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A systematic review of patients with Merkel cell carcinoma of the head and neck and a negative sentinel lymph node biopsy

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ABSTRACT

Background: A negative sentinel lymph node biopsy (SLNB) from patients with head and neck Merkel cell carcinoma (HNMCC) may allow the patient to avoid further adjunctive therapies. However, there is considerable regional variability of lymphatic drainage from primary sites involving the head and neck, and Merkel cell carcinoma (MCC) has aggressive biologic behavior.
Objective: The primary aim of this systematic review was to document the incidence of regional recurrence and mortality from HNMCC patients after a negative SLNB.
Methods: A systematic search of the English literature was conducted via Ovid Medline and Embase from inception until 2013 and the Cochrane Central Register of Controlled Trials from 1991 to January 2014.
Results: Twenty-three studies, with a total of 81 patients matched the inclusion criteria. The incidence of regional recurrence from the entire cohort was 12.3%, and there was a 5% mortality rate. The mean follow-up time, excluding the 30 patients who did not have individual follow-up times specified, was 32.8 months.
Limitations: This review included studies had variable follow-up durations and treatments for MCC.
Conclusions: Despite negative pathologic staging of the neck using SLNB in HNMCC patients, there is still a high incidence of regional recurrence and mortality, over a short follow-up period.

Introduction

Merkel cell carcinoma (MCC) is a rare aggressive neuroendocrine neoplasm that occurs most commonly in the head and neck region (Smith et al., 2012). It shows a high propensity for locoregional and distant metastases (Bichakjian et al., 2007) and has a poor 5-year survival rate ranging between 30% and 64% (Allen et al., 2005; Bichakjian et al., 2007). MCC was recently discovered to be associated with Merkel cell polyomavirus (Feng et al., 2008) and tends to present in older patients with suppressed immune systems (Agelli et al., 2010). To determine the appropriate therapy for the regional lymph node basin, staging is required. This can take place clinically via clinical examination and imaging and pathologically with the use of a sentinel lymph node biopsy (SLNB), fine-needle aspiration cytology, or regional lymph node clearance.

SLNB started to become widely used in the staging and treatment of MCC during the 1990s (Rodrigues et al., 2001; Santamaria-Barria et al., 2013), although the first trials of this technique may have been performed even earlier (Messina et al., 1997). SLNB involves selecting, surgically dissecting, and pathologically analyzing the lymph nodes that are first drained from the primary tumor site. This method can be used to predict whether further adjunctive therapy in the form of a regional lymph node clearance or regional radiotherapy is warranted. SLNB may promote quality of life for the patient by minimizing the need for these further interventions at that particular time point, should there be no metastatic disease identified in the sentinel nodes.

With regard to patients with non-site-specific MCC, data on the differences in recurrence rates between negative and positive SLNB groups are conflicting. Two meta-analyses have shown higher recurrence rates (location of recurrence not specified) in patients with positive SLNB (18.7−33%) compared with patients with negative SLNB (3–7.5%) (Mehrany et al., 2002; Warner et al., 2008). However a large single study by Fields et al. (2011) showed comparable nodal recurrence rates between the positive (2.2%) and negative (8%) SLNB groups.

It is hard to compare rates of recurrence between positive and negative SLNB groups of patients, given that the treatments to the regional lymph nodes that they typically receive are much different.

Normally, patients with negative SLNB do not undergo further surgery to the regional lymph nodes to allow comparison with radiotherapy. However, MCC is known to be a radiosensitive tumor, and a French randomized control trial published in 2012 showed that regional radiotherapy significantly reduced regional recurrence rates compared with the observation arm ($p = .007$) in a group of patients with clinically negative nodes (Jouary et al., 2012).

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Fields et al. (2011) showed that among patients with a positive SLNB and had a complete lymph node dissection (CLND) with or without nodal radiotherapy ($n = 21$) and those who had nodal radiotherapy alone ($n = 17$), there was only one nodal recurrence in the combined group, occurring in a patient who had a CLND without radiotherapy (Fields et al., 2011). This information supports the efficacy of radiotherapy for MCC and suggests that it may be as efficacious as CLND (Fields et al., 2011).

