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REVIEW ARTICLE

Management of squamous cell and basal cell carcinomas of the head and neck with perineural invasion

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ABSTRACT

Perineural invasion (PNI) occurring in non-melanoma skin cancers (NMSC) is associated with an increased risk of locoregional recurrence and reduced disease-free survival. This necessitates early and accurate diagnosis, appropriate risk-stratification and a clear management strategy. The diagnosis of PNI is based on careful clinical assessment, imaging and histopathology. Surgery, preferably with margin control, and definitive or adjuvant radiotherapy (ART) are established treatment strategies for PNI. Clinical uncertainty remains over the role of ART in incidental PNI. This review synthesises current literature to ascertain which clinicopathological features impart a higher risk to individuals with PNI in NMSC, in order to provide treatment algorithms, including the identification of patient subsets that are most likely to benefit from ART. This includes those with extratumoural PNI, involvement of larger-calibre nerves, tumour invasion beyond dermis, recurrent tumour or diffuse intratumoural spread. Patients with clinical PNI may be optimally managed by a multidisciplinary head and neck cancer service that is best placed to offer skull base surgery and intensity-modulated radiation therapy (IMRT). The management options presented are stratified by histological subtype and a new classification of PNI into low-risk, medium-risk and high-risk groups.

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INTRODUCTION

Perineural invasion (PNI) refers to tumour growth in or around a nerve.[1] It occurs by the contiguous spread of malignant cells along the potential space between a nerve and its surrounding sheath.[2] PNI occurs in less than 5% of all cutaneous malignancies.[3] It is more common among squamous cell carcinomas (SCC), involving 3–14% of cases, compared with 0.18% to 10% of basal cell carcinomas (BCC).[4]

The presence of PNI is significant in that it confers an increased risk of recurrence in both BCC and SCC and of the development of metastasis in SCC, and a poorer prognosis due to more aggressive tumour behaviour.[2] The risk of death from PNI is much less likely with BCC. This has led to

Abbreviations:

ART	adjuvant radiotherapy
BCC	basal cell carcinoma
CN	cranial nerve
CT	computed tomography
Hh	Hedgehog
IMRT	intensity-modulated radiation therapy
MMS	Mohs micrographic surgery
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NMSC	non-melanoma skin cancers
PNI	perineural invasion
RT	radiotherapy
SCC	squamous cell carcinoma
SLNB	sentinel lymph node biopsy

the inclusion of PNI in the updated 7th edition of the American Joint Committee on Cancer staging system for cutaneous SCC.[5] As illustrated in Table 1, the presence of PNI is one of the high-risk features that contribute to the upstaging of a T1 SCC to a T2 SCC.

The management of PNI commences with diagnosis through clinical assessment, imaging and histopathological review. This is followed by an evaluation of its neural distribution and extent, as well as consideration of other high-risk tumour features present.

Most consensus guidelines recommend its complete excision with microscopic control of margins, as the treatment of choice.[6] There remains, however, an increased risk of recurrence despite negative histological margins compared with tumours without demonstrable PNI.[7,8] This highlights a potential role for adjuvant radiotherapy (ART) to reduce locoregional recurrence, as has become standard treatment for high-risk non-cutaneous SCC of the head and neck.[9]

For cutaneous malignancies there remains clinical equipoise surrounding the role of ART in cases with PNI.[6] This review aims to explore clinically significant variables to assist in the risk-stratification of individuals with PNI in BCC and SCC of the head and neck and provide treatment strategies, including the identification of those that may benefit most from ART.

The evidence base for the management of PNI consists mainly of institutional observational cohort studies, with the inherent associated biases of such studies. Therefore, our recommendations are based on this level of evidence in combination with expert opinion.

Table 1 Staging for cutaneous squamous cell carcinoma. 7th Edition of American Joint Committee on Cancer staging manual[5]

Tumour	
Tumour	
Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma *in situ*
T1	Tumour ≤ 2 cm in greatest dimension with less than 2 high-risk features†
T2	Tumour > 2 cm in greatest dimension or any tumour with 2 or more high-risk features†
T3	Tumour with invasion of maxilla, mandible, orbit or temporal bone
T4	Tumour with invasion of skeleton (axial or appendicular) or perineural invasion of skull base
Nodes	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2a	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph node more than 6 cm in greatest dimension
Metastasis	
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis present

†High-risk features include depth (> 2 mm thickness; Clark level ≥ 4); perineural invasion; anatomic location (ear; non–hair-bearing lip); and differentiation (poorly differentiated or undifferentiated).

DIAGNOSIS

The accurate diagnosis of PNI is based upon clinical, radiographical and histopathological assessment.

Clinical features

In all, 60–70% of patients with histologically confirmed PNI are asymptomatic.[1] This underscores the importance of maintaining a high index of suspicion of PNI, especially for tumours overlying major nerve trunks and their branches.

