

ORIGINAL RESEARCH

# Keratinocyte cancer with incidental perineural invasion: A registry analysis of management and 5-year outcomes

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**ABSTRACT**

**Background/Objectives:** Perineural invasion within keratinocyte cancer is a hallmark of tumour aggression, and a definitive treatment paradigm for this condition remains undetermined. Our aim was to investigate the treatment and outcomes of keratinocyte cancer with incidental perineural invasion within two skin cancer databases to refine treatment protocols.

**Methods:** We retrospectively assessed the Queensland Perineural Invasion Registry for surgery, histopathology, adjuvant radiotherapy and recurrence of keratinocyte cancer five years post-definitive treatment. We also reviewed the Princess Alexandra Hospital Head and Neck clinical perineural invasion database, specifically looking at surgical margins and adjuvant radiotherapy of cutaneous squamous cell carcinoma (cSCC) with incidental perineural invasion in the primary lesion.

**Results:** There was no recurrence at 5 years in the Perineural Invasion Registry. Basal cell carcinoma (BCC) lesions with nerves <0.1 mm were more commonly treated with surgery alone, compared to lesions with nerves ≥0.1 mm which were offered adjuvant radiotherapy. Of the total BCC lesions with incidental perineural invasion, those with perineural margins ≥5 mm and peripheral tumour margins ≥3 mm were predominantly treated with surgery

alone. Eighty-nine per cent of cSCC lesions with incidental perineural invasion were treated with surgery and adjuvant radiotherapy.

**Conclusion:** Surgery alone is suitable for BCC lesions with incidental perineural invasion. The majority of BCC lesions achieved ≥5 mm perineural and ≥3 mm peripheral tumour margins. Future research can guide if adjuvant radiation is required for BCC with perineural invasion. The treatment of cSCC with incidental perineural invasion with surgery alone remains undetermined.

**Key words:** adjuvant radiotherapy, basal Cell Cancer, keratinocyte cancer, perineural invasion, squamous cell cancer.

**INTRODUCTION**

Keratinocyte cancer comprises of basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC).<sup>1</sup> The existence of perineural invasion in keratinocyte cancer is an aggressive characteristic, one which significantly impacts prognosis.<sup>2</sup> However, the incidence of tumours which exhibits perineural invasion is low.<sup>2</sup> The literature has given considerable importance to features which increase the risk of perineural invasion, and the majority of reports define this risk to be in lesions located in the head and neck, being of male gender, increasing tumour size, recurrence of tumour and poor histological differentiation.<sup>3-5</sup> The vast majority of patients who have tumours with perineural invasion are asymptomatic at diagnosis and are diagnosed by the histopathologist.<sup>2</sup> A small proportion however present with perineural invasion which is either the presentation of clinical symptoms (e.g. dysaesthesia or cranial nerve deficits) or detected on magnetic resonance imaging.<sup>2,3-5</sup>

Pathological reporting for incidental perineural invasion within keratinocyte cancer lesions plays a pivotal role in determining treatment. Unfortunately, variations in

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reporting exist, which can lead to under-treatment and ultimately progression or recurrence. The current treatment processes are also not standardised and are multimodal, including surgical excision or Mohs micrographic surgery (MMS) with or without adjuvant radiation.<sup>2,5-9</sup>

The Perineural Invasion Registry is an ongoing project co-ordinated by the Queensland Perineural Invasion Registry Group, located at the Princess Alexandra Hospital.<sup>1</sup> The registry is an up-to-date database with information on the management, outcomes and surveillance of patients diagnosed with keratinocyte cancer with incidental perineural invasion. Its purpose is to identify which therapy leads to improved disease-free survival for incidental perineural invasion in keratinocyte cancer and hence provide a definitive and dependable treatment paradigm.

This study also explores the treatment of cSCC lesions with incidental perineural invasion which despite therapy progressed to clinical perineural invasion and subsequently were treated at the Princess Alexandra Hospital, Department of Otolaryngology and Head and Neck Surgery.

