A systematic review of clinical outcomes for patients diagnosed with skin cancer spinal metastases

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OBJECT Surgical procedures and/or adjuvant therapies are effective modalities for the treatment of symptomatic spinal metastases. However, clinical results specific to the skin cancer spinal metastasis cohort are generally lacking. The purpose of this study was to systematically review the literature for treatments, clinical outcomes, and survival following the diagnosis of a skin cancer spinal metastasis and evaluate prognostic factors in the context of spinal skin cancer metastases stratified by tumor subtype.

METHODS The authors performed a literature review using PubMed, Embase, CINAHL, and Web of Science to identify articles since 1950 that reported survival, clinical outcomes, and/or prognostic factors for the skin cancer patient population with spinal metastases. The methodological quality of reviews was assessed using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) tool.

RESULTS Sixty-five studies met the preset criteria and were included in the analysis. Of these studies, a total of 25, 40, 25, and 12 studies included patients who underwent some form of surgery, radiotherapy, chemotherapy, or observation alone, respectively. Sixty-three of the 65 included studies were retrospective in nature (Class of Evidence [CoE] IV), and the 2 prospective studies were CoE II. Based on the studies analyzed, the median overall survival for a patient with a spinal metastasis from a primary skin malignancy is 4.0 months; survival by tumor subtype is 12.5 months for patients with basal cell carcinoma (BCC), 4.0 months for those with melanoma, 4.0 months for those with squamous cell carcinoma, 3.0 months for those with pilomatrix carcinoma, and 1.5 months for those with Merkel cell carcinoma (p < 0.0001). The overall percentage of known continued disease progression after spine metastasis diagnosis was 40.1% (n = 244/608, range 25.0%–88.9%), the rate of known recurrence of the primary skin cancer lesion was 3.5% (n = 21/608, range 0.2%–100.0%), and the rate of known spine metastasis recurrence despite treatment for all skin malignancies was 2.8% (n = 17/608, range 0.0%–33.3%). Age greater than 65 years, sacral spinal involvement, presence of a neurological deficit, and nonambulatory status were associated with decreased survival in patients diagnosed with a primary skin cancer spinal metastasis. All other clinical or prognostic parameters were of low or insufficient strength.

CONCLUSIONS Patients diagnosed with a primary skin cancer metastasis to the spine have poor overall survival with the exception of those with BCC. The median duration of survival for patients who received surgical intervention alone, medical management (chemotherapy and/or radiation) alone, or the combination of therapies was similar across interventions. Age, spinal region, and neurological status may be associated with poor survival following surgery.

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KEY WORDS skin cancer; spine metastasis; basal cell carcinoma; melanoma; squamous cell carcinoma; pilomatrix carcinoma; Merkel cell carcinoma; survival; oncology

ABBREVIATIONS BCC = basal cell carcinoma; CoE = Class of Evidence; IQR = interquartile range; MCC = Merkel cell carcinoma; MESCC = metastatic epidural spinal cord compression; SCC = squamous cell carcinoma.


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The overall objectives of this paper are to answer the following clinical questions: 1) What is the survival rate, rate of change in neurological status, local tumor control rate, and postoperative pain improvement rate for patients diagnosed with a primary skin malignancy overall and stratified by tumor subtype? 2) Are there any negative or positive clinical, radiographic, or histological variables in the literature that may help predict clinical outcomes for patients who undergo surgical intervention?

**Methods**

**Electronic Literature Search**

A systematic review of the literature was performed using PubMed, Embase, CINAHL, and Web of Science, as well as a review of the bibliographies of eligible articles. The broad search query was designed to include the skin cancer patient population with spinal metastases reported in the literature since 1950. Additionally, a prognostic variable search specific to metastatic skin cancer patients was conducted with emphasis on the duration of the metastasis-free interval (the duration between diagnosis of primary disease and diagnosis of the first metastasis) and survival to supplement the limited prognostic variables available in the studies reviewed. A summary of search strings, as well as inclusion and exclusion criteria are provided in Figure 1, Table 1, and Supplemental Table 1. (All supplemental tables are available online only.)

