

# Nonmelanoma Cutaneous Head and Neck Cancer and Merkel Cell Carcinoma: Current Concepts, Advances, and Controversies

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## ABSTRACT

Nonmelanoma skin cancer (NMSC) is the most common cancer worldwide and the most frequently observed malignancy in whites. Approximately 75% to 80% are basal cell carcinomas and 20% to 25% are squamous cell carcinomas. Incidence is increasing, partly reflecting an ageing population, and NMSC is more commonly seen in men. The predominant causative agent is ultraviolet solar radiation exposure, with the majority of cases occurring on the head and neck. Surgical excision is typically the treatment of choice, providing histopathologic information, high cure rates, and acceptable cosmetic and functional outcomes. Radiation therapy is reserved for cases where surgery is not the preferred choice or for high-risk cases where adjuvant therapy is recommended. Although overall mortality rates are low, patients with complex cases such as those with immunosuppression should be considered for management within multidisciplinary tumor boards. In contrast, Merkel cell carcinoma is a rare and aggressive malignancy, frequently arising on the head and neck in older whites, with a poorer prognosis. This article focuses on the current evidence guiding practice, recent advances, and areas of controversy in NMSC and Merkel cell carcinoma of the head and neck.

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## INTRODUCTION

Nonmelanoma skin cancer (NMSC) is the most common cancer worldwide, with incidence varying depending on country and latitude. It represents a major global economic and health burden. More than 2.5 million individuals in the United States are diagnosed with a NMSC each year, with basal cell carcinomas (BCCs) accounting for approximately 75% to 80% and cutaneous squamous cell carcinomas (cSCCs) approximately 20% to 25%. A majority (80% to 90%) occur on the sun-exposed areas of the head and neck (HN).<sup>1,2</sup>

NMSCs can be divided into low and high risk, based on the presence of prognostic factors and risk of local, regional, and distant relapse. The distinction is part of a continuum and hence somewhat arbitrary, with many of the prognostic factors predicting for local recurrence also predicting for regional recurrence and the uncommon event of distant relapse.<sup>3,4</sup> Approximately 5% of patients with NMSC, mainly those with cSCC, will have clinicopathologic features that predict for an increased risk of recurrence.<sup>2</sup>

Although mortality rates are higher in cSCC, the overall rate is low, with immunosuppression increasing the incidence of relapse and death in both cSCC and BCC.<sup>5</sup> The treatment of NMSC, particu-

larly in the advanced stage, is an area where high-level evidence guiding management is lacking, and it is therefore based mainly on retrospective series and low-level systematic reviews. The National Comprehensive Cancer Network (NCCN) has established consensus guidelines through a working group and recommends patients with complex cases seek consultation from a multidisciplinary tumor board.<sup>4</sup> Merkel cell carcinoma (MCC) is a rare and aggressive malignancy, frequently arising on the HN in older whites; it is more commonly seen in women.<sup>6</sup>

This article focuses on the current evidence guiding practice, recent advances, and areas of controversy in NMSC and MCC of the HN. Detailed histopathologic descriptions, screening and prevention, and management of benign, premalignant, and other skin malignancies are beyond the scope of this article.

## cSCC

### Etiologic Factors

Common risk factors include skin phenotype, cumulative ultraviolet (UV) solar radiation exposure, and immunosuppression.<sup>7</sup> Other factors include genetic conditions such as xeroderma pigmentosum, chemical exposure such as arsenic,

chronic ulcers and scars, tobacco use (particularly of lip), therapeutic ionizing radiation, and human papilloma virus infection.<sup>7,8</sup> *p53* mutations are found in 50% to 100% of NMSCs as a result of UV exposure, supporting a role in carcinogenesis.<sup>9</sup>

**Clinical Features and Diagnostic Workup**

Because cSCCs commonly arise from chronically sun-exposed areas and solar keratoses, early diagnosis of invasive cSCC can be difficult. In a study by Green et al,<sup>10</sup> the early diagnosis accuracy rate by a cohort of experienced dermatologists was found to be 39%.

After histopathologic confirmation, diagnostic imaging such as computed tomography (CT) or magnetic resonance imaging (MRI) to assess local disease extent, regional lymph node involvement, or presence of distant metastases is performed when clinically indicated. Positron emission tomography (PET) has proven useful in staging of mucosal HNSCC (mHNSCC), and although studies are lacking, it is likely that PET has a similar utility in locoregionally advanced cSCC.

