Scientific Research Publishing

Journal of Cancer Therapy, 2016, 7, 824-835
http://www.scirp.org/journal/jct
ISSN Online: 2151-1942
ISSN Print: 2151-1934

Treatment Recommendations among Radiation Oncologists in the Treatment of Cutaneous Squamous Cell Carcinoma with Perineural Invasion

Upendra Parvathaneni[1], Madhu Shetti[1], Daniel Berg[1], Seesha Takagishi[1], George E. Laramore[1], Chrysalyne D. Schmults[2], Anokhi Jambusaria-Pahlajani[3], Stephen D. Hess[3], Marvin Heyboer III[4], Jay J. Liao[1]

[1]University of Washington Medical Center, Seattle, Washington, USA
[2]Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA
[3]University of Pennsylvania, Philadelphia, Pennsylvania, USA
[4]State University of New York (SUNY), Syracuse, New York, USA
Email: upendra@uw.edu

How to cite this paper: Parvathaneni, U., Shetti, M., Berg, D., Takagishi, S., Laramore, G.E., Schmults, C.D., Jambusaria-Pahlajani, A., Hess, S.D., Heyboer III, M. and Liao, J.J. (2016) Treatment Recommendations among Radiation Oncologists in the Treatment of Cutaneous Squamous Cell Carcinoma with Perineural Invasion. *Journal of Cancer Therapy*, **7**, 824-835.
http://dx.doi.org/10.4236/jct.2016.711082

Received: September 1, 2016
Accepted: October 28, 2016
Published: October 31, 2016

Abstract

Purpose: Post-operative radiotherapy (PORT) for resected cutaneous squamous cell carcinoma (CSCC) with perineural invasion (PNI) is controversial. Therefore, we conducted a survey to review treatment recommendations among Radiation Oncologists (ROs) in the management of CSCC with PNI. Materials & Methods: In March 2011, we contacted all ROs and trainees in the US through email addresses listed in the 2009 ASTRO directory. Our web-based survey presented clinical vignettes involving Mohs micrographically resected CSCC with microscopic PNI (mPNI) or clinical PNI (cPNI). For each vignette, ROs were asked to indicate if PORT was appropriate and to further specify the dose and volume to treat. Results: Three hundred fifty two responses were completed and analyzed. The majority of ROs (72%) had over 10 years of post residency experience. 64% of the sampled ROs had a special interest in treating head and neck cancers, and 64% treated 4 or more cases per year. Approximately 95% recommended PORT for cPNI whereas 59% recommended PORT for mPNI. Post residency experience (10+ yrs vs. <10 yrs) was associated with a greater propensity to recommend PORT for mPNI (48% vs. 30%, p = 0.005) and for mPNI of deep subcutaneous non-named nerve involvement (80% vs. 60%, p = 0.001). ROs treating 8 or more cases per year (vs. <7) were more likely to recommend PORT for mPNI in immunocompromised patients (74% vs. 57%, p = 0.01). Conclusions: Our study demonstrates significant variability among ROs in the management of CSCC with mPNI. For cases of cPNI, an overwhelming majority recom-

mended PORT. In cases of mPNI, there was no consensus for recommending PORT, although experienced practitioners had a lower threshold for offering treatment. These results indicate the need for prospective clinical studies to clarify the role of PORT in CSCC patients with mPNI.

Keywords

Cutaneous Squamous Cell Carcinoma, Perineural Invasion, Head and Neck, Post Operative Radiation Therapy

1. Introduction

An estimated 700,000 new cases of cutaneous squamous cell carcinoma (CSCC) are diagnosed each year in the US, and the incidence is rising [1]-[3]. CSCC is generally cured with a surgical excision that achieves adequate microscopic margins. Perineural invasion (PNI), tumor diameter (>2 cm), deep invasion, poorly differentiated histology, and immunosuppression have been identified as negative prognostic factors for CSCC, and are often associated with a higher risk of recurrence, metastasis, and death [4]-[8].

Perineural invasion (PNI) is defined as the presence of malignant cells within the perineural space of nerves [9]. PNI is reported in approximately 5% - 10% of CSCC patients, and has been associated with other high-risk disease characteristics [10]-[12]. PNI has also been reported as an important independent negative prognostic factor for recurrence and survival [4] [6] [13] [14]. For instance, in a 2010 study of 315 patients with CSCC of the head and neck, Kygirdis *et al.* reported a 5-year recurrence free survival (RFS) of 26% and a 5-year overall survival rate of 45% in patients with PNI (compared to 82% and 76% in patients without PNI, respectively) [15].

