required an orbital exenteration for delayed eye complications (prior to the use of IMRT). At our institution, it is now largely routine to undertake an orbital exenteration for V_1 disease approximately 1 cm beyond the supraorbital notch. This is not only performed for disease clearance, but also since the sequelae from the necessary PORT to the globe are severe. In patients with V_2 and/or V_3 involvement requiring ganglion resection, an attempt is made to preserve corneal sensation by preserving the V_1 component of the ganglion. However, in those patients where the whole ganglion was resected to obtain a clear margin, no patient subsequently experienced ophthalmic issues necessitating ongoing management.

A summary of recent outcome data for imaging positive disease is outlined in Table 6. Previous studies have limited applicability as many have heterogeneous patient cohorts treated with different modalities.[3,4,11,12] This series demonstrates that long-term survival is achievable in patients treated with appropriate surgery and PORT, with almost 65% of patients alive at 5 years. Improved outcomes including 75% survival from disease at 5 years are evident, compared to previous reports of 58-65% in patients with BCC and SCC receiving radiotherapy with limited surgery.[4,19] Similarly, when compared to another series with a similar patient cohort from the state of Queensland and limited surgery, RFS was 62% in our series compared to 39%.[11]

The median time to death from disease in this series was 30 months. One patient died from contralateral spread of disease at 90 months follow-up, 15 months after it was detected. This reflects the often slow spreading nature of PNS, and the inherent ability of tumor to spread to contralateral nerve branches.[21] Local recurrence is the most common mode of treatment failure. 95% of all recurrences occurred within 5 years of treatment, reiterating the need for long-term follow-up. At our institution, patients are followed up for at least 5 years.

Recurrence was also noted to be significantly associated with worse overall survival outcome. This reflects both aggressive tumor biology and the limitations in salvage options following treatment failure, however up to a third of patients were salvaged with surgery in this series. Of the 3 patients who recurred centrally none occurred in the brainstem, suggesting that the central spread of disease was controlled by appropriate surgery and targeted PORT. The zonal extent of disease was shown to be significantly associated with risk of recurrence, with RFS at 5-years of 88% in zone 1 and 51% when zone 2 and 3 were combined. These findings demonstrate that improved disease control can be achieved with timely diagnosis and management.

Conclusion

This case series demonstrates improved outcomes with relatively low morbidity for patients with CSCCHN with clinical PNI treated with surgical resection and PORT. Careful surgical candidate selection, pre-operative planning with MR neurography and management through a specialized multidisciplinary team is recommended. Early intervention is paramount and dependent on a timely diagnosis, and this is expected to improve with advancing imaging technology and increasing clinician and patient awareness of this disease.

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Figure legends

Figure 1. Kaplan-Meier curve of overall survival for patients with perineural spread from cutaneous SCC treated with surgical resection and post-operative radiotherapy.

Figure 2. Kaplan-Meier curve of disease-specific survival for patients with perineural spread from cutaneous SCC treated with surgical resection and post-operative radiotherapy.

Figure 3. Kaplan-Meier curve of recurrence-free survival for patients with perineural spread from cutaneous SCC treated with surgical resection and post-operative radiotherapy.

Figure 4. Kaplan-Meier curve of locoregional control for patients with perineural spread from cutaneous SCC treated with surgical resection and post-operative radiotherapy.

Figure 5. Kaplan-Meier curve of recurrence-free survival by zonal disease extent for patients with perineural spread from cutaneous SCC treated with surgical resection and post-operative radiotherapy ($p= 0.05$). Zone 1 has been compared to Zone 2 and Zone 3.

Figure 6. Kaplan-Meier curve of overall survival for patients with perineural spread from cutaneous SCC treated with surgical resection and post-operative radiotherapy by margin status comparing clear/close and involved margin ($p = 0.13$).