Symptoms include sensory changes and motor deficits. Sensory symptoms include various forms of dysaesthesia, particularly formication – the sensation of ants crawling underneath the skin, tingling, pain and hypoaesthesia or numbness. Muscle weakness and fasciculation may be described by the patient or detected on cranial nerve (CN) examination. Deficits most commonly involve the facial nerve (CN VII) and its branches, and sensory changes involve the distribution of the trigeminal nerve (CN V).[10] The provisional diagnosis of Bell's palsy may be mistakenly made in a patient who is subsequently proven to have advanced PNI involving CN VII. Patients may not have had a previous diagnosis of NMSC with documented PNI but can still develop CN palsies and sensory deficits. In such circumstances, imaging followed by a biopsy confirmation of suspiciously enlarged nerves may be warranted.

Imaging

Magnetic resonance imaging (MRI) neurographic protocol is the preferred imaging modality to detect and assess the extent of macroscopic PNI, demonstrating superior soft-tissue contrast and greater sensitivity and specificity in the evaluation of large nerve PNI than computed tomography (CT) and other imaging modalities.[11,12]

Radiographic features supportive of perineural spread include enlargement or abnormal enhancement of the nerve, or obliteration of the normal fat plane surrounding the nerve. There is evidence that spatial resolution is improved by using 3-Telsa scanners, which have high-field magnets instead of traditional magnetic field strengths. Gadolinium-contrast MRI with fat suppression further increases the radiographic ability to detect early PNI, thus improving presurgical staging.[13]

A negative MRI does not, however, exclude PNI, as false negatives may occur. According to one study, the sensitivity of MRI for detection of macroscopic PNI was 95% but fell to 63% for demonstrating the entire extent of disease.[14] CT is

more useful for identifying bone invasion than changes in the nerve itself, and can detect the erosion or enlargement of the foramina associated with the involved CN.[10,15] It is a better imaging modality to assess for the involvement of regional lymph nodes, and MRI and CT complement each other.[16]

Pathology

PNI is most commonly identified as an incidental finding on histological examination of the excised tumour.[16,17] Because the diagnosis of PNI carries implications for management and prognosis, it is important to have a clear histological definition of PNI. Liebig and colleagues proposed the following, specific definition of PNI: the finding of tumour cells within any of the three layers of the nerve sheath (epineurium, perineurium and endoneurium), or tumour cells involving at least 33% of the circumference of the nerve. The latter criterion is useful for differentiating PNI from the focal abutment of a tumour in the proximity of a nerve.[18]

A high index of suspicion is important for identifying microscopic PNI. Perineural inflammation and nerve-fibre degeneration may suggest the presence of nearby PNI, and warrant careful examination through further frozen or paraffin sectioning.[1,19] Inflammation involving both neural and non-neural structures can indicate non-specific inflammation, whereas isolated perineural inflammation may be more suggestive of nerve involvement by the tumour.[19]

Histological mimics

Obtaining an accurate diagnosis of PNI also relies on awareness of common histological mimics. If not recognised, these benign cutaneous entities can result in unnecessary treatment and increased treatment-related morbidity. The most common is peritumoural fibrosis, which is present in approximately 5% of SCC and 6% of BCC.[20] This is where concentric rings of fibrous tissue are found adjacent to tumour cell nests, and may be mistaken for nerve tissue without the use of additional stains such as S100.[21] Other important mimics include epithelial sheath neuroma, re-excision PNI and reparative perineural proliferation. Epithelial sheath neuromas appear microscopically as discrete nerve complexes in the reticular dermis, consisting of central nerve trunks enveloped by mature squamous epithelium. There is no associated carcinoma or scarring from previous surgery. Re-excision PNI refers to the presence of benign squamous epithelium in the perineural spaces of previously biopsied sites. This is likely to reflect aberrant reactive proliferation of traumatised eccrine sweat glands into a plane of lower resistance. Reparative perineural proliferation consists of the appearance of concentric rings of spindle-shaped cells enveloping a nerve adjacent to scarring and reparation from previous surgery. Immunohistochemistry can distinguish this process from PNI. Spindle cells demonstrate negative staining for S100 and cytokeratins but positive staining for epithelial membrane antigen.[3,19,20,22]

Histopathological prognostic features

PNI-specific prognostic features are frequently underreported. The Royal College of Pathologists has developed reporting standards specifically for SCC and BCC. The presence of PNI is a core data item, and for re-excision specimens, the need to differentiate PNI from re-excision perineural proliferation is also highlighted. Non-core features for reporting include whether the PNI is intratumoural or extratumoural, below dermis or multifocal, the distance to the nearest margin and the size of the nerves involved.[23,24] Clinicians may have to specifically ask for these histopathological data items, given that these are not routinely reported and may impact on management, as later discussed. Synoptic reporting, as for melanoma in Australia, would help improve the completeness of pathology reports and provide decision support for treatment of NMSC.

A web-based Australian PNI registry has recently been established to standardise the method of classifying PNI, and to clarify prognostic factors associated with incidental PNI.[25] The collation of detailed outcomes data stratified by clinical and histopathological features will help to better define future best practice in the management of incidental PNI.