One of the main problems of SLNB in the head and neck region has been the variation in lymphatic drainage patterns, which make it difficult to reliably predict the sentinel lymph node (Hoetzenecker et al., 2011; Stadelmann et al., 2004; Willis and Ridge, 2007). The 2013 American National Comprehensive Cancer Network guidelines for the treatment of MCC advise performing an SLNB for lymph nodes that are disease free clinically (cN0) (National Comprehensive Cancer Network, 2013). However, these guidelines also advise that SLNB is not mandatory for the head and neck region, given that SLNB is less reliable from this region (National Comprehensive Cancer Network, 2013).

There is little research documenting the value of SLNB in MCC of the head and neck. This is important information for a number of reasons. First, an SLNB may detect occult disease (Fields et al., 2011; Lok et al., 2012). Second, an SLNB is complicated by the variation in lymphatic drainage from the head and neck, which may cause false-negative results (Stadelmann et al., 2004; Willis and Ridge, 2007). Third, it has implications for further treatment. A positive SLNB for metastasis means that the patient will be offered further adjunctive therapies, including lymph node dissection, radiation therapy, and potentially chemotherapy (Fields et al., 2011; National Comprehensive Cancer Network, 2013). However, a negative SLNB may result in the patient not being offered adjunctive treatment to the regional lymph nodes (National Comprehensive Cancer Network, 2013), which could impair disease-free survival and overall survival rates (Clark et al., 2007; Veness et al., 2005) and increase the risk of regional recurrence (Clark et al., 2007). Hence, it is important to closely examine how patients with head and neck MCC who have a negative SLNB biopsy are managed and what their prognosis is.

The primary purpose of this paper was to conduct a systematic review of the English literature to determine the regional recurrence and mortality rates among patients with head and neck MCC who have a negative SLNB. Second, the aim was to determine whether adjunctive radiotherapy to either the primary tumor site or the regional lymphatic basin had any significant influence on the regional recurrence or mortality rates among patients with head and neck MCC who a negative SLNB.

Methods

A systematic literature search, limited to the English language, was conducted by using Ovid Medline from 1946 until 2013, Embase search through Embase and Medline records from 1966 until 2013, and the Cochrane Central Register of Controlled Trials from 1991 to January 2014 (Fig. 1). Abstracts were filtered for content, and original papers that discussed MCC were selected for further perusal.

Inclusion criteria were as follows: studies with a minimum of two patients; patients with MCC of the head and neck; patients with a negative SLNB; and information pertaining to the survival status or recurrence of MCC for each patient undergoing SLNB. Patients were included if they had a follow-up period of 3 months or more. Studies that did not specify individual follow-up periods but indicated an average or median follow-up of 3 months or more were also included.

Studies were excluded if no follow-up duration was specified and if there were duplicated reports. From the studies that were included, patients who could be identified as having no follow-up duration specified were also excluded. Single case reports were excluded to minimize potential bias of reporting. Cross-referencing from these papers was also conducted to locate other relevant papers that matched the inclusion criteria.

The following features were noted, if provided: gender, age, type of surgery and local and regional radiotherapy provided at the time of diagnosis, time to recurrence, follow-up duration, location of recurrence, and time to death if it occurred.

Two-tailed Fisher tests were conducted to determine if radiotherapy to the primary site or regional lymphatic basin in patients with head and neck MCC who had a negative SLNB significantly influenced the incidence of regional MCC recurrence. A significant result was regarded as a p value $< .05$. Missing or unknown data were excluded from analysis. Statistical analyses were performed using GraphPad Software 2013.