**Staging and Prognostic Factors**

**T stage.** The Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC) published revised TNM skin cancer staging classifications in 2009 and 2010, respectively.<sup>11,12</sup> These classifications base early T stage (T1/2) on size criteria ( $\leq 2$  v  $> 2$  cm in greatest dimension), with more advanced disease (T3/T4) reflecting invasion into surrounding structures and perineural invasion (PNI) of skull base. To improve its prognostic value, the AJCC further defines T stage based on the presence of high-risk features (T1  $<$  two and T2  $\geq$  two high-risk factors). These features have been determined on the available evidence and findings from multivariable analyses. In addition to size ( $> 2$  cm), they include:  $> 2$  mm thickness, Clarke level  $\geq 4$ , PNI, primary site (ears, non-hair-bearing lip), and poor differentiation.<sup>11,12</sup>

Clayman et al<sup>13</sup> reported a reduction in disease-specific survival (DSS) in patients with local recurrence at presentation, increasing size and depth, invasion beyond subcutaneous tissues, and PNI. Patients with  $\geq$  one risk factor compared with no risk factors had a significantly inferior 3-year DSS (70% v 100%).

Although both the AJCC and UICC staging systems are relatively simple to apply, some aspects limit their utility. UICC T1 classification is solely based on size and therefore may not account for poor outcomes in some early-stage tumors that harbor high-risk features.<sup>14</sup> The Brigham and Women’s Hospital reported outcomes based on an alternative staging system, assigning T stage solely on number of risk factors (T1, zero; T2a, one; T2b, two to three; T3, four risk factors or bone invasion). It concluded its staging classification resulted in improved prognostication, with T2b/T3 tumors defining a high-risk group.<sup>14</sup>

**N stage.** Previously, N stage was based on the absence or presence of involved lymph nodes (N0-N1). This failed to capture important information regarding number, size, and location of involved nodes. The current system now reflects N staging similar to that for mHNSCC. Some authors have also proposed further refinement by differentiating intraparotid and cervical nodal involvement.<sup>15</sup> Prognostic factors and risk stratification for NMSC of the HN are summarized in Table 1.

**Treatment**

Figure 1 shows the treatment algorithm for primary site.

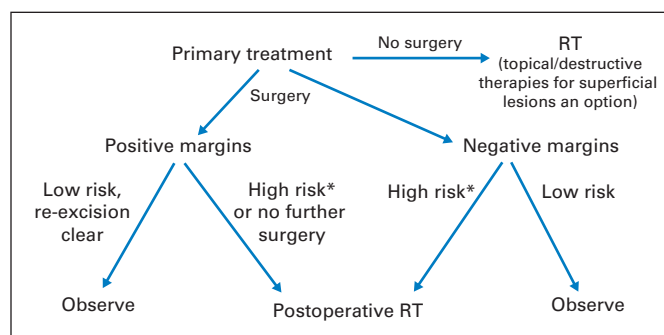
**Table 1.** Prognostic Factors and Risk Stratification for NMSC of HN

Risk Factor	Low Risk	High Risk
Tumor size, cm	$\leq 2$	$> 2$
T stage	T1-2	T3-4
Tumor thickness (SCC), mm	$< 2$	$\geq 2$ or Clarke level $\geq 4$
Site		Lip or mask areas of face
Differentiation	Well	Poor
Subtype (SCC)		Basosquamous, desmoplastic, or adenosquamous
PNI	Absent or single small nerve	Multifocal small nerve or named nerve
Rapid growth	Absent	Present
Borders	Well defined	Poorly defined or in transit
LVSI	Absent	Present
Margin status	Negative	Positive
Immune status		Immunosuppressed
Chronic inflammation or scars (SCC)	Absent	Present
Previous RT	Absent	Present

Abbreviations: HN, head and neck; LVSI, lymphovascular space involvement; NMSC, nonmelanoma skin cancer; PNI, perineural invasion; RT, radiation therapy; SCC, squamous cell carcinoma.

**Local.** The preferred treatment modality is dependent on site, extent of disease, comorbidities, and patient preference. Ninety-five percent of cSCCs are low risk, with surgery typically the treatment of choice, providing histopathologic evaluation, high cure rates, and acceptable cosmetic and functional outcomes. Mohs micrographic surgery (MMS) is a technique that provides excellent control rates while aiming to remove the least amount of normal tissue necessary to obtain clear margins. Leibovitch et al<sup>16</sup> reported a 5-year recurrence rate with MSS of 2.6%. However, its broad applicability for all NMSCs remains questionable because of a lack of randomized evidence demonstrating its superiority over standard surgery for simple lesions, coupled with the additional time, capital, and expense required.<sup>17</sup> Thus, MMS is generally favored for selected lesions, such as those involving poorly defined borders, location in anatomically sensitive areas (eg, periorbita), presence of PNI, or either recurrent or residual disease after previous treatment.<sup>16,18</sup>

**Adequacy of surgical margins.** There is a correlation between the diameter of a lesion and risk of recurrence. One study examining margin status demonstrated that to obtain a 95% clear resection margin rate for lesions  $\leq 2$  cm, a 4-mm margin was required, whereas for



**Fig 1.** Treatment algorithm for primary site. RT, radiation therapy. (\*) Figure 2 provides treatment algorithm for regional nodal basin.