PNI may be classified into two broad categories: microscopic PNI (mPNI) or more extensive clinical PNI (cPNI) [16]. mPNI is defined as involvement of small (<1 mm), peripheral, non-named nerves usually of the reticular dermis. Microscopic involvement is commonly found incidentally in an asymptomatic patient's pathology specimen obtained at the time of tumor resection with Mohs surgery. Specimens can include biopsies, excision specimens, or frozen sections. By definition, mPNI cannot be detected on radiographic studies. mPNI is generally associated with reduced morbidity and mortality [16], perhaps because of reduced volume of disease. In contrast, cPNI is defined as clinically detected disease. In addition, we also included radiographically detected disease as cPNI as this is usually accompanied by clinical symptoms.

Approximately 60% - 70% of all cases of PNI have mPNI [16]. As Mohs surgeons are diagnosing mPNI accurately in earlier stages [9], the incidence continues to rise. The prognosis of cPNI is significantly worse than mPNI with local control rates of approximately 50% vs. 80% - 90% respectively [14] [16]-[21]. Local control with cPNI that extends to the skull base is only 25% and long-term survival with cPNI is approximately 20% - 30% [14] [16]-[21]. Although the prognosis of cPNI is poor, radiotherapy is effective in providing symptom control, and may improve survival for some patients [19]

[21]-[24]. Cases of cPNI are usually referred for radiotherapy [25]. On the other hand, it is likely that not all cases of mPNI require post-operative radiotherapy (PORT) as many are cured with surgery alone [26]. Thus, it is difficult from the literature to establish who may or may not benefit from PORT [16] [27]. Additionally, while it is generally believed that radiotherapy is an effective treatment, PORT may be inconvenient for patients as it requires multiple daily visits to a Radiation treatment center, and is not without toxicity [18].

The uncertainties and controversies in the literature are reflected in a 2010 survey of Mohs surgeons that demonstrated a great variability in the management of CSCC with PNI, including indications for radiotherapy referral [25]. The treatment recommendations among Radiation Oncologists (ROs) in the management of CSCC with PNI are unknown. Therefore, we designed a web-based survey to determine whether there is a consensus among ROs for recommending PORT in standardized cases of CSCC with PNI. A second objective was to determine if there is a consensus regarding radiotherapy dose and elective volumes treated, which will be reported in a separate publication.

2. Methods

This study was approved by our Institutional Review Board in 2010 (IRB #7211).

2.1. Participants

According to the American College of Radiology's 2003 Survey of Radiologists and Radiation Oncologists, 97% of post-training, professionally active radiation oncologists are members of ASTRO [28]. Thus, in March 2011, we conducted a web-based survey of all ROs and trainees residing in the USA with an email address listed in the 2009 ASTRO directory. We invited all physicians via email and then contacted non-responders every two weeks for a total of three cycles. Collected data was de-identified and stored using http://www.surveymonkey.com to protect responders' privacy. Respondents also provided demographic information including years of post residency experience, whether they had a special interest in treating head and neck cancers, number of cases of CSCC with PNI treated per year, and whether they practiced in an academic vs. private setting.

2.2. Survey Design

We defined a standardized patient as a healthy 50 year old asymptomatic male who is status post Mohs surgical resection of a 1.0 cm well differentiated CSSC of the infra orbital medial cheek region that is confined to the dermis. Negative margins were obtained after two stages of excisions. There were no clinical symptoms suggestive of cPNI, nor radiographic evidence of PNI on an MRI. There was no clinical or radiographic evidence of lymph node involvement. Adjuvant chemotherapy was not an available option (**Table 1**).

In the first clinical vignette, the standardized patient presents with incidentally detected mPNI and ROs were asked if they would recommend PORT (**Figure 1**). If they

did recommend PORT, the RO was asked to specify the dose used at standard fractionation as well as volume they would treat *i.e.* to the operative bed and/or any elective treatment to lymph nodal regions or neural pathways.

Six subsequent vignettes followed each introducing one additional poor prognostic factor (Table 1). In each case, ROs indicated if PORT was appropriate followed by dose and volume recommendations. The overall tendency to recommend PORT for patients with mPNI was calculated as an average of Questions 1 - 3. Similarly, PORT recommendations for patients with cPNI were calculated as an average of Questions 4 - 7.

Table 1. Clinical vignettes and PORT recommendations.