Results

Twenty-three English language studies, containing 81 patients who matched the inclusion criteria of the study, were identified (Tables 1 and 2). One study was excluded because it was unclear how long all the patients in the group received follow-up (Wong et al., 2009). In this study, there were 6 patients with head and neck MCC and a negative SLNB; of these patients, at least 1 experienced regional recurrence. There were 3 patients in this study who had a recurrence documented with a follow-up duration; however, no follow-up had been recorded for patients who had no recurrence documented. The authors decided to exclude all 6 patients from this study on the basis of selection bias (if only the 3 patients with recurrence were to be included).

Two papers (Hill et al., 1999; Koljonen and Suominen, 2008) were excluded as their data came from the same institute with overlapping timeframes as two other larger papers that were included (Koljonen et al., 2011; Lok et al., 2012). Patients in the studies from Shnayder et al. (2008) and Civantos et al. (2006) came from the same institute; however, reviewing individual patient data revealed one new patient in the study by Civantos et al. (2006) who was not in the study by Shnayder et al. (2008) Similarly, although the patients from the studies by Schmalbach et al. (2005) and Su et al. (2002) came from the same institute, comparing the individual patient records showed that there was one patient from the Su et al. (2002) study who was not in the Schmalbach et al. (2005) study, and therefore this patient was included in this study.

Five papers of interest could not be accessed despite author correspondence (Cirillo et al., 2003; Haefliger et al., 2009; Li et al., 1997; Pascone et al., 2003; Rosa de Almeida, 2002). Cross-referencing did not reveal any further papers that matched the inclusion and exclusion criteria.

The average follow-up time was 32.8 months (excluding 30 patients who did not have individual follow-up durations specified). Of the four studies that had median follow-up times, the minimum in the range of follow-up durations was 1 month. Table 2 summarizes patient characteristics, treatment modalities, and patient outcomes. Ten of the 81 (12.3%) SLNB-negative patients had regional (nodal) recurrence, including 1 patient who also had a distant recurrence (i.e., outside of the local tumor site and beyond the regional lymph nodes). Nine of these 10 patients who had regional recurrence did not receive regional radiotherapy, and in the case of one patient, the report did not specify if the patient received regional radiotherapy. Of the total number of SLNB-negative patients, 2 (5%) had distant recurrence.

Seven patients from the entire cohort were documented to have received radiotherapy to the regional lymph nodes as part of their original treatment despite negative SLNB, and 55 did not receive any regional radiotherapy at the time of negative SLNB. It was unclear whether the remaining 19 patients received regional radiotherapy at time of original treatment for their MCC. No regional recurrence was documented for the 7 patients who received regional radiotherapy.

Of the surviving 7 patients who had regional or distant recurrence (see Table 1 – patient reference numbers [PRN]: 2, 20, 34, 35, 48, 62, and 80), all underwent further treatment. Six patients (see Table 1 – PRN 2, 20, 34, 35, 62, and 80) received regional salvage surgery and adjuvant radiotherapy, and one patient (see Table 1 – PRN 48) received radiotherapy alone. Four patients (see Table 1 - PRN 2, 20, 48, and 80) were disease free at 14,