**Table 2.** Tumor Type, Risk Classification, Recommended Minimum Surgical Margin, and 3-Year Local Control Rates

Tumor Type	Recommended Minimal Margin (mm)	3-Year Local Control (%)
<b>BCC</b>		
Low risk	2 to 4	≥ 98
High risk	4 to 10	90 to 95
<b>SCC</b>		
Low risk	4 to 6 mm	80 to 95
High risk	≥ 10	60 to 80

Abbreviations: BCC, basal cell carcinoma; SCC, squamous cell carcinoma.

lesions > 2 cm in diameter, a 6-mm margin was required.<sup>19</sup> For lesions > 2 cm, a 10-mm minimum resection margin is generally recommended, but this is often difficult to achieve in the HN, especially at depth.<sup>8</sup> Table 2 summarizes tumor type, risk classification, recommended minimum surgical margins, and 3-year local control rates.

**Radiation therapy.** Although radiation therapy (RT) is predominantly used in the adjuvant and palliative settings, it is an accepted alternative definitive treatment where surgery is contraindicated, impractical, or not preferred. Despite its use, there is a paucity of high-level evidence supporting an optimal RT technique, dose, and fractionation schedule. Small lesions (≤ 2 cm) are more commonly treated with hypofractionated RT, with excellent control rates. A more fractionated course is typically used for larger lesions or where optimal cosmetic results are desirable.<sup>8,20</sup> Cognetta et al,<sup>21</sup> examining more than 1,700 patients with NMSC treated with superficial x-ray therapy, reported 2- and 5-year control rates of 98.1% and 95%, respectively.

Similar to surgical margins, recommended clinical target volumes tend to be smaller for low-risk lesions (5 to 10 mm) and wider for larger high-risk lesions (≥ 10 mm).<sup>20,22</sup> Table 3 lists recommended RT doses and fractionation schedules based on treatment intent.

**Destructive and topical therapies.** Destructive and topical therapies are typically used for actinic keratoses and SCC in situ, but they may also be used in certain circumstances in superficial low-risk lesions. However, their use may result in inferior cure rates and mask deeper recurrences. Not all treatments are supported by evidence, nor have all been approved by the US Food and Drug Administration. US Food and Drug Administration–approved treatments include 5% imiquimod and 5% Efidex (topical fluorouracil; Valeant Pharmaceuticals, Costa Mesa, CA), photodynamic therapy, and cryotherapy. Other treatment options, such as intralesional agents, are considered off label and often have limited evidence to support their efficacy.<sup>8,23,24</sup>

**Locoregionally Advanced Disease**

**High-risk local disease.** Where the only high-risk feature is a positive margin, further surgery should be attempted to achieve local control with single-modality treatment. Only in cases where further surgery is not preferred, such as where it is likely to cause disfigurement, should adjuvant RT (aRT) be considered (Fig 1).

**Role of aRT.** Because of the lack of high-level evidence confirming the benefit of aRT, there are no universally adopted guidelines as to the presence of which adverse prognostic factors warrant adjuvant therapy. Therefore, its use is predominantly based on clinician prefer-

**Table 3.** Recommended RT Dose and Fractionation Schedule Based on Treatment Intent for NMSC

Intent*	Dose (Gy)†	Fractionation	Times per Week
<b>Primary definitive</b>			
≤ 2 cm	24‡	4	1
	35	5	3 to 5
	45	10 to 15	5
	50	20	5
	50 to 55	20	5
> 2 cm	64	32	5
	66	33	5
	<b>Primary postoperative, high risk</b>		
	<b>Negative margins</b>		
50	20	5	
60	30	5	
<b>Positive margins</b>			
As per primary definitive			
<b>Regional nodes, unresected§</b>		5	5
66		35	5
<b>Regional nodes, resected  </b>		As per primary postoperative, negative margins	
66¶		33	5
<b>Regional elective (SCC)</b>			
<b>Postoperative N0</b>		25	5
<b>Surgical bed#</b>		27	5

Abbreviations: NMSC, nonmelanoma skin cancer; RT, radiation therapy; SCC, squamous cell carcinoma.