## MATERIALS/METHODS

Ethics approval for this study was granted from the University of Queensland Ethics Committee and Princess Alexandra Hospital Human Research Ethics Committee (2005/197).

### Queensland Perineural Invasion Registry Database

The Queensland Perineural Invasion Registry currently encompasses 522 patients with keratinocyte cancers with documented incidental perineural invasion. The data were collected between 2013 and 2017 from three Dermatology and Plastic Surgery Practices within the Brisbane metropolitan area. We conducted a prospective analysis of the data set looking at the treatment, histopathology and five-year outcomes. The inclusion criteria consisted of cases with histopathologically confirmed perineural invasion associated with keratinocyte cancer lesion who underwent definitive treatment and a minimum of five-year surveillance.

We stratified the analysis into two groups, BCC and cSCC. Histopathology information on nerve size (categorised into  $\geq 0.1$  and  $< 0.1$  mm), perineural margins (peripheral and deep), as well as tumour margins (peripheral and deep) and the use of adjuvant radiotherapy was extracted. The peripheral and deep margins were grouped into three main measures:  $< 3$  mm, 3-4.9 and  $\geq 5$  mm.

In the Perineural Invasion Registry, a number of BCC lesions were removed using MMS, and therefore, a histopathological report from a pathologist was not available. These BCC lesions were assigned to the  $\geq 5$  mm perineural and tumour margin category. Furthermore, lesions that had undergone re-excision and were reported to have clear margins or lesions which had a report stating clear margins by the histopathologist were also assigned to this category.

### Princess Alexandra Hospital Head and Neck Database

The Princess Alexandra Hospital Otolaryngology Department maintains a data set which currently holds over 200 keratinocyte cancer lesions with clinical perineural invasion. A more detailed description of the database is published in Warren *et al* 2016.<sup>10</sup> These patients were treated within the Otolaryngology Department at the Princess Alexandra Hospital for keratinocyte cancer with clinical perineural invasion between 1998 and 2015. The histopathology details of the primary lesions which displayed incidental perineural invasion were assessed for histology subtype, perineural invasion, nerve size, perineural margins (peripheral and deep), tumour margins (peripheral and deep) and the use of adjuvant radiotherapy. Primary lesions with incidental perineural invasion were treated at various non-specialist clinics, which preceded the symptoms of clinical perineural invasion by a median time of 16 months.

### Statistical analysis

The data were imported into Excel spreadsheets and analysed using the 2017 version of IBM SPSS statistical software. Confidence interval (CI) for nerve size and surgical treatment +/- adjuvant radiation was calculated using normal approximation method. The SPSS program was utilised to determine whether there were any associations or significant relationships between the aforementioned nominal variables via cross-tabulations and Fisher 2-sided exact test.

## RESULTS

### Queensland Perineural Invasion Registry Database

Of the 522 patients in the Perineural Invasion Registry, 163 BCC and 28 cSCC lesions were available for analysis. A total of 34 (21%) BCC lesions were excised using MMS and the remaining 79% with surgical excision. No cSCC lesions were removed using Mohs surgery. No keratinocyte cancer lesions with incidental perineural invasion in this analysis recurred at a minimum of 5 years following definitive therapy.

In the BCC group, 74% of lesions with perineural invasion had nerve size  $< 0.1$  mm and the remaining 26% lesions involved nerves  $\geq 0.1$  mm. Eighty-seven per cent of BCC lesions with nerves  $< 0.1$  mm were managed with surgery alone whilst 13% were treated with surgery and adjuvant radiotherapy. Thirty-eight per cent of BCC lesions with nerve size  $\geq 0.1$  mm were treated surgically, compared to 62% of lesions treated with surgery and adjuvant radiotherapy (Table 1). Overall, BCC with perineural invasion in nerves  $\geq 0.1$  mm was more than twice as likely as those  $< 0.1$  mm to be treated with adjuvant radiation as opposed to surgery alone (Odd Ratio (OR) 2.5, 95% CI 1.5-3.4).