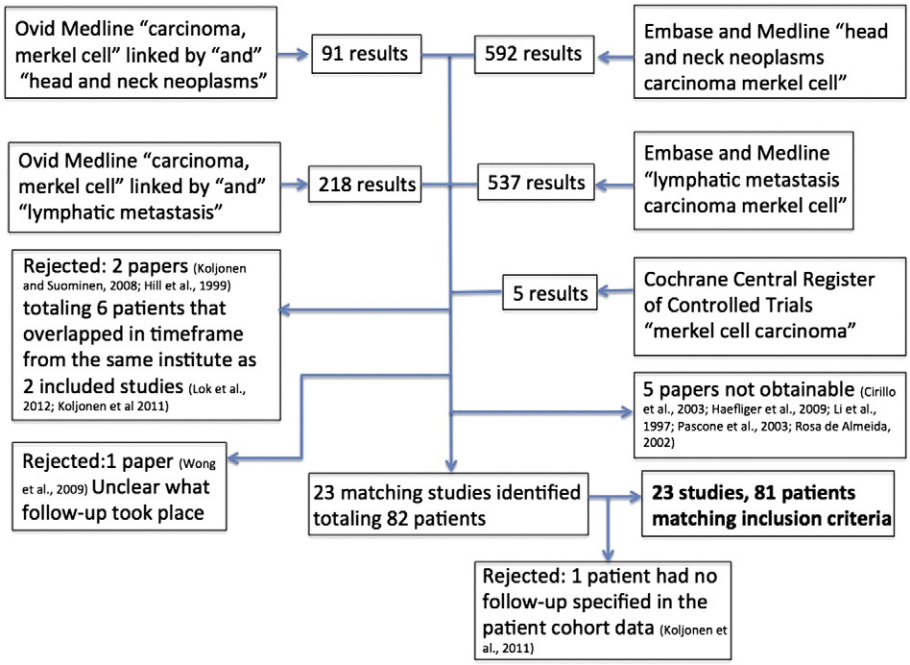

Fig. 1. The literature search process.

30, 15, and 36 months' follow-up, respectively. In two patients (see Table 1 – PRN 34 and 35), the subsequent outcome was said to be "successful." It was unknown if PRN 62 (see Table 1) had further disease recurrence.

PRN 28 (see Table 1) had recurrence to the supraclavicular region and distantly to the liver and ultimately died as a result of metastatic MCC. PRN 50 (see Table 1) had distant recurrence to the lungs detected at 8 months and died as a result of disease at 18 months.

Two-tailed Fisher tests did not reveal any significant correlation between regional recurrence and radiotherapy to the primary site ($p = .30$) or the regional lymphatic basin ($p = .58$).

Discussion

The primary purpose of this paper was to conduct a systematic review of the English literature to determine the regional recurrence and mortality rates among patients with head and neck MCC and a negative SLNB. Second, the aim was to determine whether adjunctive radiotherapy to either the primary tumor site or regional lymphatic basin had any significant influence on regional recurrence or mortality rates among these patients.

This systematic review revealed a 12.3% incidence (10/81) of regional MCC recurrence from primary head and neck MCC that had a negative SLNB. Regional recurrence occurred early, within the first 20 months following a negative SLNB. This is consistent with the aggressive biologic behavior of these tumors (Medina-Franco et al., 2001) and the tendency for early recurrence within the first 12 to 24 months (Allen et al., 2005; Medina-Franco et al., 2001; Smith et al., 1995). There was a 5% mortality rate (4/81) attributable to MCC from this study population, including 3 patients with regional recurrent disease and 1 patient with only distant recurrence, over an average follow-up duration of 32.8 months.

At least 8.6% of this study population received radiotherapy to the regional lymphatic basin despite a negative SLNB. It was unclear whether 23% (19/81) of this patient cohort received regional radiotherapy. No significant correlation was found between radiotherapy (at the time of negative SLNB) to the regional lymphatic basin and the incidence of regional MCC recurrence. Despite this, no regional recurrence occurred in the 7 patients who were documented to have received regional radiotherapy, and 16% (9/55) of the patients documented to have received no regional radiotherapy had regional recurrence. However, the small size of the study population and incomplete treatment data on some patients limits the extrapolation of these findings.

In comparison, a randomized open trial with 83 patients with MCC who were clinically node negative, which was performed to determine if regional radiation improved overall survival and reduced regional recurrence, showed no significant difference for overall survival ($p = .989$) (Jouary et al., 2012). However, there was a statistically significant reduction in regional recurrence rates among those who received regional radiotherapy ($p = .007$). The problem in these data is that without SLNB, patients with undetected positive lymph nodes could have been randomized to radiotherapy, and others with possibly negative lymph nodes received no radiotherapy; therefore, even if radiotherapy improved survival for the first group, the survival difference could have been masked, as the groups were not even at baseline. For that study, the median follow-up time was 57.7 months (range 12.8–130), and in 43.4% of the patient cohort, the primary MCC sites involved the head and neck region. This trial was prematurely terminated when the recruitment number dropped, which was attributed to the introduction of SLNB for managing MCC. As MCC is known to be a highly radiosensitive tumor (Hruby et al., 2013), it is necessary to further explore what survival advantage regional radiation therapy may confer on negative SLNB patients.