\*Higher doses tend to be used for SCC compared with basal cell carcinoma for equivalent tumor size and extent.

†Choice of RT technique (eg, superficial x-ray therapy) dependent on tumor and patient factors.

‡Superficial lesions (< 4 mm, superficial x-ray therapy, or orthovoltage).

§Role of concurrent chemotherapy adopted but unproven in cutaneous SCC.

||No evidence of dose intensification or addition of chemotherapy in presence of extracapsular extension for NMSC.

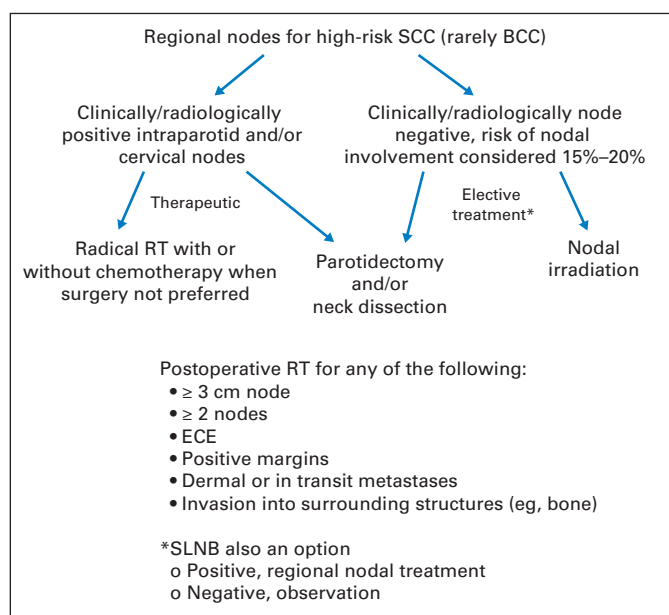
¶Consider for extracapsular extension.

#As per TROG 05.01 (Trans Tasman Radiation Oncology Group) protocol (ClinicalTrials.gov identifier NCT00193895).

ence and institutional policy. Accepting the inherent selection bias, retrospective series on the use of aRT have demonstrated a reduction in locoregional recurrence rates for advanced disease, and aRT is considered in patients with T3-4 disease, regional nodal involvement, clinical PNI (cPNI), and immunosuppression.<sup>25,26</sup>

In the TROG 05.01 (Trans Tasman Radiation Oncology Group) randomized trial (ClinicalTrials.gov identifier NCT00193895) examining the role of aRT (60 to 66 Gy over 6 to 6.5 weeks in daily 2-Gy fractions) with or without weekly concurrent chemotherapy (carboplatinum area under curve 2) in high-risk cSCC, high-risk disease was defined as either locally advanced primary disease (T3-4 [according to AJCC or UICC] or in-transit disease) or high-risk nodal disease (any of the following: extracapsular extension [ECE] of any node size, intraparotid nodal metastasis regardless of size or number, ≥ two cervical nodes, and/or cervical node ≥ 3 cm). Results are expected mid 2016.

**Regional lymph nodes.** Intraparotid and cervical nodes are the most common regional nodal basins involved in cSCC of the HN and are typically staged with either CT and/or PET-CT. Risk of occult regional nodal disease is based on the presence of primary-site high-risk features. The decision of when to offer elective treatment is often arbitrary, with many considering a 15% to 20% perceived risk of occult disease as the trigger for therapy. In addition, surgical series



**Fig 2.** Treatment algorithm for regional nodal basin. BCC, basal cell carcinoma; ECE, extracapsular extension; RT, radiation therapy; SCC, squamous cell carcinoma; SLNB, sentinel lymph node biopsy.

have shown that in the presence of intraparotid nodal disease, the risk of synchronous occult cervical nodal disease is approximately 15% to 20%, justifying the need for elective neck treatment with either surgery or RT.<sup>27</sup>

Given the variability of draining lymph nodes in cSCC of the HN, sentinel lymph node biopsy (SLNB), with a reported positive predictive value of  $> 90\%$  and negative predictive value of 95% to 98% in cSCC, may be helpful in guiding further management and avoiding an unwarranted neck dissection.<sup>28</sup> However, more studies supporting its routine use are required.