The standardized patient: 50 yr. old asymptomatic male, status post Mohs surgical resection with negative margins of a 1.0 cm well differentiated CSSC of the medial cheek that is confined to the dermis. You receive the following additional information[a]:	% ROs recommending PORT	95% CI
1. Pathology: Tumor is 1.0 cm with mPNI.	43	0.37 - 0.48
2. As in #1, but patient had a renal transplant and is on immunosuppressive medications.	61	0.56 - 0.67
3. sPNI: As in #1, but extends deep along a non-named subcutaneous nerve and required a third Mohs stage for clearance. Post-op MRI: clear.	74	0.69 - 0.79
4. cPNI: As in #1, but pre-op exam revealed numbness along V2 distribution. Post-op MRI: clear.	87	0.82 - 0.90
5. nPNI: Tumor is 1.0 cm with PNI involving the infraorbital nerve. Required excision through infraorbital foramen. Patient is asymptomatic. Post-op MRI: clear.	96	0.93 - 0.98
6. cPNI: As in #5, AND Pre-op exam showed numbness along V2. Post-op MRI: clear.	98	0.95 - 0.99
7. cPNI: As in #6, AND Post-op MRI shows thickening/enhancement of infraorbital nerve (V2) up to the foramen rotundum.	99	0.97 - 0.99

Abbreviations: mPNI is microscopic PNI. nPNI is PNI of a named nerve. cPNI is symptomatic PNI or radiologically detectable tumor. NB: nPNI is also considered as cPNI; a. Questions 1 - 3 consider a patient with mPNI, and Questions 4 - 7 consider a patient with cPNI.

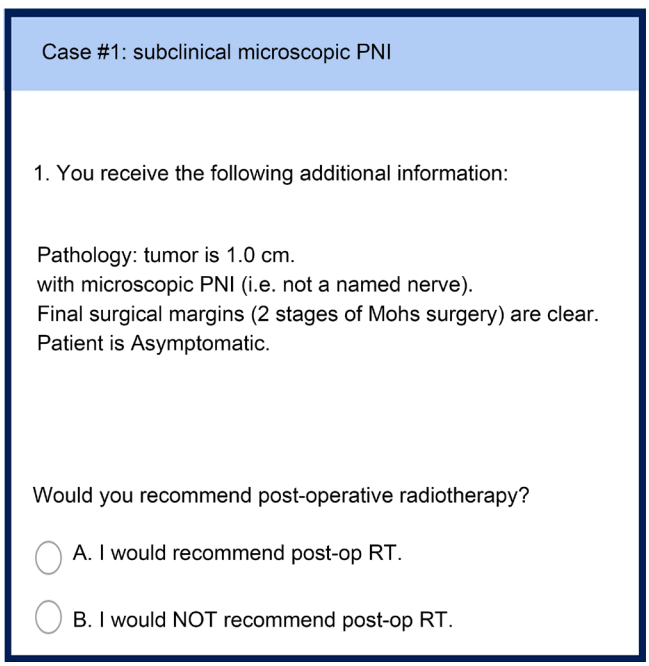

Figure 1. Sample clinical vignette.

2.3. Statistical Analysis

All statistical analyses were performed using SPSS version 16. We used standard descriptive statistics and frequency tabulation. Associations between willingness to recommend PORT for each vignette were assessed by cross-tabulation and 95% confidence intervals calculated using the Wald method. Responses were stratified according to years of post residency experience (<10 yrs vs. 10+ yrs), special interest in treating head and neck cancers and number of cases treated per year (0 - 7 cases vs. 8+ cases). Associations between sub-categorical variables were assessed via cross-tabulation and Fisher's exact test to generate two tailed p values and differences were considered statistically significant when the p value was <0.05.

3. Results

3.1. Demographics

Three thousand six hundred eighty eight physicians were contacted to participate in our survey, of which 368 of the emails were undeliverable for various reasons and 636 opened the survey. One hundred ten responded requesting not to participate in this or any other surveys in the future due to a lack of time. One hundred eighty four responded indicating they preferred not to participate in this survey due to a lack of experience in treating CSCC with PNI. Finally, 352 completed responses were eligible for analysis. Characteristics of the respondents are listed in Table 2.

Table 2. Characteristics of survey respondents.

Variable	Total % of respondents (n = 352)
Years post-residency	
1 - 3	8 (29)
3 - 5	5 (16)
5 - 10	11 (40)
10+	70 (245)
Currently in residency	6 (21)
Practice location	
Academic	32 (102)
Private	57 (183)
Both	11 (34)
Special interest in treating H & N cancer?	
Yes	64 (207)
No	36 (115)
Number of CSCC with PNI cases treated in past year	
0 - 3	36 (117)
4 - 7	38 (123)
8 - 10	16 (51)
11 or more	10 (34)

3.2. Threshold to Offer PORT

Recommendations of the ROs to offer PORT for each clinical vignette are listed in Table 1.

The majority of ROs (95%) recommended PORT for patients with cPNI (including nPNI). However, opinion was divided among respondents for cases of mPNI. 59% of ROs indicated they would offer PORT to patients presenting with mPNI. With each additional poor prognostic factor such as immunosuppression, there was a greater willingness to offer PORT. The majority of ROs (74%) also recommended PORT for cases of PNI involving a subcutaneous nerve (sPNI, 95% CI, 69% - 79%).