CLASSIFICATION OF PNI

PNI can be broadly classified as either incidental or clinical. Incidental PNI is identified only at histopathology in clinically asymptomatic patients with negative imaging. Other terms used in the literature to describe incidental PNI include minimal or microscopic PNI. PNI is classified as clinical when the patient exhibits sensory or motor changes, or there is radiographic evidence of PNI.[26–28] It may also be referred to as extensive or macroscopic PNI. It is uncommon to observe imaging-positive PNI in an asymptomatic individual.[29]

The distinction between incidental and clinical PNI is prognostically significant. One study found a 5-year local control rate of 80% for cutaneous malignancies with incidental PNI, compared with 54% for clinical PNI despite aggressive treatment with radiotherapy with or without surgery or chemotherapy, or both.[30] The study population included patients with SCC, BCC and basosquamous carcinomas.

TREATMENT

The management of PNI is based upon this classification into incidental and clinical disease. The following discussion will first review the role of surgery, including Mohs micrographic surgery (MMS), and radiotherapy (RT) and then propose treatment algorithms stratified by histological subtype.

Incidental PNI

In incidental PNI, MMS has consistently demonstrated superior local control rates compared to standard excision for NMSC with PNI.[2,17,31] This is due to significant differences in

the technique used to examine excision specimens. Standard assessment with vertical sectioning examines <1% of the margins. By using *en face* sections, MMS enables examination of close to 100% of the peripheral and deep margins, allowing the better detection of PNI and more complete excision.[32]

The results of a recent multicentre prospective study found that SCC with incidental PNI were larger, more poorly differentiated, had greater subclinical extension and larger postoperative defects than tumours without PNI.[33] The association of incidental PNI with these established clinicopathological indicators of poor prognosis highlights the importance of early detection and aggressive management. These features also emphasise the invasive nature of tumours with PNI and the importance of margin-controlled surgery, particularly MMS. These results are consistent with the 10-year Australian Mohs database that investigated both SCC and BCC. The high sensitivity of MMS in detecting excision margin PNI, and the low 5-year recurrence rate compared with standard excision makes MMS a valuable management strategy for NMSC with incidental PNI.[7,8]

While MMS appears to offer the highest chance of cure for NMSC with incidental PNI, recurrence rates remain significantly higher than for tumours without PNI, despite negative histological margins and clinically negative nodes.[7,8] These results have previously been explained as due to the presence of skip areas. However, recent work discredits this idea and suggests that all PNI is contiguous.[34,35] Skip lesions refer to the histopathological finding of PNI with intervening segments of disease-free nerve. This is most likely a result of a processing artefact, where asymmetrical tumour growth around a nerve and tissue manipulation during sectioning may result in a false negative margin.[3,7] Other explanations for skip areas have included an inflammatory reaction with immune-mediated tumour regression, or true skipping of regions of nerves as single malignant cells along the perineurium.[3]

After achieving histologically clear margins in tumours with PNI, some Mohs surgeons excise an extra tissue level and either examine it once again with frozen sections or send it for standard paraffin sections because of the possibility of undetected PNI. This approach, however, is nonspecific and does not confer assurance of complete tumour removal. Furthermore, the additional removal of tissue with clear histological margins does not allow for maximal tissue conservation, which is particularly significant in areas of functional and cosmetic importance.[3]

Improving local control rates in the presence of incidental PNI while maximising tissue conservation compels consideration of wide field local ART. ART can be effective in sterilising microscopic deposits of cancer cells that may be present after surgical excision and, in select cases, electively treating regional nodes without the need for regional surgery.

In cases of incidental PNI, it is important to consider the histological subtype and the extent and distribution of PNI when planning management.

The histological subtype has significant prognostic implications for NMSC with incidental PNI. One study investigating incidental PNI reported better local control rates for BCC than with SCC, when all patients were treated with surgery plus ART.[4] Much of the published literature investigating different management approaches to PNI includes a mixed population of SCC and BCC, with most being SCC. We have endeavoured to separate the literature as best as possible to provide suggestions for the optimal management of PNI occurring in SCC and BCC.

SCC

While cutaneous SCC with incidental PNI has consistently demonstrated poorer outcomes compared with BCC,[4,36] there is still a need to further sub-stratify these patients to determine those most likely to benefit from ART. In the Skin and Cancer Foundation Australia series focusing on PNI in SCC, 37/70 patients underwent MMS + ART, and 33/70 patients underwent MMS alone.[7] This decision was based on clinical and histological findings, with higher risk individuals receiving ART. In the 5-year follow-up period, recurrences occurred only in the MMS + ART group. This demonstrates that a subset of patients with incidental PNI and SCC histology are cured using MMS alone. Thus, a consideration of other PNI-specific features is important in determining the need for ART.

Prognostic features Certain histopathological features, including the distribution and extent of PNI, have been shown to be prognostic and are summarised in Table 2. Firstly, extratumoural PNI, that is, invasion outside the main tumour mass, is associated with more aggressive tumour behaviour than intratumoural PNI.[32] This is supported by results from a study focusing on non-cutaneous head and neck SCC, which reported reduced disease-free survival associated with extra-tumoural PNI.[37]

Secondly, the size of the involved nerve is significant. Ross and colleagues compared outcomes for SCC with PNI that involved small-calibre nerves < 0.1 mm with those with the involvement of larger-calibre nerves ≥ 0.1 mm. They found significantly lower risks of recurrence and metastasis, as well as increased disease-specific and overall survival, when PNI was limited to small diameter nerves.[38] Another study reported that the involved nerve diameter was not a significant factor in terms of 5-year local failure and regional relapse. This study, however, compared nerves with a diameter ≤ 0.1 mm with nerves with a diameter > 0.1 mm.[36] Further research is required to determine if a 0.1 mm diameter is the ideal cut-off point for determining the prognostic significance of nerve involvement, and whether these findings apply equally to BCC.