Type of surgery—elective or therapeutic—depends on the location of the primary site and potential or clinically or radiologically evident sites of nodal spread. Interestingly, 10% to 15% will not have an identifiable synchronous or metachronous index lesion.<sup>25</sup>

**Role of adjuvant therapy.** Figure 2 shows the treatment algorithm for the regional nodal basin. Depending on the nodal risk factors present, reported regional relapse rates after therapeutic surgery alone range between 20% and 80%.<sup>25</sup> Multiple series have reported predictors of regional recurrence, including size of involved nodes  $\geq 3$  cm, multiple involved nodes ( $> 2$  nodes), ECE, close or positive margins, dermal nodal infiltration, in-transit disease, invasion of surrounding structures such as bone or nerves, and immunosuppression.<sup>25</sup> Reporting on the 5-year disease-free survival in patients with metastatic cSCC to lymph nodes, Veness et al<sup>29</sup> found a statistically superior outcome in patients undergoing surgery and receiving aRT compared with surgery alone (73% v 54%;  $P = .004$ ). However, Ebrahimi et al<sup>30</sup> identified a low-risk subset of patients with a 3-year DSS of 97% after surgery alone to the parotid bed and/or cervical neck; these patients had one involved node  $< 3$  cm in maximal diameter and no ECE.

Despite the lack of confirmatory randomized evidence justifying its use, a number of institutions have adopted postoperative chemRT in selected cases, such as those involving patients with ECE or positive

margins, based on findings from randomized studies demonstrating a benefit in high-risk mHNSCC.<sup>31,32</sup> NCCN guidelines recommend concurrent postoperative chemotherapy, cisplatin (100 mg/m<sup>2</sup> every 3 weeks or 30 mg/m<sup>2</sup> weekly), and RT (60 to 66 Gy over 6 to 6.5 weeks) in the presence of extensive ECE or multiple involved nodes.<sup>4</sup>

### Systemic Treatment for Advanced SCC

There are no universal evidence-based guidelines for the management of patients with medically or surgically inoperable locally advanced cSCC, recurrent disease after previous treatment, or presence of distant metastatic disease. Cohort series and case reports have reported activity with cisplatin, carboplatinum, fluorouracil, capecitabine, bleomycin, methotrexate, doxorubicin, paclitaxel, and docetaxel. These can be used either as single agents or in combination, with response rates up to 80% and median duration of approximately 4 to 6 months.<sup>33</sup> One small prospective study reported an 86% overall response rate with concurrent carboplatinum and RT in patients with locally advanced cSCC ineligible for surgery.<sup>34</sup>

Biologic therapies such as interferon alfa and 13-*cis*-retinoic acid also demonstrate tumor response as single agents and in combination after chemotherapy.<sup>33</sup> Recent studies examining the role of anti-epidermal growth factor receptor (EGFR) agents such as cetuximab and panitumumab have reported disease control rates of approximately 70%.<sup>35,36</sup> Because of low numbers of unresectable or metastatic cSCC, the frequency of EGFR expression in cSCC is relatively unknown. The relationship between prognosis and response to therapy and EGFR overexpression, gene copy number, and protein expression is yet to be fully evaluated. Unlike in metastatic colorectal cancer, there seems to be no proven association with *KRAS* or *BRAF* mutations and response to anti-EGFR therapies.<sup>33</sup>

A phase II study recently closed to accrual examined the addition of erlotinib in the neoadjuvant and adjuvant settings, with planned surgery or definitive RT for locally advanced disease ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01059305) identifier NCT01059305). Currently accruing are a phase II study examining the addition of concurrent cetuximab to aRT ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01979211) identifier NCT01979211) and a study examining cetuximab as preoperative treatment for high-risk cSCC ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02324608) identifier NCT02324608).

### Special Considerations

**PNI.** PNI is seen more frequently in SCC (5% to 10%), where it is associated with greater morbidity and mortality than in BCC (2% to 5%).<sup>37</sup> Many patients with cPNI have no preceding history of incidental (pathologic) PNI (pPNI). The trigeminal and facial nerves are most commonly affected in cases of cPNI, which typically involves retrograde progression. Extratumoral disease, large-diameter nerve involvement, and multifocal PNI are associated with more aggressive behavior.<sup>37</sup> Recent evidence supports targeted MRI using 3-Tesla neurography as the investigation of choice in the evaluation of cPNI.<sup>38</sup>

There is an important prognostic distinction between pPNI and cPNI. Jackson et al<sup>39</sup> reported improved 5-year local control (90% v 57%;  $P < .0001$ ) and DSS (90% v 76%;  $P = .002$ ) for pPNI compared with cPNI, respectively, after treatment.