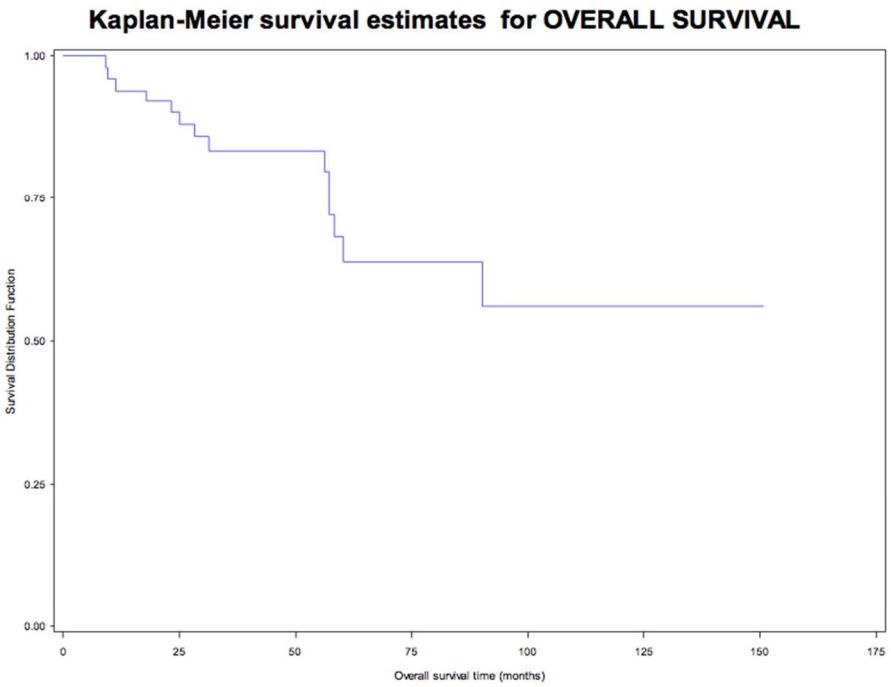

Figure 1
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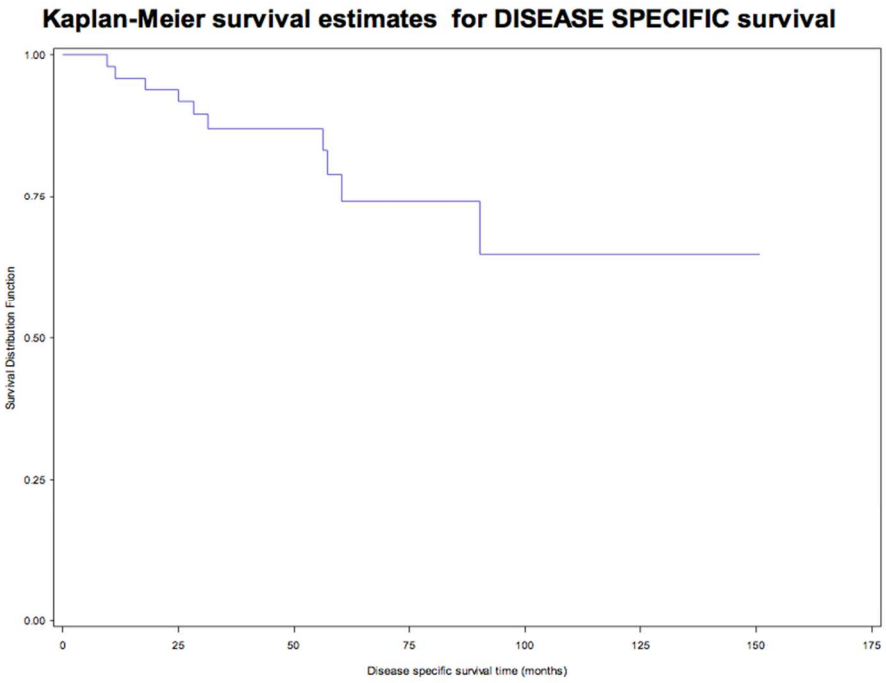

Figure 2
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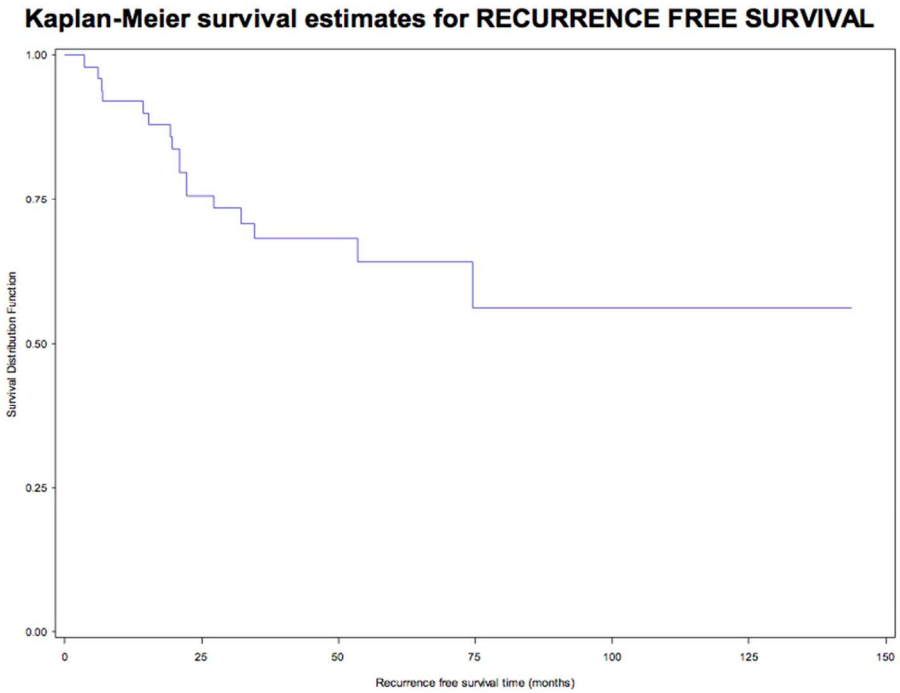