In comparison with the mortality rates published in other reports, our study population with negative SLNBs had a much lower disease-specific mortality rate compared with another population of patients with cN0 head and neck MCC who had not had SLNB (Gillenwater et al., 2001). That study by Gillenwater et al. (2001) showed that there was a disease-specific mortality rate of 43% (22/51) among cN0 patients who had had a minimum follow-up of 6 months. In this group of cN0 patients, 39% (20/51) had received multimodal treatment (surgery and locoregional radiotherapy). The large difference in mortality rates between the present study and that by Gillenwater et al. (2001) suggests that a negative SLNB from head and neck primary tumor sites may indicate an improved survival outcome.

This suggestion is also supported by data from a large American study on patients with head and neck MCC ($n = 2104$), which showed that patients with pathologically proven negative lymph nodes have

Table 1
Patient characteristics, treatment modalities, and patient outcomes.

Patient (reference)	Age/Gender	Surgery primary	XRT local	XRT regional	Regional Recurrence (months)	Follow-up (months)
1 (Pan et al., 2002)	44 M	WLE	No	No	No	A (25)
2 (Pan et al., 2002)	58 F	WLE	No	No	Yes (3)	A (14)
3 (Su et al., 2002)	77 F	WLE	No	No	No	A (19)
4 (Koljonen and Suominen, 2008)	72 F	WLE	Yes	Yes	No	A (22)
5 (Alex, 2004)	83 F	WLE	Yes	No	No	A (29)
6 (Alex, 2004)	77 F	WLE	No	No	No	A (28)
7 (Alex, 2004)	88 F	WLE	No	No	No	A (13)
8 (Alex, 2004)	90 M	WLE	NS	NS	No	A (20)
9 (Alex, 2004)	82 F	WLE	No	No	No	A (11)
10 (Koljonen et al., 2011)	NS	WLE	NS	NS	No	A (>10)
11 (Koljonen et al., 2011)	NS	WLE	NS	NS	No	A (>10)
12 (Koljonen et al., 2011)	NS	WLE	NS	NS	No	A (>10)
13 (Koljonen et al., 2011)	NS	ExcN	NS	NS	No	A (>10)
14 (Koljonen et al., 2011)	NS	ExcN	NS	NS	Yes (NS)	DOD (NS)
15 (Howle and Veness, 2012)	86 M	NS	NS	No	No	DOC (4)
16 (Howle and Veness, 2012)	61 F	NS	NS	No	No	A (34)
17 (Howle and Veness, 2012)	62 M	NS	NS	No	No	A (5)
18 (Schmalbach et al., 2005)	84 F	WLE	No	No	No	A (33)
19 (Schmalbach et al., 2005)	55 F	WLE	No	No	No	A (31)
20 (Schmalbach et al., 2005)	74 M	ExcB, WLE	No	No	Yes (9)	A (30)
21 (Schmalbach et al., 2005)	84 F	WLE	No	No	No	A (28)
22 (Schmalbach et al., 2005)	83 F	WLE	No	No	No	A (27)
23 (Schmalbach et al., 2005)	85 M	WLE	No	No	No	A (58)
24 (Schmalbach et al., 2005)	71 F	WLE	No	No	No	A (57)
25 (Schmalbach et al., 2005)	68 F	WLE	No	No	No	A (12)
26 (Shnayder et al., 2008)	NS	WLE	Yes	Yes	No	A (13)
27 (Shnayder et al., 2008)	NS	WLE	Yes	Yes	No	A (45)