The additional benefit of aRT in the management of PNI, particularly in pPNI, is inconclusive.<sup>40</sup> However, because of poor outcomes with surgery alone with cPNI, aRT is commonly recommended.<sup>39,41</sup> From an operability perspective, cPNI is subdivided into three zones, relating to proximity of disease to the skull base. With modern surgical

techniques, tumors previously considered unresectable, such as those with extension up to the Gasserian ganglion (zone two), may nowadays be considered surgical candidates with the potential of improved DSS and acceptable morbidity.<sup>42</sup> The use of highly conformal RT techniques, such as intensity-modulated RT, may provide durable local control with lower long-term complications rates. In a study by Balamucki et al,<sup>43</sup> RT alone for inoperable cPNI resulted in a 5-year local control rate of 54%, which was comparable to that in patients with operable tumors receiving aRT. The role of elective nodal treatment and/or adjuvant chemoRT in cPNI in the absence of other adverse prognostic factors remains inconclusive.

**Immunosuppression.** Recipients of solid-organ transplants have a 65- to 250-fold increased risk of developing a cSCC compared with the general population.<sup>5</sup> Tumors develop at a younger age, with many exhibiting high-risk features. Reduction in the level of immunosuppression depending on type of transplantation should be considered in these patients.<sup>8</sup> In a study of patients with node-negative cSCC and chronic lymphocytic leukemia, regional recurrence occurred in 36% and disease-specific death in 33%, despite surgery and aRT.<sup>44</sup>

### Follow-Up and Surveillance

Ongoing monitoring after treatment is commonly based on the treating clinician or institution policy and patient and tumor risk factors. NCCN guidelines provide detailed recommended follow-up policies for NMSC.<sup>4</sup>

## BCC

### Etiologic Factors

With the addition of nevoid basal cell carcinoma (NBCC) syndrome (Gorlin syndrome), the causative factors for the development of BCCs are essentially similar to those of cSCC.

### Clinical Features and Diagnostic Workup

There are four distinct clinical subtypes: nodular (most common subtype), superficial, morphoeic (fibrosing), and fibroepithelial (fibroepithelioma of Pinkus). Confusion arises when histopathologic patterns such as cystic, micronodular, and basosquamous BCC become entwined with clinical subtypes.<sup>7</sup>

Early lesions and those with subtle changes on the background of sun-affected skin can be difficult to diagnose. Evidence supports the role of dermoscopy performed by a skilled clinician to increase the accuracy of clinical diagnosis and assist in distinguishing a lesion from other nonpigmented lesions and a melanoma from a pigmented BCC.<sup>8</sup>

### Staging

The current staging classification is the same as that for cSCC, but with limited prognostic utility because of its low metastatic potential.

### Prognostic Factors

Prognostic factors are summarized in Table 1. Mortality resulting from BCC is quite rare, and when it does occur, it is primarily associated with either immunosuppression, NBCC syndrome, and/or neglected tumors. The age-adjusted mortality rate is estimated at 0.12 per 100,000.<sup>7</sup>

### Treatment

Recommended surgical margins are usually smaller than those for cSCC of the same size.<sup>45</sup> Table 2 lists recommended minimum surgical margins. Figures 1 and 2 provide a summary of treatment algorithms.

**RT.** RT is an effective alternative treatment where surgery may be difficult or not preferred. A comprehensive review of the role of RT in BCC by Cho et al<sup>46</sup> reported high cure rates (79% to 100%), with > 90% experiencing excellent cosmetic results (when recorded). Control rates were comparable to published outcomes with MMS, standard surgery, photodynamic therapy, and curettage and electrodissection.

aRT is seldom required, but it is considered for high-risk lesions, for recurrent disease, or where further surgery in the presence of positive margins would be associated with marked morbidity, such as disfigurement.<sup>20</sup>

**Systemic therapy.** A majority of BCCs, either sporadic or associated with NBCC syndrome, have enhanced hedgehog signaling, often because of mutations in the tumor suppressor gene patch-1 (*PTCH 1*) and less commonly the smoothed gene (*SMO*).<sup>47</sup>

A recent development has been the successful targeting of the hedgehog pathway with smoothed inhibitors.<sup>47-49</sup> In a randomized study, vismodegib was found to significantly reduce the BCC burden and inhibit growth of new BCCs in patients with NBCC syndrome. However, just more than half of patients had to discontinue treatment because of adverse events.<sup>47</sup> Results of SMO inhibitor clinical trial outcomes in BCC are listed in Table 4.