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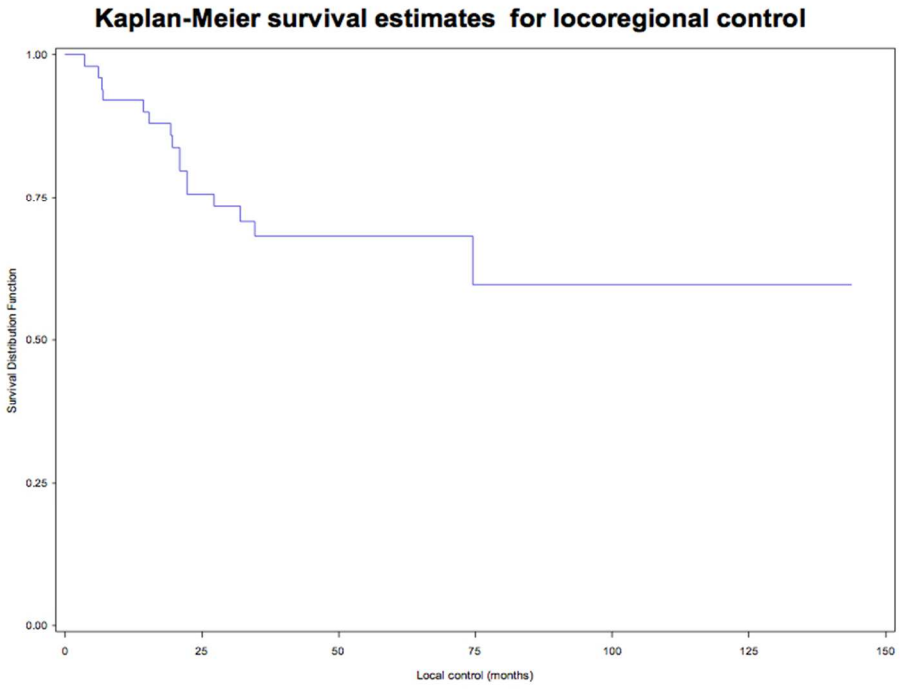

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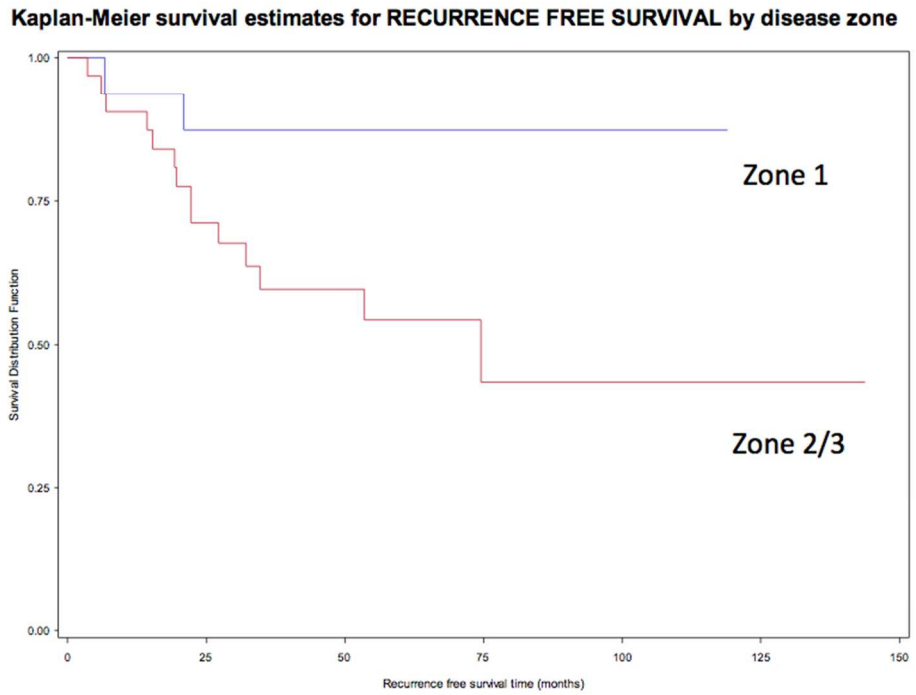