3.3. Stratification Based on Years of Post-Residency Experience

ROs with over ten years' of experience were more willing to offer PORT for mPNI than the less experienced ROs (48% vs. 30% p = 0.005). The majority of ROs with over ten years' of experience (80%) also indicated they would offer PORT for cases of sPNI, compared to 60% by those with less than 10 years' experience (p = 0.001).

3.4. Stratification Based on Number of CSCC with PNI Cases Treated per Year

ROs treating a greater case volume (8+ cases per year) are more likely to offer PORT for an immunocompromised patient with mPNI (74% vs. 57%, p = 0.011).

3.5. Stratification Based on Head and Neck Interest

Special interest in treating head and neck cancers was associated with a borderline significance to offer PORT for sPNI (78% vs. 67% p = 0.053).

4. Discussion

Cutaneous squamous cell carcinoma is a common cancer, and its incidence is increasing [1]-[3]. Perineural invasion is diagnosed in 5% - 10% of all CSCC cases [10], and has been identified as a high-risk characteristic in CSCC [15]. PNI has also been shown to influence disease progression, with local control rates of 80% - 90% reported for mPNI and 25% - 54% for cPNI [16] [17]. Additionally, PNI has been associated with poor overall survival [15], and higher disease-specific death [27], compared to CSCC with other high-risk factors.

Our study demonstrated a wide variability among ROs in the management of CSCC with mPNI. For cases of cPNI, an overwhelming majority of ROs recommended PORT. In contrast, for cases of mPNI there was no clear consensus on PORT. To our knowledge, this is the first study that examines the treatment recommendations among ROs in the management of CSCC with PNI.

These results are strikingly similar to a study by Jambusaria-Pahalajani *et al.* who evaluated the patterns of practice among fellowship trained Mohs surgeons through a survey [25]. They demonstrated a parallel lack of consensus regarding the indications for PORT in cases of mPNI. On the other hand, there was a consensus among the Mohs

surgeons to refer a patient with cPNI for radiotherapy.

The uncertainty surrounding the management of CSCC with mPNI is not surprising. Published data do not establish who may or may not benefit from PORT after a microscopically clear resection of CSCC with incidentally detected mPNI [15] [16] [26] [27]. Emerging subcategories of mPNI, concerning the extent of nerve involvement, may contribute to conflicting opinions. Recent studies have found that more extensive nerve involvement [26] [29] and larger nerve caliber [12] [30] are associated with worse prognosis. Sapir *et al.* recently reported data on 102 patients with CSCC on the head and neck all presenting with mPNI. They found that PORT improved the two-year recurrence free survival (RFS) for patients with >2 involved nerves (94% with PORT versus 25% without PORT). On the other hand, in patients with 1 - 2 involved nerves, there was not a significant difference in RFS between patients treated with and without PORT [26]. These data suggest a subset of mPNI patients may not require PORT. However, this was a retrospective study and needs to be confirmed prospectively.

Furthermore, in an investigator-blinded retrospective cohort study of 48 patients, Ross *et al.* reported that 32% with CSCC with "larger nerve" involvement (≥0.1 mm) died of their disease and 50% had a local recurrence [30]. In contrast, none with "smaller" nerve involvement (<0.1 mm) died from their disease and only 5% developed a local recurrence. While both the groups of patients in this study were well balanced for most prognostic factors, the group with "larger" nerve involvement had a disproportionate number of recurrent cancers (13 vs. 1). Recurrent cancers are known to have a worse prognosis [4] [6] [14]. 11 of the 23 patients with the "smaller" nerve involvement received PORT. Although both groups were well balanced in this regard, the details of radiotherapy were not included and therefore the contribution from PORT to the results is unclear. These data are quite intriguing and may have profound implications for clinical practice and the design of future studies.

Additionally, while it is generally believed that radiotherapy is an effective treatment, PORT may be inconvenient for some patients, as it requires multiple daily visits to a Radiotherapy center for five to six weeks, and may be associated with toxicity. Garcia-Serra *et al.* reported that 10% of patients treated with PORT had treatment-related toxicity, including soft tissue necrosis, bone exposure, and osteoradionecrosis [18]. However, modern radiotherapy is significantly less morbid and complications such as osteonecrosis are rare [31]-[33].

Currently available management guidelines [34] vary with regard to the role of PORT for CSCC with PNI. The NCCN guidelines currently recommend PORT following a clear Mohs resection for cPNI, but do not comment on the use of PORT in patients with mPNI [34].

Some caution is required in interpreting the results of any voluntary survey. Selection bias and sampling errors are inherent issues as respondents usually represent a "self-selected" group and their views may not reflect those of the wider community of clinicians thus, limiting their generalizability. For example, the majority (70%) of ROs that responded to our survey had greater than 10 years of experience and 64% had a self-

identified special interest in treating head and neck cancers.