Systemic therapy has a potential role in the rare entity of metastatic BCC and in locally advanced or multiple BCCs, either preoperatively or as palliative treatment. A review of 53 aggregated cases reported an 83% response rate with platinum-based chemotherapy, 37% being complete, and median time to progression of 24 months.<sup>50</sup> EGFR is expressed in approximately 38% of BCCs, and activity with cetuximab has been seen in case reports where platinum-based chemotherapy had previously failed.<sup>51</sup>

## MCC

### Etiologic Factors

The major etiologic factor is chronic UV solar exposure; Merkel cell polyomavirus (MCV or MCPyP), recently identified, is also postulated to be causative.<sup>52,53</sup> MCC is highly immunogenic, with a greater incidence in immunosuppressed patients.<sup>54</sup>

It has been suggested that the prevalence of MCV may vary in distinct geographic locations and possibly reflect differences in treatment outcomes. There is evidence that suggests virally associated MCC in Australia is less common compared with other regions. A study comparing 16 North American with 21 Australian patients reported a 69% versus 24% prevalence for the virus, respectively.<sup>55</sup> In contrast, a study comparing 136 German with 38 Australian patients documented no difference (85.3% v 86.8%, respectively).<sup>56</sup> In another series of 104 Australian patients, only 18.3% of patient cases were positive for MCV, with an even lower rate (7.7%) for tumors in sun-exposed HN locations versus non-HN sites.<sup>57</sup> Although evidence is inconclusive, it is plausible that the etiology of MCC in the Australian population is more a result of UV-associated rather than virally associated carcinogenesis, compared with other geographic locations.

**Table 4.** SMO Inhibitor Clinical Trial Outcomes in BCC

Cohort	No. of Patients	Response Rate (%)	Reduction in New Lesions	Median Duration of Response (months)	Serious AE Rate (%)	Discontinue Rate (%)	
						Patient Choice	AE
Vismodegib (metastatic) <sup>49</sup>	33	Response, 30; composite of RECIST and measurement of external dimensions and ulceration	NA	Independent review, 7.6; investigator assessment, 12.9	25	6	12
Vismodegib (locally advanced) <sup>49</sup>	63	CR, 21; overall response, 43	NA	Independent review and investigator assessment, 7.6	25	25	12
Vismodegib (NBCC syndrome) <sup>48</sup>	41 (active drug, 26; placebo, 15)	Mean reduction in size of existing BCC, 65% v 11%; no progression seen with vismodegib	2 (active) v 29 (placebo) new lesions per year	8	40	NA	54
Sonidegib (locally advanced) 200 mg <sup>50</sup>	66	CR, 3; PR, 44; DCR, 91	NA	Median PFS not reached; 12-month EFP, 83%	14		21
Sonidegib (metastatic) 200 mg <sup>50</sup>	13	CR, 0; PR, 15; DCR, 93	NA	PFS, 13.1; 12-month EFP, 65%	14		21
Sonidegib (locally advanced) 800 mg <sup>50</sup>	128	CR, 0; PR, 35; DCR, 78	NA	Median PFS not reached; 12-month EFP, 86%	30		36
Sonidegib (metastatic) 800 mg <sup>50</sup>	23	CR, 0; PR, 17; DCR, 83	NA	PFS, 10; 12-month EFP, 16%	30		36

Abbreviations: AE, adverse event; BCC, basal cell carcinoma; CR, complete response; DCR, disease control rate (defined as % of patients with CR, PR, and stable disease); EFP, event-free probability; NA, not applicable; PFS, progression-free survival; PR, partial response.

**Clinical Features and Diagnostic Workup**

Skin lesions generally grow rapidly over a few weeks, appearing as red, pink, blue, or violet lesions. The incidence of occult or clinically evident nodal metastases at presentation ranges between 30% and 50% and 20% to 25%, respectively.<sup>6,58</sup>

**Staging and Prognosis**

Current T stage is classified by tumor size or extension into surrounding structures (T1, ≤ 2 cm; T2, 2 to 5 cm; T3, > 5 cm; T4, invasion to bone, muscle, fascia, or cartilage).<sup>11</sup> Stages I (T1N0) and II (T2-4N0) are further categorized (as A or B) depending on whether nodes have been evaluated pathologically or clinically, on the basis that patients with pathologically evaluated negative lymph nodes experience better survival compared with clinically node-negative patients.<sup>59</sup> Of note, 10% to 15% of patients will have nodal metastases without an identifiable primary lesion and seem to experience better prognosis compared with those presenting with a synchronous or metachronous primary lesion.<sup>60</sup> MCC also has a high rate of distant spread, with a disease-specific mortality rate of 25% to 50%.<sup>6</sup> Presence of lymphovascular space involvement has been shown to be highly predictive for DSM.<sup>61</sup> The prognostic significance of the presence of MCV remains unclear, with some authors suggesting a better DSS in MCV-positive patients.<sup>53</sup> MCV-specific CD8 T cells can be detected in the blood of patients with MCC, which seems to correlate with disease progression and response to treatment.<sup>62</sup> Afanasiev et al<sup>62</sup> reported programmed death ligand 1 (PD-L1), which is associated with diminished host antitumor immune response, was expressed in nine of 13 MCCs tested. Dowlatshahi et al<sup>63</sup> reported that subsets of immune cells within MCC expressed PD-1, PD-L1, and PD-L2, and infiltrating T cells showed reduced activation, evidenced by decreased expression of CD69 and CD25. A number of immune checkpoint inhibitors are