Table 2 Perineural invasion (PNI)-specific features associated with poor prognosis

Extra-tumoural PNI[32,37]
Involvement of larger-calibre nerves (≥ 0.1 mm)[38]
Invasion beyond the dermis, through to the subcutis or muscle[36]
PNI detected in recurrent tumour[36]
Diffuse intratumoural perineural spread[2]

A study focusing on incidental PNI reported that depth of invasion was of prognostic significance, with better outcomes associated with tumours limited to the dermis than with those invading the subcutis or muscle. This study also found a significantly higher rate of local and regional failures in individuals with PNI detected at relapse compared with those with PNI diagnosed at initial presentation.[56]

Finally, Han and Ratner described differences in outcome based on the extent of intratumoural perineural involvement in SCC. They reported better outcomes when PNI was limited to a few small dermal nerves and minimal focal disease, than with more diffuse perineural spread within the tumour mass.[2] Formal pathology reporting of preoperative biopsy specimens may be useful in identifying intratumoural PNI that may otherwise not be detected during MMS. Improved diagnostic and prognostic information may also be obtained by examining the central debulking tissue, either with frozen sections at the time of Mohs surgery or subsequent standard paraffin sections.

While this review focuses on PNI-specific prognostic factors, it is important to consider other adverse clinical and histological features that may be present and significantly influence the management approach.

A study conducted over 11 years that focused on PNI in SCC demonstrated that the presence of additional tumour-related high-risk factors was associated with poorer outcomes, and concluded that these patients should also be considered for ART.[59] Factors identified included poor differentiation, tumour diameter ≥ 2 cm and invasion beyond subcutaneous fat. Significantly, patients with large nerve (≥ 0.1 mm) involvement were also found to be more likely to have such concomitant adverse features. These tumour-related high-risk factors are comprehensively outlined in multidisciplinary clinical practice guidelines, including the National Comprehensive Cancer Network (NCCN) guidelines for BCC and SCC.[40]

Immunosuppression is another well-documented adverse prognostic feature for cutaneous malignancies.[40] SCC has been shown in particular to demonstrate increased biological aggressiveness in organ-transplant recipients.[41,42] This is characterised by poor differentiation, rapid growth, increased perineural and lymphatic invasion, and higher risk of developing regional and distant metastases.[43,44] The presence of incidental PNI in an immunocompromised host may therefore warrant a lower threshold for ART to reduce the risk of recurrence, but this should be decided on a case by case basis.[45,46] Reduction of immunosuppression may also be a reasonable adjuvant management strategy for transplant recipients with multiple, recurrent or life-threatening skin cancers.[47] Changing to a mammalian target-of-rapamycin inhibitor-based immunosuppressive regime may also be beneficial for reducing the incidence of NMSC in this patient group.[48,49]

It is important to recognise that the addition of ART does not replace the preference for MMS as the surgical excision strategy for cutaneous malignancies with incidental PNI. A recent study by Kropp and colleagues determined that MMS plus ART improved cause-specific survival and local control rates in patients with incidental PNI, compared with conventional surgical excision plus ART. The 5-year cause-specific survival for MMS patients was 84% compared with 68% for non-MMS patients, and the local control rates were 86% and 76%, respectively.[50] While this study included patients with both SCC and BCC, results were not stratified by histological subtype and most (89%) cases were SCC. This limits the application of these findings to other NMSC.

Treatment algorithm Our proposed approach to the management of SCC with PNI is summarised in Figure 1. We have sub-stratified SCC with PNI into low, medium and high-risk groups.

Low-risk includes incidental PNI that is intratumoural, focal, involves small nerves, is limited to dermis, and occurs in primary tumours. For this group of patients, surgery alone may be appropriate. MMS is the preferred primary excision strategy where PNI is diagnosed on biopsy. ART should be considered if patients are immunosuppressed, or additional high-risk tumour-related features are present such as tumour size ≥ 2 cm, or poor differentiation.

The medium-risk group includes incidental PNI with any of the high-risk features identified in Table 2. These patients would possibly benefit most from ART regardless of the primary surgical approach used. High-risk patients are those with clinical PNI in whom management may involve nerve resection, usually by a skull base surgeon, with the addition of ART or alternatively definitive RT, as later discussed.

Sentinel lymph node biopsy (SLNB) SCC with nodal metastases portends a worse prognosis, with an expected 5-year survival rate of 60–75%.[51] Early identification of subclinical nodal metastasis may be valuable for predicting prognosis and guiding further management. PNI is associated with an increased incidence of nodal metastases compared with tumours without PNI.[45] Subclinical lymph node involvement may be present in approximately 15–20% of patients with SCC and incidental PNI. It has been suggested, therefore, that patients with SCC and PNI may benefit from elective treatment of clinically negative regional nodes in addition to wide field local ART to the tumour bed.[4,29,50] However, not all clinicians would follow this approach and alternatively may elect to observe regional nodes.