The overall response rate to this survey was approximately 10%. However, the completion rate, which represents the ratio of opened and completed surveys, was 55% which is within the reference range for an e-mail-based survey [35]. There were 352 completed responses that could be analyzed and this number is consistent with other recent large-scale radiation oncology survey studies [36]-[41]. Our survey was open to all ROs, regardless of interest or experience with a relatively uncommon clinical scenario. In fact, 184 ROs responded that they lack the expertise/experience with CSCC with PNI to participate in this survey. Surveys that target practitioners with a special interest in a particular topic tend to receive a higher response rate [25] [42]. While the response rates appear better in these studies, this does not increase their statistical power, which is based on the absolute number of analyzable responses. The number of completed responses in our survey (n = 352) compare well with the survey of Mohs surgeons (n = 118), although their response rate is higher at 47% due the fewer invited participants [25]. Given that the American Board of Radiology reported 3943 full-time equivalent ROs in 2010 [43], and approximately 9.5% of ROs specialize in head and neck cancers [28], this survey was successful in garnering treatment recommendations from an estimated 60% of all ROs specializing in head and neck cancers. Hence, we believe the findings of our survey are valid.

In this survey, we examined the impact of prognostic factors that are common in clinical practice. Iatrogenic immunosuppression in organ transplant recipients is a major risk factor for morbidity and mortality in CSCC [4] [5] [22] [44]. Deep invasion has also been described as a poor prognostic factor in studies based on major prospective databases [5] [6]. We addressed this issue with a question involving sPNI. sPNI was defined as PNI involving a subcutaneous nerve. The anatomic tumor location on the cheek has also been associated with a higher risk for metastasis in CSCC [45]. Thus, we chose a head and neck-mid face location for the index lesion. Although there are other known prognostic factors, we could test only a limited number as we had to balance between the length and complexity of the survey. However, the vignettes provided in this survey are representative of common CSCC presentations and thus bear clinical relevance.

Further research is needed to clearly define, and determine the treatment related implications, of mPNI of varying extents. For example, a controlled prospective study where PORT is omitted for patients with mPNI but is substratified according to the known prognostic factors is necessary to fully elucidate the role of PORT in this population of patients.

5. Conclusion

The results of this study demonstrate wide variability without a clear consensus in the management of CSSC with mPNI among U.S. based ROs. A good first step in situations where there is uncertainty in practice is to conduct a survey to attempt to understand the views of practitioners. In this survey, experienced practitioners in general had a

lower threshold to offer treatment. In cases of cPNI, there was a clear consensus with an overwhelming majority of ROs recommending PORT. On the other hand, treatment recommendations from ROs were split in cases of mPNI. More data from carefully designed prospective studies are necessary to establish a clear standard of care for CSCC with mPNI.

References

[1] Alam, M. and Ratner, D. (2001) Cutaneous Squamous-Cell Carcinoma. *The New England Journal of Medicine*, **344**, 975-983. http://dx.doi.org/10.1056/NEJM200103293441306

[2] Squamous Cell Carcinoma. https://www.aad.org/public/diseases/skin-cancer/squamous-cell-carcinoma

[3] Rogers, H.W., Weinstock, M.A., Harris, A.R., Hinckley, M.R., Feldman, S.R., Fleischer, A. B. and Coldiron, B.M. (2010) Incidence Estimate of Nonmelanoma Skin Cancer in the United States, 2006. *Archives of Dermatology*, **146**, 283-287. http://dx.doi.org/10.1001/archdermatol.2010.19

[4] Rowe, D.E., Carroll, R.J. and Day Jr., C.L. (1992) Prognostic Factors for Local Recurrence, Metastasis, and Survival Rates in Squamous cell Carcinoma of the Skin, Ear, and Lip. Implications for Treatment Modality Selection. *Journal of the American Academy of Dermatology*, **26**, 976-990. http://dx.doi.org/10.1016/0190-9622(92)70144-5

[5] Brantsch, K.D., Meisner, C., Schonfisch, B., Trilling, B., Wehner-Caroli, J., Rocken, M. and Breuninger, H. (2008) Analysis of Risk Factors Determining Prognosis of Cutaneous Squamous-Cell Carcinoma: A Prospective Study. *The Lancet Oncology*, **9**, 713-720. http://dx.doi.org/10.1016/S1470-2045(08)70178-5

[6] Clayman, G.L., Lee, J.J., Holsinger, F.C., *et al.* (2005) Mortality Risk from Squamous Cell Skin Cancer. *Journal of Clinical Oncology*, **23**, 759-765. http://dx.doi.org/10.1200/JCO.2005.02.155

[7] Frierson Jr., H.F. and Cooper, P.H. (1986) Prognostic Factors in Squamous Cell Carcinoma of the Lower Lip. *Human Pathology*, **17**, 346-354. http://dx.doi.org/10.1016/S0046-8177(86)80457-9