Figure 5
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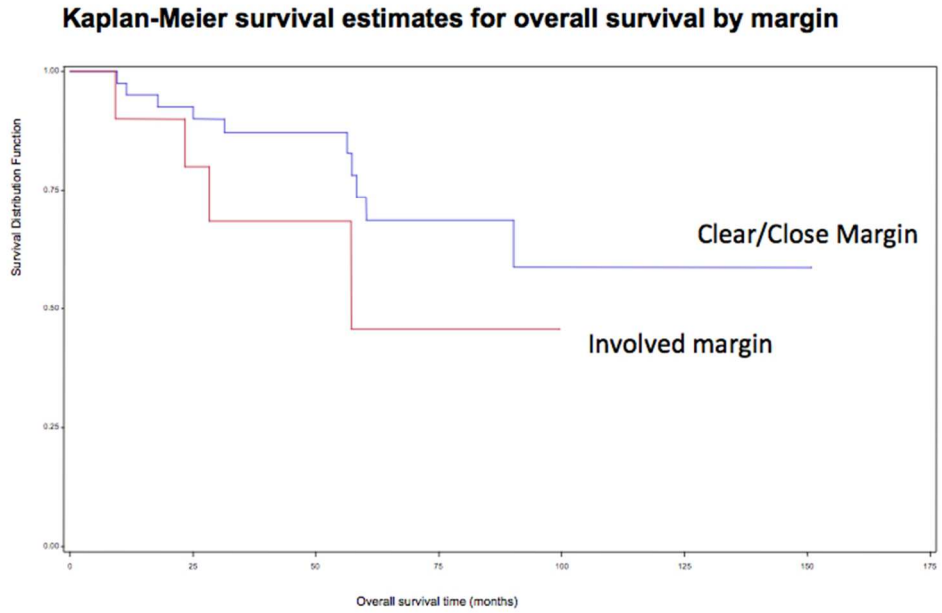

Figure 6
275x177mm (72 x 72 DPI)

Table 4. Surgical management of perineural spread (adapted from Panizza & Warren[13])

Nerve	Zone 1	Zone 2	Zone 3
V1	*From the periphery to the superior orbital fissure*	*from Zone 1 to the Gasserian ganglion cistern*	*proximal to the Gasserian ganglion into the cisterns or brainstem*
V2	*From the periphery to the external aperture of the foramen rotundum*	*from Zone 1 to the Gasserian ganglion cistern*	*proximal to the Gasserian ganglion into the cisterns or brainstem*
V3	*From the periphery to the external aperture of the foramen ovale*	*from Zone 1 to the Gasserian ganglion cistern*	*proximal to the Gasserian ganglion into the cisterns or brainstem*
VII	*From the periphery to the external aperture of the stylomastoid foramen*	*from Zone 1 up to the lateral end of the internal auditory canal, including the Geniculate ganglion and the labyrinthine segment*	*proximal to the lateral end of the internal auditory canal, into the cisterns or brainstem*

Table 1
297x209mm (150 x 150 DPI)

Table 2. Patient and primary tumor features

Patient and primary features	No. of patients (%)
Age	
Mean	60 years
Range	34-91 years
Gender	
Male	41 (82)
Female	9 (18)
Follow-up	
Median	50 months
Range	9 - 151 months
Primary tumor classification (AJCC)	
TX	14 (28)
T0	6 (12)
T1	10 (20)
T2	20 (40)
T3	0 (0)
T4	0 (0)
Primary site	
Unknown	14 (28)
Cheek	10 (20)
Nose	8 (16)
Temple	7 (14)
Forehead	4 (8)
Pre-auricular	4 (8)
Post-auricular	1 (2)
Ear	1 (2)
Eyelid	1 (2)
Primary margins (if treated)	
Clear	11 (32)
Close	8 (24)
Involved	12 (35)
Unknown	3 (9)
Incidental PNI in primary tumor	
No	11 (36.6)
Yes	19 (63.3)
Nerve diameter (no. of patients=12; range)	0.03mm - 0.9mm

209x297mm (150 x 150 DPI)