The utility of SLNB for high risk cutaneous SCC, including SCC with PNI, is yet to be definitively established. Recent reviews suggest that SLNB is a reliable staging modality to assess regional disease in cutaneous SCC.[52,53] One study found a negative predictive value of 98% for sentinel lymph node status in high-risk patients.[53] A systematic review focusing on cutaneous SCC of the head and neck similarly reported that regional recurrence occurred in only 5% of patients when the SLNB had been negative. This false negative rate is comparable to that for head and neck melanoma where SLNB is an established staging investigation.[52]

There are still several unanswered questions that preclude definitive recommendations over the application of SLNB for staging cutaneous SCC. The interaction of high-risk factors, including PNI, on the probability of a positive

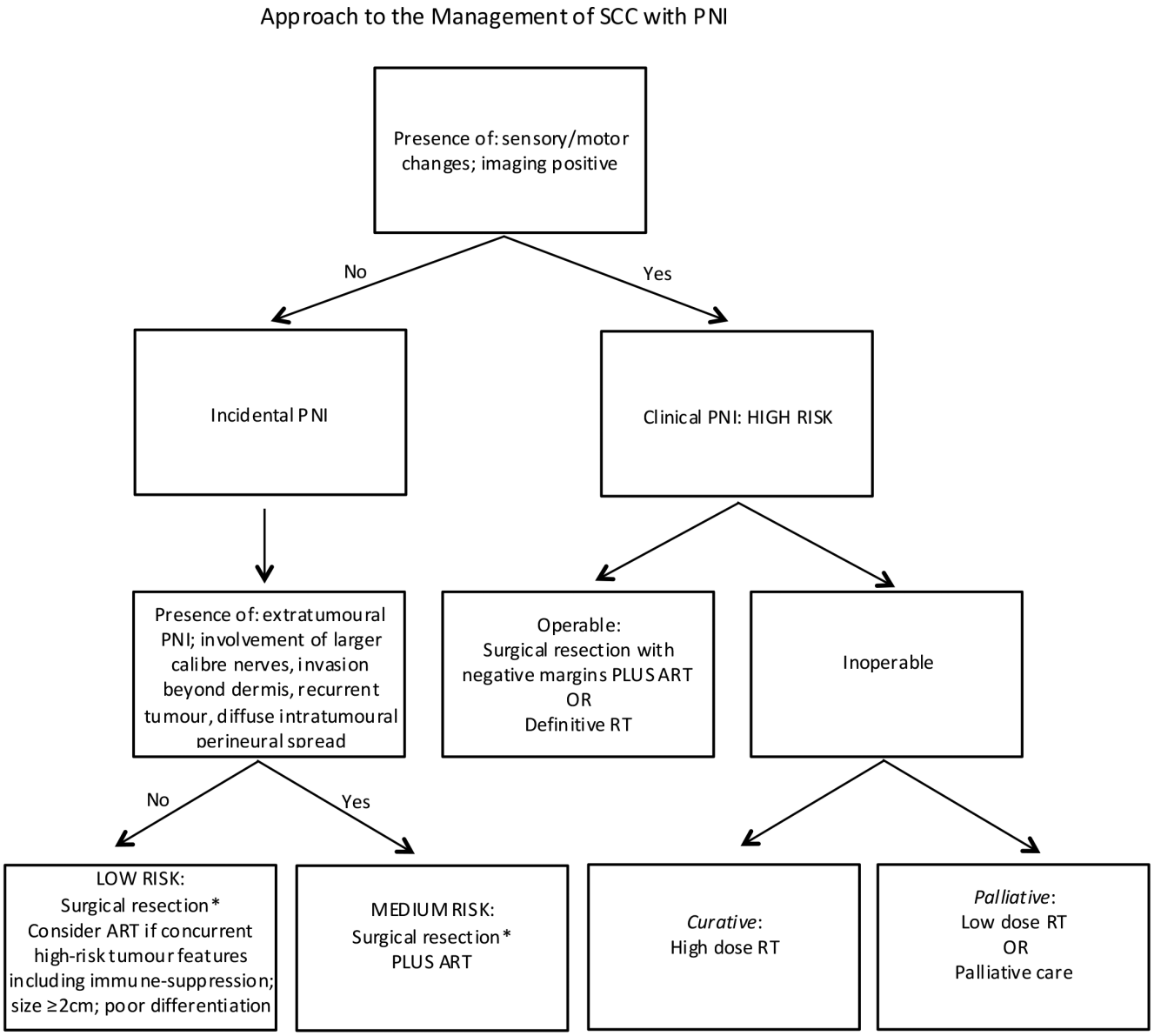

Figure 1 Approach to the management of squamous cell carcinoma (SCC) with perineural invasion (PNI). ART, adjuvant radiotherapy MMS, Mohs micrographic surgery, RT, radiotherapy.