[8] Moore, B.A., Weber, R.S., Prieto, V., *et al.* (2005) Lymph Node Metastases from Cutaneous Squamous Cell Carcinoma of the Head and Neck. *Laryngoscope*, **115**, 1561-1567. http://dx.doi.org/10.1097/01.mlg.0000173202.56739.9f

[9] Dunn, M., Morgan, M.B. and Beer, T.W. (2009) Perineural Invasion: Identification, Significance, and a Standardized Definition. *Dermatologic Surgery*, **35**, 214-221. http://dx.doi.org/10.1111/j.1524-4725.2008.34412.x

[10] Porceddu, S.V. (2015) Prognostic Factors and the Role of Adjuvant Radiation Therapy in Non-Melanoma Skin Cancer of the Head and Neck. Am Soc Clin Oncol Educ Book, e513-518. http://dx.doi.org/10.14694/EdBook_AM.2015.35.e513

[11] Campoli, M., Brodland, D.G. and Zitelli, J. (2014) A Prospective Evaluation of the Clinical, Histologic, and Therapeutic Variables Associated with Incidental Perineural Invasion in Cutaneous Squamous Cell Carcinoma. *Journal of the American Academy of Dermatology*, **70**, 630-636. http://dx.doi.org/10.1016/j.jaad.2013.11.034

[12] Carter, J.B., Johnson, M.M., Chua, T.L., Karia, P.S. and Schmults, C.D. (2013) Outcomes of Primary Cutaneous Squamous Cell Carcinoma with Perineural Invasion: An 11-Year Cohort Study. *JAMA Dermatology*, **149**, 35-41. http://dx.doi.org/10.1001/jamadermatol.2013.746

[13] Ballantyne, A.J., McCarten, A.B. and Ibanez, M.L. (1963) The Extension of Cancer of the Head and Neck through Peripheral Nerves. *The American Journal of Surgery*, **106**, 651-667. http://dx.doi.org/10.1016/0002-9610(63)90074-6

[14] Goepfert, H., Dichtel, W.J., Medina, J.E., Lindberg, R.D. and Luna, M.D. (1984) Perineural Invasion in Squamous Cell Skin Carcinoma of the Head and Neck. *The American Journal of Surgery*, **148**, 542-547. http://dx.doi.org/10.1016/0002-9610(84)90385-4

[15] Kyrgidis, A., Tzellos, T.G., Kechagias, N., *et al.* (2010) Cutaneous Squamous Cell Carcinoma (SCC) of the Head and Neck: Risk Factors of Overall and Recurrence-Free Survival. *European Journal of Cancer*, **46**, 1563-1572. http://dx.doi.org/10.1016/j.ejca.2010.02.046

[16] Han, A. and Ratner, D. (2007) What Is the Role of Adjuvant Radiotherapy in the Treatment of Cutaneous Squamous Cell Carcinoma with Perineural Invasion? *Cancer*, **109**, 1053-1059. http://dx.doi.org/10.1002/cncr.22509

[17] Balamucki, C.J., Mancuso, A.A., Amdur, R.J., Kirwan, J.M., Morris, C.G., Flowers, F.P., Mendenhall, W.M., *et al.* (2012) Skin Carcinoma of the Head and Neck with Perineural Invasion. *American Journal of Otolaryngology*, **33**, 447-454. http://dx.doi.org/10.1016/j.amjoto.2011.11.004

[18] Garcia-Serra, A., Hinerman, R.W., Mendenhall, W.M., Amdur, R.J., Morris, C.G., Williams, L.S. and Mancuso, A.A. (2003) Carcinoma of the Skin with Perineural Invasion. *Head Neck*, **25**, 1027-1033. http://dx.doi.org/10.1002/hed.10334

[19] McCord, M.W., Mendenhall, W.M., Parsons, J.T., Amdur, R.J., Stringer, S.P., Cassisi, N.J. and Million, R.R. (2000) Skin Cancer of the Head and Neck with Clinical Perineural Invasion. *International Journal of Radiation Oncology, Biology, Physics*, **47**, 89-93. http://dx.doi.org/10.1016/S0360-3016(99)00533-7

[20] McCord, M.W., Mendenhall, W.M., Parsons, J.T. and Flowers, F.P. (1999) Skin Cancer of the Head and Neck with Incidental Microscopic Perineural Invasion. *International Journal of Radiation Oncology, Biology, Physics*, **43**, 591-595. http://dx.doi.org/10.1016/S0360-3016(98)00474-X