Of 163 BCCs with perineural invasion, 44 (27%) had peripheral perineural margins  $\geq 5$  mm, 67 (42%) had

margins 3-4.9 mm, and the remainder 52 (31%) had margins <3 mm. We found 12 (7%) of BCCs with perineural invasion had deep perineural margins  $\geq 5$  mm, 40 (25%) had 3-4.9 mm margins and 111 (68%) had margins <3 mm. There were 58 (35%) of BCC lesions with perineural invasion that had peripheral tumour margins  $\geq 5$  mm, 68 (42%) with margins 3-4.9 mm and 37 (23%) with margins <3 mm. We found 28 (17%) of BCC lesions with perineural invasion had deep tumour margins  $\geq 5$  mm, 38 (23%) with 3-4.9 mm margins and 97 (60%) had margins <3 mm (Table 2). As expected, we observed significant differences in the use of radiation therapy by excision margins. Of all excision margins, we found that 22-50% of those with margins <3 mm were treated with adjuvant radiation, compared with 10-37% of those with margins 3-4.9 mm, and 0-31% of those with excision margins  $\geq 5$  mm ( $P < 0.001$ ), see Table 2.

In the group of cSCC patients with perineural invasion ( $n = 28$ ), 17 lesions involved nerve size <0.1 mm and 11 lesions involved nerves  $\geq 0.1$  mm. Following surgical excision, 89% of all cSCC lesions with perineural invasion received adjuvant radiotherapy. The three cSCC lesions with perineural invasion that did not receive adjuvant radiation all involved nerves  $\leq 0.1$  mm; all patients were offered adjuvant radiotherapy but declined. None of these three cSCC lesions with incidental perineural invasion recurred after 5 years despite declining adjuvant radiotherapy. These lesions had perineural margins of  $\geq 2.5$  mm and tumour margins  $\geq 4$  mm.

**Table 1** BCC with incidental perineural invasion showing margins and surgery +/- adjuvant radiation

| Margin category | Treatment                    | Peripheral PNI margins | Deep PNI margins | Peripheral tumour margins | Deep tumour margins |
|-----------------|------------------------------|------------------------|------------------|---------------------------|---------------------|
| <3 mm           | Surgery                      | 26 (50)                | 32 (29)          | 20 (54)                   | 76 (78)             |
|                 | Surgery + Adjuvant radiation | 26 (50)                | 79 (71)          | 17 (46)                   | 21 (22)             |
|                 | Total                        | 52 (100)               | 111 (100)        | 37 (100)                  | 97 (100)            |
| 3-4.9 mm        | Surgery                      | 51 (76)                | 30 (75)          | 61 (90)                   | 24 (65)             |
|                 | Surgery + Adjuvant radiation | 16 (24)                | 10 (25)          | 7 (10)                    | 14 (37)             |
|                 | Total                        | 67 (100)               | 40 (100)         | 68 (100)                  | 38 (100)            |
| $\geq 5$ mm     | Surgery                      | 44 (100)               | 12 (100)         | 40 (69)                   | 21 (75)             |
|                 | Surgery + Adjuvant radiation | 0 (0)                  | 0 (0)            | 18 (51)                   | 7 (25)              |
|                 | Total                        | 44 (100)               | 12 (100)         | 58 (100)                  | 28 (100)            |

**Table 2** BCC with incidental perineural invasion showing nerve size and surgery +/- adjuvant radiation

| Treatment                    | Nerve < 0.1 mm | Nerve $\geq 0.1$ mm |
|------------------------------|----------------|---------------------|
| Surgery                      | 105 (87)       | 16 (38)             |
| Surgery + Adjuvant radiation | 16 (15)        | 26 (62)             |
| Total                        | 121 (100)      | 42 (100)            |