SLNB requires further study.[54] It is likely that patients exhibiting multiple high-risk features will ultimately benefit from SLNB. Furthermore, the optimal treatment of occult nodal metastasis in the setting of high-risk cutaneous SCC needs to be established. Most patients are currently offered completion lymph node dissection or ART, or both.[52] Finally, it has not yet been shown whether the early detection of occult lymph node metastasis improves disease-free or overall survival.[55] Large, prospective multi-institutional trials are required to better identify risk factors for occult metastasis, define optimal further management and evaluate the cost-benefit ratio of SLNB in patients with high-risk cutaneous SCC.

BCC

Incidental PNI in BCC has been shown to have a good outcome with either MMS alone or standard surgical excision plus ART.[4] A recent study demonstrated a 91% 5-year relapse-free survival for BCC with incidental PNI treated

with surgery plus ART.[56] This result is similar to the outcomes reported in a large prospective Australian study where most of the patients were treated with MMS alone. The 5-year relapse-free survival was 92% when only 7% (20/283) of patients had received ART.[8] This suggests that ART may not confer an advantage to most patients with BCC treated with MMS. There are no data specifically evaluating the outcomes of incidental PNI in BCC managed with standard surgical excision alone.

It is important to recognise that BCC with PNI still has a higher recurrence rate than BCC without PNI.[8] Studies to date investigating BCC alone have been unable, however, to conclusively identify tumour-specific or PNI-specific factors warranting more aggressive initial management due to the low number of recurrences.[56]

In the absence of BCC-specific studies, it may be reasonable to extrapolate data from combined BCC and SCC studies to help define groups as low, medium and high risk. One possible explanation for the better overall prognosis of incidental PNI in BCC may be a reduced tendency for PNI to demonstrate the earlier-identified adverse features related to extent and distribution (Table 2), given the less aggressive biological nature of BCC. When present, however, factors such as extratumoural PNI are likely to be significant prognostically, independent of histological type.

The main differences in managing BCC compared to SCC relate to tumour-specific high-risk features such as those outlined in the NCCN clinical practice guidelines.[40] In particular, PNI is more frequently associated with aggressive BCC subtypes, including infiltrative, morphoeic, sclerosing and micronodular variants.[25] The locally invasive nature of these BCC subtypes may warrant consideration of local ART, especially in the setting of incidental PNI.

Treatment algorithm Low-risk tumours that may be managed with surgery alone are those with limited incidental PNI confined to the primary tumour. In these cases, MMS is still the preferred excision strategy where the diagnosis of PNI has been made on biopsy. ART is recommended for medium-risk tumours, as defined by the presence of any of the adverse features listed in Table 2, regardless of the initial surgical approach taken. Additionally, those with concurrent high-risk features such as immunosuppression or aggressive histological subtype may benefit from ART. The high-risk group consists of patients with clinical PNI, as discussed in the next section. Our proposed treatment algorithm for PNI in BCC is summarised in Figure 2.

The role of RT as a primary treatment strategy for high-risk BCC and SCC, including tumours demonstrating PNI, remains a source of debate. The NCCN guidelines for BCC and SCC include definitive RT as a treatment option for non-surgical candidates.[40] It has also been suggested this be generally reserved for patients older than 60 years due to concerns about long-term sequelae.[40,56] Despite this, in younger patients RT may still be considered as an efficacious curative option in appropriate circumstances. Radiotherapy is contraindicated when the patient has a genetic condition predisposing to skin cancer, including basal cell naevus syndrome (Gorlin syndrome) and xeroderma pigmentosum.[40] In these cases, appropriate surgical excision followed by close surveillance is recommended. The NCCN guidelines outline appropriate dose and fractionation regimes for radiation therapy, as shown in Table 3.[40]

Clinical PNI

For a patient with clinical PNI, management is tailored to the extent and resectability of the PNI, and also the patient profile. A multidisciplinary approach, often including staging and planning with MRI, surgical excision under general anaesthetic, preferably with frozen section control, and RT is often required. MMS of the primary tumour may be a valuable supplement; however patients with clinical PNI often have involvement of structures that precludes this approach.[29] Patient-specific factors including their age, performance status and preference, together with the presence of comorbidities, also need to be considered when determining appropriate management.

While the natural history of PNI usually involves central progression, this can be an unpredictable, long and indolent process. Many years may elapse from diagnosis of a head and neck primary cutaneous tumour with PNI before invasion into the central nervous system.[57,58] Furthermore, the patient group that appears to be most at risk of PNI are older Caucasian men, many with comorbid disease and a history of multiple previous skin cancers.[59] These become particularly significant considerations when contemplating aggressive treatment and weighing the potential survival benefit against the side-effect profile in this subset of patients.

SCC portends a more unfavourable prognosis than BCC as for incidental PNI. A recent study reported a 5-year relapse-free survival of 39% for patients with clinical PNI and SCC versus 80% for BCC when both patient groups were treated with radiotherapy or surgery, or both.[60] For this reason, we have stratified management by histological subtype.