being assessed in clinical trials, such as the PD-1 antibody pembrolizumab ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02267603) identifier NCT02267603), anti-PD-L1 MSB0010718C ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02155647) identifier NCT02155647), and anti-CTLA-4 ipilimumab ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02196961) identifier NCT02196961).

PET scanning seems useful in the staging of MCC. In a study by Siva et al,<sup>64</sup> PET staging had an impact on management in almost 40%, including upstaging in 17%. On multivariable analysis, PET stage was significantly associated with overall survival (*P* < .001).

**Treatment**

*Local disease.* Treatment recommendations are generally based on single-institution retrospective studies with data collected over many years. As a result, there are variations in treatment philosophy, particularly with respect to the need for aRT.

Wide local excision remains a standard approach, with a 1- to 2-cm minimum margin recommended for small lesions (≤ 2 cm). Although aRT in the presence of close margins has shown to lower the risk of local recurrence, some omit its use for small lesions with wide margins (> 1 cm) and no other adverse features.<sup>65,66</sup> Despite the lack of randomized studies, RT is an effective alternative to surgery, resulting in high (75% to 85%) in-field control rates.<sup>67</sup> Proponents of combined treatment advocate margin-negative surgery, without the need for wide margins, followed by aRT.<sup>68</sup>

*Regional lymph nodes.* Patient selection for elective nodal treatment remains a clinical dilemma. Tumor size is an important predictor of occult nodal disease. However, even small lesions harbor a 15% to 20% risk of nodal involvement, supporting the need for either pathologic nodal assessment or elective therapy in many cases.<sup>69</sup> SLNB offers the potential to assess regional nodes for occult disease and appropriate selection for further treatment.<sup>65</sup>

Patients with a positive SLNB should proceed to either lymphadenectomy or regional RT.<sup>4</sup> Because most patients with nodal metastases will still be candidates for nodal aRT—particularly in the setting of multiple nodes, ECE, and close soft tissue margins—synchronous RT to the primary site and elective nodal basin without performing a lymphadenectomy may be considered, avoiding combined-modality treatment to the neck.

RT doses are generally lower for MCC than for NMSC because of increased radioresponsiveness. Doses range from 60 to 66 Gy for gross disease, 56 to 60 Gy for microscopic disease, 50 to 56 Gy for clear margins, and 46 to 50 Gy for elective nodal treatment, in conventionally fractionated 2-Gy doses.<sup>4</sup>

**Systemic therapy.** Despite effective locoregional therapy, 30% to 70% of patients will experience distant relapse.<sup>70</sup> Chemotherapy in the definitive setting remains unproven.<sup>71</sup> As in small-cell carcinoma of the lung, carboplatinum and etoposide have been used. Single-arm studies of chemotherapy with or without RT in MCC have documented feasibility and efficacy.<sup>70</sup> However, a recent large retrospective survival analysis did not show a benefit from adjuvant chemotherapy for stage III disease.<sup>72</sup> In addition, many patients are older with comorbidities and unable to tolerate chemotherapy. A phase II study to evaluate the efficacy of chemoRT in achieving locoregional control and the value of PET in staging, RT planning, and treatment response assessment is currently being conducted (TROG 09.03; [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01013779) identifier NCT01013779).

Response rates of 60% to 70% have been demonstrated with palliative chemotherapy.<sup>73</sup> Other potential targets include antiapoptotic agents, inhibitors of c-Met and vascular endothelial growth factor receptor 2, and agents directed toward somatostatin receptors.

## SUMMARY

Despite the frequency of NMSC, there remains a lack of high-level evidence in the management of locally advanced disease, and patients with complex cases warrant referral to MDT boards. Retrospective series support consideration of aRT in the presence of advanced primary disease (T3-4), regional nodal involvement, cPNI, and immunosuppression. MCC is a highly aggressive disease that carries a poor prognosis and remains a therapeutic challenge because of the high rate of nodal and distant relapse.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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**AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

**Nonmelanoma Cutaneous Head and Neck Cancer and Merkel Cell Carcinoma: Current Concepts, Advances, and Controversies**

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