[21] Mendenhall, W.M., Amdur, R.J., Williams, L.S., Mancuso, A.A., Stringer, S.P. and Price Mendenhall, N. (2002) Carcinoma of the Skin of the Head and Neck with Perineural Invasion. *Head Neck*, **24**, 78-83. http://dx.doi.org/10.1002/hed.10025

[22] Veness, M.J. (2005) Treatment Recommendations in Patients Diagnosed with High-Risk Cutaneous Squamous Cell Carcinoma. *Australasian Radiology*, **49**, 365-376. http://dx.doi.org/10.1111/j.1440-1673.2005.01496.x

[23] Warren, T.A., Panizza, B., Porceddu, S.V., Gandhi, M., Patel, P., Wood, M., Redmond, M., *et al.* (2016) Outcomes after Surgery and Postoperative Radiotherapy for Perineural Spread of Head and Neck Cutaneous Squamous Cell Carcinoma. *Head Neck*, **38**, 824-831. http://dx.doi.org/10.1002/hed.23982

[24] Balamucki, C.J., DeJesus, R., Galloway, T.J., Mancuso, A.A., Amdur, R.J., Morris, C.G., Mendenhall, W.M., *et al.* (2015) Impact of Radiographic Findings on for Prognosis Skin Cancer with Perineural Invasion. *American Journal of Clinical Oncology*, **38**, 248-251. http://dx.doi.org/10.1097/COC.0b013e3182940ddf

[25] Jambusaria-Pahlajani, A., Hess, S.D., Katz, K.A., Berg, D. and Schmults, C.D. (2010) Uncertainty in the Perioperative Management of High-Risk Cutaneous Squamous Cell Carcinoma among Mohs Surgeons. *Archives of Dermatology*, **146**, 1225-1231. http://dx.doi.org/10.1001/archdermatol.2010.323

[26] Sapir, E., Tolpadi, A., McHugh, J., Samuels, S.E., Elalfy, E., Spector, M., Eisbruch, A., *et al.* (2016) Skin Cancer of the Head and Neck with Gross or Microscopic Perineural Involve-

ment: Patterns of Failure. *Radiotherapy and Oncology*, **120**, 81-86. http://dx.doi.org/10.1016/j.radonc.2016.06.011

[27] Jambusaria-Pahlajani, A., Miller, C.J., Quon, H., Smith, N., Klein, R.Q. and Schmults, C.D. (2009) Surgical Monotherapy versus Surgery plus Adjuvant Radiotherapy in High-Risk Cutaneous Squamous Cell Carcinoma: A Systematic Review of Outcomes. *Dermatologic Surgery*, **35**, 574-585. http://dx.doi.org/10.1111/j.1524-4725.2009.01095.x

[28] Lewis, R.S. and Sunshine, J.H. (2007) Radiation Oncologists in the United States. *International Journal of Radiation Oncology*, *Biology*, *Physics*, **69**, 518-527. http://dx.doi.org/10.1016/j.ijrobp.2007.02.053

[29] Lin, C., Tripcony, L., Keller, J., Poulsen, M., Martin, J., Jackson, J. and Dickie, G. (2012) Perineural Infiltration of Cutaneous Squamous Cell Carcinoma and Basal Cell Carcinoma without Clinical Features. *International Journal of Radiation Oncology*, *Biology*, *Physics*, **82**, 334-340. http://dx.doi.org/10.1016/j.ijrobp.2010.09.040

[30] Ross, A.S., Whalen, F.M., Elenitsas, R., Xu, X., Troxel, A.B. and Schmults, C.D. (2009) Diameter of Involved Nerves Predicts Outcomes in Cutaneous Squamous Cell Carcinoma with Perineural Invasion: An Investigator-Blinded Retrospective Cohort Study. *Dermatologic Surgery*, **35**, 1859-1866. http://dx.doi.org/10.1111/j.1524-4725.2009.01354.x

[31] Ben-David, M.A., Diamante, M., Radawski, J.D., Vineberg, K.A., Stroup, C., Murdoch-Kinch, C.A., Eisbruch, A., *et al.* (2007) Lack of Osteoradionecrosis of the Mandible after Intensity-Modulated Radiotherapy for Head and Neck Cancer: Likely Contributions of Both Dental Care and Improved Dose Distributions. *International Journal of Radiation Oncology*, *Biology*, *Physics*, **68**, 396-402. http://dx.doi.org/10.1016/j.ijrobp.2006.11.059

[32] Nutting, C.M., Morden, J.P., Harrington, K.J., Urbano, T.G., Bhide, S.A., Clark, C., Hall, E., *et al.* (2011) Parotid-Sparing Intensity Modulated versus Conventional Radiotherapy in Head and Neck Cancer (PARSPORT): A Phase 3 Multicentre Randomised Controlled Trial. *Lancet Oncology*, **12**, 127-136. http://dx.doi.org/10.1016/S1470-2045(10)70290-4

[33] Parvathaneni, U., Yu, T., Mason, B.E., *et al.* (2007) Superior Cochlear and Parotid Sparing and Conformality by Intensity-Modulated Radiation Therapy over Wedge Pair Technique for Unilateral Treatment of Tonsil Carcinoma. *International Journal of Radiation Oncology*, *Biology*, *Physics*, **68**, 396-402.