SCC

The main challenge in managing patients with clinical PNI is achieving durable control of their disease.[60] Appropriate resection with margin control plus ART is likely to offer select SCC patients with clinical PNI the best chance of cure. Even tumours previously considered potentially unresectable, such as those with extensive intracranial PNI involving CN up to the Gasserian ganglion (zone 2) may be operable, and this treatment potentially offers improved survival rates with acceptable morbidity.[61] Previously, authors have recommended definitive high-dose RT for such skull base tumours due to the technical challenges associated with surgical resection. While nerve resection may be of potential benefit, it should be appreciated that this is often major surgery, at times requiring craniotomy, and thus best limited to select patients in specialised units. Many patients are elderly men with comorbid disease, for whom major skull base surgery would not realistically be contemplated. Furthermore, many patients still proceed onto ART, so it is perhaps still unclear if this type of surgery adds significant benefit compared with highly conformal

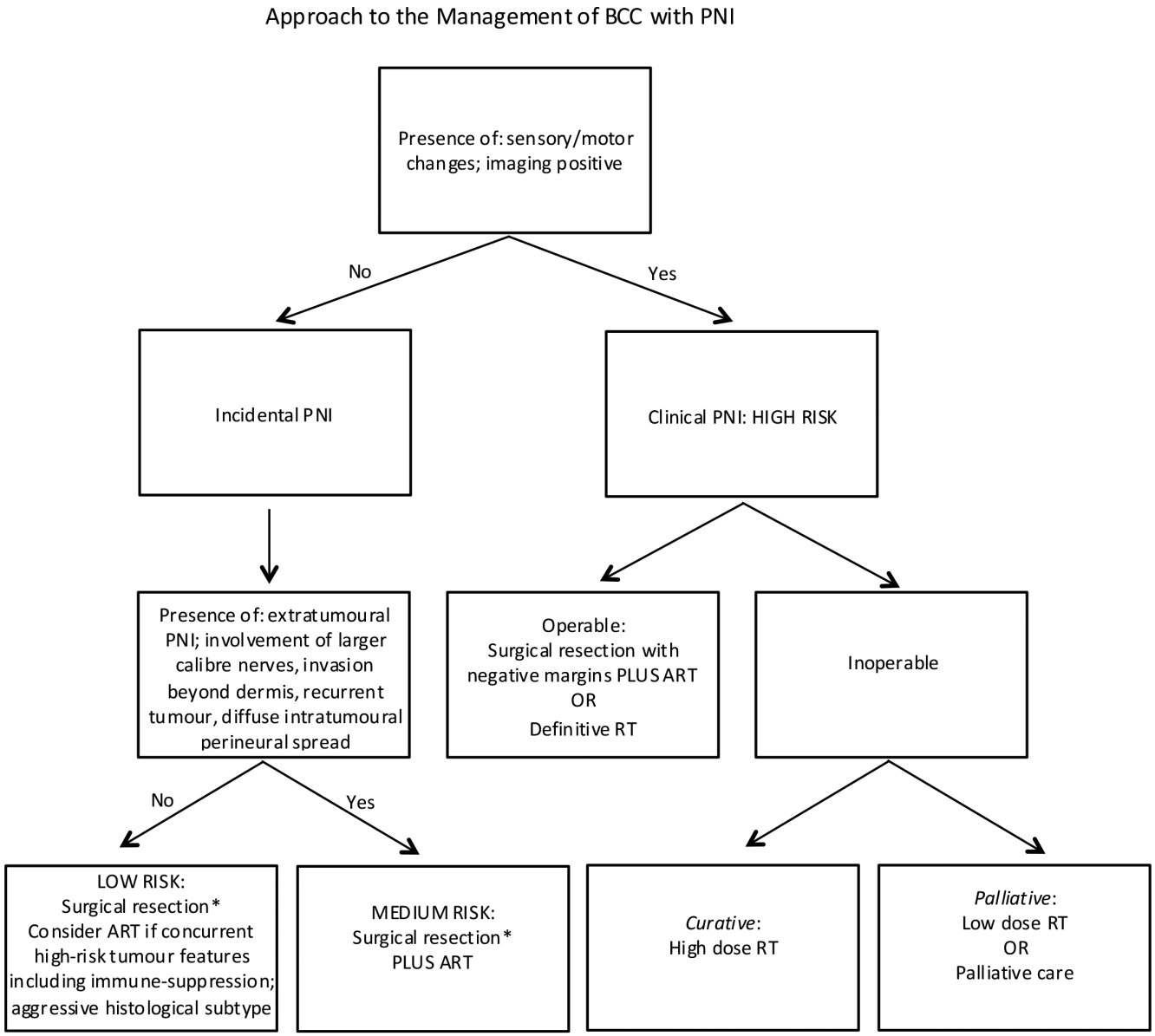

Figure 2 Approach to the manangement of basal cell carcinoma (BCC) with perineural invasion (PNI). ART, adjuvant radiotherapy MMS, Mohs micrographic surgery, RT, radiotherapy.

intensity-modulated RT (IMRT) alone. Extension beyond the Gasserian or Geniculate ganglion (zone 3) generally deems a patient to be inoperable due to the risks of exposing cerebrospinal fluid to tumour cells, and subsequent seeding in the brainstem and spinal cord. Patients with such extensive PNI, as well as those who are medically unfit for surgery, may be managed with RT alone (definitive or palliative), or alternatively, best supportive care. RT is often effective in palliating debilitating neuropathic pain and preventing, or delaying, the progression of intracranial disease and its associated consequences. High-dose definitive RT alone can also offer the chance of cure in ~50–60% of suitable patients, but with associated acute and late side-effects.[30]