Table 3. Features of perineural spread

Feature of perineural spread	No. of patients (%)	
Classification of perineural spread (AJCC)	Clinical	Pathological
TX	14 (28)	14 (28)
T0	6 (12)	6 (12)
rT1	10 (20)	10 (20)
T2	1(2)	1(2)
rT2	19 (38)	19 (38)
N0	47 (94)	46 (92)
N1	2 (4)	2 (4)
N2	1 (2)	2 (4)
M0	50 (100)	50 (100)
M1	0 (0)	0 (0)
Imaging diagnosis		
MR neurogram: PNS positively identified	46/48 (95.8)	
CT: PNS positively identified	1/2 (50)	
Imaging zonal extent		
Zone 1	16/50 (32)	
Zone 2	30/50 (60)	
Zone 3	2/50 (4)	
N/A*	2/50 (4)	
Nerve involved		
Single nerve	34 (68)	
Multiple nerves	16 (32)	
V1	18 (36)	
V2	21 (42)	
V3	14 (28)	
VII	18 (36)	
VII and V3	12 (24)	
Great auricular nerve	2 (4)	
Neck dissection		
Yes	5 (10)	
No	45 (90)	
Nerve margin status		
Clear	35 (70)	
Close (<5mm)	5 (10)	
Involved	10 (20)	
Tumor differentiation		
Well	3 (6)	
Moderate	22 (44)	
Poor	22 (44)	
Undifferentiated	3 (6)	
Post-operative radiotherapy		
No	3 (6)	
Yes	47 (94)	
Dose (range)	50-63 Gray	
Fractionation (range)	25-30 Fractions	

Footnotes: *Two patients with great auricular nerve involvement were N/A as spinal nerves are not currently provided for in the zonal system. Abbreviations: perineural spread (PNS).

Table 3
209x297mm (150 x 150 DPI)

Table 4. Surgical management of perineural spread (adapted from Panizza & Warren[13])

Nerve involved	Zone 1	Zone 2	Zone 3
V1	to supraorbital notch: resect nerve; approx 1 cm beyond notch: orbital exenteration +/- superior orbital fissure	include ganglion via a lateral craniotomy or transorbital approach	XRT alone; consider subtotal resection
V2	infraorbital nerve resection + pterygopalatine fossa contents + maxillary division via transfacial (endoscopic or sublabial)	include ganglion via an anterior or lateral craniotomy approach	XRT alone; consider subtotal resection
V3	ascending mandibulectomy + infratemporal fossa contents via combined superior and inferior approach	include ganglion via a lateral craniotomy	XRT alone; consider subtotal resection
VII	radical parotidectomy + mastoid segment of VII	include ganglion via temporal bone resection	XRT alone; consider surgery: geniculate ganglion + surrounding dura + contents of IAM
VII + V3	radical parotidectomy + ascending mandibulectomy + infratemporal fossa contents	include ganglia via lateral approach and temporal bone resection	XRT alone; consider subtotal resection

Table 4
209x297mm (150 x 150 DPI)

Table 5. Patterns of recurrence and failure

First recurrence pattern	Total no. of patients (%)	% of recurrences (no. of patients)
Local in-field (total)	10 (20)	56% (10/18)
Peripheral	7 (14)	39% (7/18)
Central	1(2)	6% (1/18)
Peripheral and central	2 (4)	11% (2/18)
Local out-of-field (peripheral)	6 (12)	33% (6/18)
Regional nodal in-field	0 (0)	0% (0/18)
Regional nodal out-field	1 (2)	6% (1/18)
Distant metastasis	0 (0)	0% (0/18)
Local in-field, regional out-field and distant	1 (2)	6% (1/18)
Failure pattern		
Peripheral failure	2 (4)	
Central failure (all non-brainstem)	6 (12)	
Distant metastasis	2 (4)	
Death from disease	10 (20)	
Death from other causes	4 (8)	

Table 5
297x209mm (150 x 150 DPI)

Table 6. Summary of 5-year outcomes for perineural spread

Study	Institution	No. of patients	Overall survival	Disease-specific survival	Recurrence-free survival	Loco-regional control
Current study	Princess Alexandra Hospital, Brisbane 2000-2011	50 (SCC)	64%	75%	62%	62%
Balamucki et al.[18] (imaging-positive cohort)*	University of Florida, Gainesville 1965-2009	54 (SCC 91%, BCC 9%)	50-52%	58-65%	47-54%	47-54%
Lin et al.[11]	Royal Brisbane Hospital, Brisbane 1991-2004	44 (SCC)	-	-	39%	-

*Balamucki *et al.* subdivided imaging-positive patients into either minimal/moderate peripheral disease or central/macroscopic disease.[18]

Table 6
297x209mm (150 x 150 DPI)