## Princess Alexandra Hospital Head and Neck Database

An initial analysis in 2015 of 120 keratinocyte cancer lesions with perineural spread identified only two BCC (basosquamous subtype) tumours with clinical perineural invasion. Of 120 patients with cSCC clinical perineural spread, 76 (63%) had identifiable histology of primary lesions and 42 (55%) of the 76 cSCC lesions had incidental perineural invasion within the primary specimen. A total of 33 (79%) of the 42 cSCC lesions had involved or close peripheral margins (<5 mm). Of the 33 cSCC lesions with involved or close margins, 60% of patients underwent adjuvant radiotherapy following surgery. A total of 9 of the 42 lesions (21%) were reported as having clear ( $\geq 5$  mm) peripheral tumour margins. Only two of the nine patients with clear margins received adjuvant radiotherapy following definitive surgical treatment. Five of the nine lesions deemed clear on the histopathology failed to mention the size of the nerve involved. Of the remainder, one was reported as <0.1 mm and three lesions had nerve size  $\geq 0.1$  mm. One histopathology report included the perineural margins and found the nerve to be 0.5 mm to the peripheral margin.

## DISCUSSION

Keratinocyte cancer is a prolific cancer in the fair skinned population. perineural invasion within keratinocyte cancer denotes a state of increased morbidity and mortality due to more aggressive tumour behavior.<sup>2-5</sup>

The Perineural Invasion Registry analysis demonstrates successful treatment modalities with no recurrence at 5 years.

The registry review identified that BCC lesions with incidental perineural invasion of nerves <0.1 mm were more common than BCC lesions with nerves  $\geq 0.1$  mm. In BCC lesions with incidental perineural invasion of nerves  $\geq 0.1$  mm, the predominant treatment was surgery followed by adjuvant radiotherapy. Comparison of all BCC lesions with incidental perineural invasion showed that perineural margins (peripheral and deep)  $\geq 5$  mm and peripheral tumour margins  $\geq 5$  mm were more commonly treated with surgery alone. Thirty-eight per cent of BCC lesions with perineural invasion of nerve size  $\geq 0.1$  mm treated with surgery alone did not recur within 5 years. However, we did not find a significant relationship between BCC lesions with nerves  $\geq 0.1$  mm and surgery without adjuvant radiotherapy. In the perineural invasion registry, the predominant treatment modality for cSCC with incidental perineural invasion was surgery and adjuvant radiotherapy. Three cSCC lesions from the perineural invasion registry were treated with surgery alone and demonstrated disease-free survival at 5 years.

The Princess Alexandra Hospital Head and Neck data set shows disease progression from incidental to clinical perineural invasion following surgical excision can occur even with tumour margins  $\geq 5$  mm and also after adjuvant

radiotherapy. In the Princess Alexandra Hospital database, the predominant keratinocyte cancer with clinical perineural invasion was cSCC (98%). The only BCC subtype to exhibit clinical perineural invasion was basosquamous.

Current literature supports consideration of post-operative adjuvant radiotherapy for all keratinocyte cancer lesions that display incidental perineural invasion. A number of reports on the type of surgical intervention necessary to achieve good treatment outcomes (>90% disease-free survival at 5 years) for BCC with incidental perineural invasion have indicated the use of MMS alone or standard surgical excision together with adjuvant radiotherapy.<sup>4-6</sup> Gupta *et al* postulated a management process for both keratinocyte cancer exhibiting incidental perineural invasion and cSCC with clinical perineural invasion. They classify BCC into low, moderate or high risk based on perineural invasion specific features that are associated with increased morbidity. This then follows with a treatment algorithm consisting of MMS or surgery and the use of adjuvant radiotherapy.<sup>5</sup> Gupta *et al* outline that definitive treatment for cSCC with incidental perineural invasion is with surgical resection and adjuvant radiotherapy. Separate to incidental perineural invasion, it is substantiated by Panizza *et al.*, and Warren *et al.*, that improved long-term survival is achieved in patients with clinical perineural invasion from cSCC following surgery and adjuvant radiotherapy. Miller *et al* described the terms intra-tumoural, peripheral and extratumoural perineural invasion. They also demonstrated a trend towards the histopathological extent of perineural invasion correlating with patient outcome.<sup>7</sup> This study supports the literature with histopathological features of perineural invasion and tumour margins being significant measures in determining patient outcomes at five years. However, to date there are no other studies looking at surgical margins and surveillance of patients up to five years with keratinocyte cancer and incidental perineural invasion.