Gluck and colleagues analysed patterns of failure in patients with clinical PNI in cutaneous head and neck SCC in order to define an optimal target volume for delivering adjuvant or definitive RT. The authors proposed inclusion of the following in the target volume; the portions of the nerve proximal and distal to the tumour site, skin innervated by

Table 3 NCCN guidelines for radiotherapy for squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) of the head and neck[40]

Primary tumour (SCC, BCC)

Tumour diameter (cm)	Margins (cm)	Electron beam dose (Gy)	Fractions	Duration of treatment (weeks)
< 2	1–1.5	64	32	6–6.4
		55	20	4
		50	15	3
		35	5	5 days
≥ 2	1.5–2	66	33	6–6.6
		55	20	4
Post-operative adjuvant		50	20	4
		60	30	6

Regional disease (SCC): all doses at 2 Gy per fraction using shrinking field technique

	Electron beam dose (Gy)	Duration of treatment (weeks)
After lymph node dissection		
Head and neck; with extracapsular extension (ECE)	60–66	6–6.6
Head and neck, without ECE	56	5.6
No lymph node dissection		
Clinically (-) but at risk for subclinical disease	50	5
Clinically evident adenopathy of head and neck	66–70	6.6–7

the diseased nerve, major communicating branches and the compartment in which the nerve is embedded, such as the parotid gland for CN VII.[62] The rationale for this is to treat both antegrade and retrograde PNI, as well as crossover spread from one major nerve or branch to another. Treatment algorithms proposed by recent studies also propose inclusion of the first echelon of regional lymph nodes in the RT target volume due to the risk of subclinical disease in the setting of clinical PNI.[4,65] IMRT offers the ability to accurately treat defined volumes considered to be at risk, or involved, and at the same time limit the RT delivered to important structures at risk, such as the visual pathways and brain. The fusing of diagnostic MRI scans with RT simulation scans allows the improved determination of the target volume.[64]

Experimental approaches There may be a role for adjuvant or definitive chemoradiotherapy, with platin-based chemotherapy (as a radiosensitiser), in the management of clinical PNI in cutaneous SCC in select patients. There is level 1 evidence for this approach in the setting of mucosal head and neck SCC, with a demonstrated survival benefit.[65] A randomised controlled trial evaluating the addition of chemotherapy to ART for high-risk cutaneous SCC is currently being undertaken in Australia and New Zealand under the auspices of the Trans Tasman Radiation Oncology Group.

Where the tumour is considered inoperable, cetuximab (epidermal growth factor receptor inhibitor) may provide palliative relief, but this should also be considered experimental.[57,66]

BCC

The fundamental concepts of managing clinical PNI in BCC are similar to SCC, with assessment for surgery plus ART, and definitive RT for inoperable tumours. There is a paucity of literature defining the role of RT for BCC.[67]

RT treatment volumes should be individualised based on tumour location and extent, as determined by MRI.[16] As the extent of subclinical disease can be difficult to define, it is recommended that more generous initial radiation volumes are used due to low rates of subsequent salvage.[68] This may involve extending RT fields to include at-risk nerves to the base of skull, where indicated.

Experimental approaches For advanced BCC with PNI, the use of Hedgehog (Hh) pathway inhibitors such as vismodegib represents an as yet unexplored treatment option. Vismodegib has recently been Therapeutic Goods Administration approved for the treatment of adult patients with metastatic BCC or with locally advanced BCC where surgery and radiotherapy are not appropriate. A phase II trial found a response rate of 43% in patients with locally advanced BCC, with a complete response reported in 21%.[69] Remaining challenges with this therapy include a significant adverse effect profile, development of resistance and disease rebound after the drug is discontinued. To overcome this, consideration is being given to the possible role for Hh inhibitors as adjuvant therapy to surgical excision or MMS. The rapid effect of Hh inhibitors in shrinking tumour size may enable definitive management in anatomically difficult or high-risk sites such as the head and neck. New Hh inhibitors are also being developed, including saridegib and sonidegib, with the aim of reducing adverse effects while maintaining clinical efficacy.[70]

CONCLUSIONS

The prognostic implications of PNI occurring in cutaneous malignancies evidence the need for a clear and targeted

management approach. For clinical PNI, surgery plus ART is a validated management strategy for resectable tumours. Definitive RT may be recommended where the PNI is deemed inoperable or for non-surgical candidates. The approach to incidental PNI is more contentious. Data available to date indicate that the histological subtype, as well as PNI distribution and extent, may affect prognosis and therefore optimal management. Patients who are likely to benefit most from ART include those with extratumoural PNI, the involvement of large-calibre nerves, tumour invasion beyond dermis, recurrent tumour or diffuse intratumoural spread. Patients with extensive PNI may warrant referral to a multidisciplinary head and neck cancer service with the experience to offer skull base surgery and IMRT. In the future, the collation of complete records of all cutaneous NMSC by cancer registries would improve the evidence base for PNI and help further define best management. Further research, optimally a randomised controlled trial comparing MMS alone with MMS plus ART, with results stratified by histological type, would also be useful in clearly delineating the efficacy of each treatment strategy and identifying the target patient subsets for each.

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