28 (Shnayder et al., 2008)	NS	WLE	No	No	Yes (20)§	DOD (NS)
29 (Shnayder et al., 2008)	NS	WLE	No	No	No	A (12)
30 (Shnayder et al., 2008)	NS	WLE	No	No	No	A (40)
31 (Shnayder et al., 2008)	NS	WLE	Yes	Yes	No	A (15)
32 (Luaces et al., 2008)	55 F	WLE	No	No	No	A (18)
33 (Luaces et al., 2008)	62 F	WLE	No	No	No	A (9)
34 (Lok et al., 2012)	NS	NS	NS	No	Yes (3, 2–5)*	NS (35, 1–220)*
35 (Lok et al., 2012)	NS	NS	NS	No	Yes (3, 2–5)*	NS (35, 1–220)*
36 (Lok et al., 2012)	NS	NS	NS	NS	No	NS (35, 1–220)*
37 (Lok et al., 2012)	NS	NS	NS	NS	No	NS (35, 1–220)*
38 (Lok et al., 2012)	NS	NS	NS	NS	No	NS (35, 1–220)*
39 (Messina et al., 1997)	NS	WLE	NS	NS	No	A (10.5)†
40 (Messina et al., 1997)	NS	WLE	NS	NS	No	A (10.5)†
41 (Messina et al., 1997)	NS	WLE	NS	NS	No	A (10.5)†
42 (Messina et al., 1997)	NS	WLE	NS	NS	No	A (10.5)†
43 (Messina et al., 1997)	NS	WLE	NS	NS	No	A (10.5)†
44 (Zeitouni, 2000)	78 F	Mohs	Yes	Yes	No	A (16)
45 (Wasserberg, 2000)	68 F	WLE	Yes	No	No	A (8)
46 (Maza et al., 2006)	70 F	WLE	No	No	No	A (66)
47 (Maza et al., 2006)	55 M	WLE	No	No	No	A (69)
48 (Warner et al., 2008)	78 F	WLE	No	No	Yes (4)	A (15)
49 (Warner et al., 2008)	69 F	WLE	Yes	NS	No	A (16, 4–75)*
50 (Righi et al., 2013)	73 F	NS	NS	No	No (8)‡	DOD (11)
51 (Righi et al., 2013)	74 F	NS	NS	No	Yes (8)	DOD (18)
52 (Righi et al., 2013)	90 M	NS	NS	No	No	A (64)
53 (Righi et al., 2013)	72 F	NS	NS	No	No	A (3)
54 (Righi et al., 2013)	81 F	NS	NS	No	No	DOC (33)
55 (Righi et al., 2013)	67 M	NS	NS	No	No	A (67)
56 (Righi et al., 2013)	81 F	NS	NS	No	No	DOC (10)
57 (Righi et al., 2013)	85 F	NS	NS	No	No	A (64)
58 (Righi et al., 2013)	66 M	NS	NS	No	No	A (54)
59 (Righi et al., 2013)	74 F	NS	NS	No	No	DOC (102)
60 (Maalouf et al., 2012)	NS	ExcN	NS	Yes	No	A (18.7, 14–26)*
61 (Maalouf et al., 2012)	NS	ExcN	NS	Yes	No	A (18.7, 14–26)*
62 (Maalouf et al., 2012)	NS	NS	No	No	Yes (6)	A (18.7, 14–26)*
63 (Maury et al., 2011)	85 F	WLE	Yes	No	No	A (27.6)†
64 (Maury et al., 2011)	69 F	WLE	Yes	No	No	A (27.6)†
65 (Maury et al., 2011)	59 F	WLE	Yes	No	No	A (27.6)†
66 (Civantos et al., 2006)	NS	WLE	NS	NS	No	A (36)
67 (Morand et al., 2013)	52 F	Exc	No	No	No	A (18)
68 (Morand et al., 2013)	64 M	Exc	Yes	NS	No	A (72)
69 (Morand et al., 2013)	57 F	Exc	No	No	No	A (66)
70 (Morand et al., 2013)	73 F	Exc	No	No	No	A (74)
71 (Morand et al., 2013)	65 F	Exc	Yes	NS	No	A (39)
72 (Parvathaneni et al., 2012)	NS	Exc	No	No	No	A (12, 4–45)*
73 (Parvathaneni et al., 2012)	NS	Exc	No	No	No	A (12, 4–45)*
74 (Parvathaneni et al., 2012)	NS	Exc	No	No	No	A (12, 4–45)*
75 (Parvathaneni et al., 2012)	NS	Exc	No	No	No	A (12, 4–45)*