[34] Squamous Cell Skin Cancer (2016) Version 1. http://www.nccn.org/professionals/physician_gls/pdf/squamous.pdf

[35] Hewson, C., Yule, P., Laurent, D. and Vogel, C. (2003) Internet Research Methods: A Practical Guide for the Behavioural and Social Sciences. Sage, London. http://dx.doi.org/10.4135/9781849209298

[36] Cmelak, A.J., Choy, H., Shyr, Y., Mohr, P., Glantz, M.J. and Johnson, D.H. (1999) National Survey on Prophylactic Cranial Irradiation: Differences in Practice Patterns between Medical and Radiation Oncologists. *International Journal of Radiation Oncology*, *Biology*, *Physics*, **44**, 157-162. http://dx.doi.org/10.1016/S0360-3016(98)00557-4

[37] Fairchild, A., Barnes, E., Ghosh, S., Ben-Josef, E., Roos, D., Hartsell, W., Chow, E., *et al.* (2009) International Patterns of Practice in Palliative Radiotherapy for Painful Bone Metastases: Evidence-Based Practice? *International Journal of Radiation Oncology*, *Biology*, *Physics*, **75**, 1501-1510. http://dx.doi.org/10.1016/j.ijrobp.2008.12.084

[38] Schaefer, N.G., Huang, P., Buchanan, J.W. and Wahl, R.L. (2011) Radioimmunotherapy in Non-Hodgkin Lymphoma: Opinions of Nuclear Medicine Physicians and Radiation Oncologists. *Journal of Nuclear Medicine*, **52**, 830-838. http://dx.doi.org/10.2967/jnumed.110.085589

[39] Showalter, T.N., Ohri, N., Teti, K.G., Foley, K.A., Keith, S.W., Trabulsi, E.J., Gomella, L.G., *et al.* (2012) Physician Beliefs and Practices for Adjuvant and Salvage Radiation Therapy after Prostatectomy. *International Journal of Radiation Oncology*, *Biology*, *Physics*, **82**, e233-e238. http://dx.doi.org/10.1016/j.ijrobp.2011.04.003

[40] Jolly, S., Kong, F., Komaki, R., Gaspar, L., Bonner, J.A., Sun, A., Movsas, B., *et al.* (2009) Factors Associated with Patterns of Practice for Elective Nodal Irradiation in Non-Small Cell Lung Cancer Patients among US Radiation Oncologists. *International Journal of Radiation Oncology*, *Biology*, *Physics*, **75**, S129-S130. http://dx.doi.org/10.1016/j.ijrobp.2009.07.310

[41] Sturgeon, J.D. and Zouain, N. (2011) A Survey of Androgen Deprivation Patterns of Practice in Prostate Cancer by Radiation Oncologists in the United States. *International Journal of Radiation Oncology*, *Biology*, *Physics*, **81**, S431-S432. http://dx.doi.org/10.1016/j.ijrobp.2011.06.711

[42] Arvold, N.D., Catalano, P.J., Sweeney, C.J., Hoffman, K.E., Nguyen, P.L., Balboni, T.A., Beard, C.J., *et al.* (2010) Patterns of Care for Stage I Seminoma: A Survey of American Radiation Oncologists. *International Journal of Radiation Oncology*, *Biology*, *Physics*, **78**, S193. http://dx.doi.org/10.1016/j.ijrobp.2010.07.469

[43] Smith, B.D., Haffty, B.G., Wilson, L.D., Smith, G.L., Patel, A.N. and Buchholz, T.A. (2010) The Future of Radiation Oncology in the United States from 2010 to 2020: Will Supply Keep Pace with Demand? *Journal of Clinical Oncology*, **28**, 5160-5165. http://dx.doi.org/10.1200/JCO.2010.31.2520

[44] Stasko, T., Brown, M.D., Carucci, J.A., Euvrard, S., Johnson, T.M., Sengelmann, R.D., Tope, W.D., *et al.* (2004) Guidelines for the Management of Squamous Cell Carcinoma in Organ Transplant Recipients. *Dermatologic Surgery*, **30**, 642-650.

[45] Brougham, N.D., Dennett, E.R., Cameron, R. and Tan, S.T. (2012) The Incidence of Metastasis from Cutaneous Squamous Cell Carcinoma and the Impact of Its Risk Factors. *Journal of Surgical Oncology*, **106**, 811-815. http://dx.doi.org/10.1002/jso.23155