The constraints of this study include low case numbers, with access to 322 patients in the registry only 163 BCC and 28 cSCC lesions met the follow-up criteria. The analysis required detailed histopathology, and given that 21% of BCC lesions were removed using MMS, these lesions were allocated into the  $\geq 5$  mm margin group for both tumour and perineural invasion. Given that the literature supports the use of MMS for BCC lesions with incidental perineural invasion, we presumed that clear margins were obtained.<sup>3-5</sup> Furthermore, lesions that had undergone re-excision or were deemed clear on the histopathology report were allocated to margins  $\geq 5$  mm, this may have affected the significance of the data within these allocations inaccurately. A further constraint is the variable pathology reports from different providers within Queensland who are now standardised to report on the presence or absence of perineural invasion but fail to report on other important prognostic features of perineural invasion.<sup>5</sup> A proportion of the histopathology reports in the study failed to contain all the relevant information on perineural margins and were thus not included in a margin category.

All primary keratinocyte cancer lesions with incidental perineural invasion from the Perineural Invasion Registry were referred for adjuvant radiotherapy. The decision to undergo adjuvant radiotherapy was then made between the radiation oncologist and the patient.

This analysis brings to light the accuracy and adequacy of the current tumour margins in keratinocyte cancer with incidental perineural invasion within the Perineural Invasion Registry. Due to the fact that there was no recurrence at five years within the data set, it raises the question of whether keratinocyte cancer with incidental perineural invasion is being overtreated. Surgical treatment with over-zealous margins in cosmetically or functionally important regions of the head and neck, together with the use of adjuvant radiotherapy, is not without morbidity. Thus, the establishment of the optimal surgical margins required in keratinocyte cancer with incidental perineural invasion as well as the addition of adjuvant radiotherapy will inevitably lead to improved overall patient outcomes, not only oncologically but also functionally and aesthetically.

As no recurrences were observed in Perineural Invasion Registry, we draw the conclusion that BCC lesions with incidental perineural invasion of nerve size  $< 0.1$  mm can be treated with surgical excision alone with perineural margins (peripheral and deep)  $\geq 5$  mm and peripheral margins  $\geq 5$  mm. It is difficult to substantiate the appropriate treatment of cSCC with incidental perineural invasion with such a low sample size within the perineural invasion registry. Perhaps there is a role for single modality treatment with appropriate margins for cSCC with incidental perineural invasion, but this would take careful consideration and further research. Hence, high-risk keratinocyte cancer with incidental perineural invasion may benefit from a multidisciplinary team assessment.

The Princess Alexandra Hospital Head and Neck data set analysis revealed that no BCC lesions demonstrated clinical perineural invasion, unless of basosquamous subtype. Perhaps we can also conclude that clinical perineural invasion is a disease characteristic manifested solely by squamous differentiation. It is important to highlight that despite other subtypes of BCC not being able to demonstrate significant and clinical PNS, the presence of perineural invasion in these tumours increases local recurrence.<sup>3,4,6,7</sup>

In future, standardised pathology reporting with tumour and perineural invasion parameters is crucial for similar prospective studies, given incidental perineural invasion is a disease state solely diagnosed by the histopathologist. Studies looking at other characteristics such as tumour size, histological differentiation and recurrence would augment the process in delineating best practice. Further research including prospective studies needs to be undertaken to establish the precise surgical margins for keratinocyte cancer with incidental perineural invasion with or without adjuvant radiotherapy to reduce morbidity and mortality.

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