Table 1 *(continued)*

Patient [reference]	Age/Gender	Surgery primary	XRT local	XRT regional	Regional Recurrence (months)	Follow-up (months)
76 (Parvathaneni et al., 2012)	NS	Exc	No	No	No	A (12, 4–45)*
77 (Parvathaneni et al., 2012)	NS	Exc	No	No	No	A (12, 4–45)*
78 (Parvathaneni et al., 2012)	NS	Exc	No	No	No	A (12, 4–45)*
79 (Parvathaneni et al., 2012)	NS	Exc	No	No	No	A (12, 4–45)*
80 (Bleyen et al., 2010)	71 F	Exc	No	No	Yes (4)	A (36)
81 (Hamill and Messina, 2010)	77 M	WLE	Yes	NS	No	DOC (60)

WLE, wide local excision; ExcB, excisional biopsy; NS, non-specified; ExcN, excision narrow margin; Exc, excision, uncertain if wide margin; A, alive; DOD, died of disease; DOC, died of other cause.

* median time for study cohort, followed by range.

† mean time for study cohort, followed by range when available.

‡ distant recurrence.

§ regional and distant recurrence.

improved disease-specific survival compared with those who do not have lymph nodes histologically examined (Smith et al., 2012). Despite this, the same study also showed that disease-specific survival was not different between negative ($n = 133$) and positive ($n = 40$) SLNBs from patients with head and neck MCC ($p = .14$) (Smith et al., 2012). One possible explanation may be that SLNB-positive patients receive greater adjunctive treatment at the time of diagnosis compared with SLNB-negative patients (Fields et al., 2011; Gupta et al., 2006). Other hypotheses with regard to the finding that there is no survival difference between positive and negative SLNBs in head and neck MCC include that the SLNB misses micrometastatic disease (false-negative rate), perhaps as a result of the spread of Merkel cell polyomavirus, and that, as discussed by Fields et al. (2011), SLNB may effectively treat micrometastatic disease.

In terms of regional recurrence rates, this review showed a lower regional recurrence rate of 12.3% (10/81), compared with other studies of cN0 patients with head and neck MCC who did not have an SLNB, where regional recurrence rates ranged between 20% and 53% (3/15 (Brissett et al., 2002); 27/51 (Gillenwater et al., 2001)). This may be a result of the differences between the groups in follow-up durations, treatment modalities, and clinicopathologic features of the primary tumors or the possibility that a negative SLNB may help predict future regional recurrence rates.

The incidence of regional recurrence in this review of the literature (12.3%) were similar to regional recurrence rates (2.5-17.7%) from larger studies (Fields et al., 2011; Tarantola et al., 2013) and a meta-analysis (Mehrany et al., 2002) of non-site-specific MCC with a negative SLNB. In two of these studies, it was reported that 88% (Mehrany et al., 2002) and 92% (Fields et al., 2011) of patients with a negative SLNB received no further treatment to the regional lymphatic basin. In the group of patients from this review, at least 68% of patients received no further surgery or radiotherapy to the regional lymphatic basin. In their review of the literature, which included 22 studies, Warner et al. (2008) showed that there was a 7.5% incidence of recurrence following a negative SLNB in a population of patients with non-site-specific MCC. However, in this literature review, recurrence was not specified as regional recurrence.

Table 2
Summary of the included patients from the systematic review.

Characteristic		n (%)
Gender	Female	36 (44)
	Male	12 (15)
	Not specified	33 (41)
Mean age (year)	72 (SD = 11.1, Range 44–90)	
Surgery to primary site	Wide local excision	43 (53)
	Mohs	1 (1)
	Excision, Margins unspecified	14 (17)
	Excision, Narrow Margin	4 (5)
	Not specified	19 (23)
Radiotherapy to primary site	Yes	14 (17)
	No	34 (42)
	Not specified	33 (41)
Radiotherapy to regional lymphatics	Yes	7 (9)
	No	55 (68)
	Not specified	19 (23)
Neck dissection as part of initial treatment	Yes	0 (0)
	No	69 (85)
	Not specified	12 (15)
MCC recurrence (regional, distant)	Yes	11 (14)
	No	70 (86)
Death from MCC	Yes	4 (5)
	No	67 (83)
	Not specified	10 (12)

SD, standard deviation; MCC, Merkel cell carcinoma.

One of the strengths of our study was the specific citing of regional recurrence outcomes and not locoregional recurrence outcomes. It is important to differentiate between these two recurrences, as it is regional recurrence that is the relevant outcome measure for SLNB studies (Fields et al., 2011). To date, the largest study examining patients with MCC of the head and neck, which featured 133 patients with a negative SLNB taken from the Surveillance, Epidemiology and End Results program of the National Cancer Institute in the United States in 2012, did not report on recurrence rates (Smith et al., 2012).

There were several limitations to the present study: (1) The searches were limited to the English language literature. (2) There was signification variation in follow-up durations in this cohort of patients. The shorter follow-up duration in the case of some included patients did not permit reliable disease-specific survival calculations from these data, nor did it provide sufficient time for regional or distant recurrence to develop. Therefore, the incidence rates of mortality and recurrence in this study are likely to be underestimates. (3) The pathologic analyses of the sentinel lymph node may vary among institutes (Su et al., 2002). Routine immunostaining for CK-20, in addition to hematoxylin and eosin staining, increases the diagnostic reliability of finding lymph nodes metastatically involved by MCC (Su et al., 2002). Future institutional studies should aim to control for this variable. (4) The different modalities of treatment received by patients present confounding variables that impair the evaluation of how a negative SLNB prognosticates for recurrence or survival. This is also an issue when comparing recurrence and survival between negative and positive SLNBs. (5) No information on primary tumor characteristics was included in the analysis. This was the result of lack of information about the majority of patients included in this study. (6) Lack of information pertaining to the nature of treatment received by some patients, including improved immunosuppression, limited the ability to draw conclusions about what adjunctive therapies following a negative SLNB may be most beneficial.

In addition, several studies that were reviewed had a cohort of negative SLNB MCC patients, from a variety of sites around the body, including from the head and neck region. However, studies in which it was impossible to determine the outcome that could be directly attributed to the cohort of patients with head and neck MCC had to be excluded.

In summary, SLNB should become a routine part of the workup in patients with head and neck MCC who are clinically staged as disease free. SLNBs aid in the detection of occult disease and positive SLNBs provide clear indications for adjunctive treatment; however, a negative

SLNB also provides important information. A negative SLNB in patients with head and neck MCC is likely to indicate an improved disease-specific survival and reduced risk of regional disease recurrence compared with patients who are clinically staged as disease free and who do not undergo further pathologic evaluation of the lymph nodes in the head and neck region. However, close follow-up is still necessary for all patients with head and neck MCC, including those with a negative SLNB.

This systematic review has indicated that what adjunctive treatment should be provided following a negative SLNB and surgery to the primary tumor in patients with head and neck MCC still remains unclear. To determine the most appropriate treatment for these patients, it would be ideal to perform a randomized controlled trial to determine the need for regional radiotherapy. Given that even in the case of small tumors (<0.5 cm), there is still a significant risk for lymph node metastasis (Iyer et al., 2014); such a study would help avoid stratification of patients based on tumor size. Further case series studies with longer follow-up durations beyond 2 years, comparing treatments provided to patients with negative SLNBs from head and neck MCC primary tumor sites, are another option to determine the best approach to treating this uncommon tumor.

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