**Data Extraction**

With respect to operative techniques, the following data were extracted: patient population (number of patients with spinal metastases and percentage of skin cancer patients making up the entire study population), survival information (postoperative survival time and/or postoperative survival rate), change in neurological function (percentage of skin cancer cohort with preoperative neurological deficit, and percentage of skin cancer cohort with identical or worse postoperative neurological deficit), and local tumor control rate (percentage, evaluated at a mean or median follow-up ≥ 12 months).

**Study Eligibility and Quality Assessment**

All potentially eligible studies were determined by 2 reviewers (A.L. and E.W.S.). A third reviewer (C.R.G.) resolved instances of disagreement. After finalizing the series of studies to be analyzed, 2 reviewers (A.L. and E.W.S.) extracted data to answer the inquiries posed in the objectives. A third reviewer independently reviewed and confirmed all results (C.R.G.).

We excluded papers reporting on patients who had an unknown primary lesion during their entire length of follow-up, metastatic lesions that did not originate from cutaneous lesions, or tumors that were not metastatic as well as papers that focused on leptomeningeal disease and/or included heterogeneous cohorts without results specific to skin cancer metastases to the spine. We used the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) tool as applicable to assess the methodological quality of the included studies.

In assessing individual studies, the following grades...
were assigned: high, moderate, low, or insufficient. “High” was assigned to studies that were Class of Evidence (CoE) I or II, and for which there was confidence that the true effect was close to the estimated effect. “Moderate” was assigned to studies that were CoE II or III, and for which the true effect may be close to the estimated effect, although it is constrained by other factors. “Low” was assigned to studies that were CoE III or IV, and the true effect may have been significantly different than the estimated effect. “Insufficient” was assigned if

TABLE 1: Selection criteria

<table>
<thead>
<tr>
<th>Search Engine</th>
<th>Number of Results From Key Search String(s)</th>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>PubMed*†</td>
<td>737 results</td>
<td>(a) Publication date: 1950 or later</td>
<td>(a) Articles that did not provide clinical outcomes &amp; statistics specific to the skin cancer spinal metastases patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(b) Language: English or w/ a complete English translation</td>
<td>(b) Articles that lumped all skin cancer spinal metastases cohort outcomes w/ that of other primary tumor types</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(c) Articles describing operative techniques used to treat spinal metastases in cancer patients</td>
<td>(c) Articles on nonhumans</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(d) Articles describing medical interventions used to treat spinal metastases in cancer patients</td>
<td>(d) Same as above</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(e) Fully published, peer-reviewed, retrospective or prospective studies including randomized controlled trials, nonrandomized trials, cohort studies, case-control studies, &amp; case series</td>
<td>(e) Same as above</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(f) Must be of cutaneous origin, with known primary</td>
<td>(f) Must be study of human patients</td>
</tr>
<tr>
<td>Embase*†</td>
<td>1649 results</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CINAHL*</td>
<td>59 results</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Web of Science*</td>
<td>376 results</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cochrane Library*</td>
<td>33 results: 25 Cochrane Reviews 8 trials</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Search string in Supplemental Table 1.
† The Pubmed and Embase searches were limited to humans only. No other limitations were placed on the searches. All searches were run on September 23, 2014.
there was very little confidence in the estimated result, no evidence, or too little evidence to estimate an effect. Overall strength could be downgraded if results were inconsistent, evidence was indirect, effect estimates were imprecise, or there were no a priori subgroup analyses. In contrast, overall strength could be upgraded if there was a large magnitude of effect or a dose-response gradient.

Statistical Methods

All survival statistics and Kaplan-Meier curves were calculated using GraphPad Prism 5.0. All cases from the literature were included as applicable. Cases with unknown follow-up or survival times were excluded from the analysis.

Results

Study Selection

We performed a literature search using PubMed, Embase, CINAHL, and Web of Science, as well as a search through the bibliographies of eligible articles.

Ultimately, 65 studies were included in this review based on the eligibility criteria (22 melanoma, 28 BCC, 9 MCC, 4 squamous cell carcinoma, and 2 case reports on pilomatrix carcinoma).

Of the 65 studies, 25 mentioned surgical intervention with or without other treatments, 40 studies mentioned radiation with or without other treatments, 25 studies mentioned chemotherapy with or without other treatments, and 12 studies had no or unknown treatment interventions. Of note, immunotherapy was used only for the treatment of metastatic melanoma. There were 25 studies that involved a combination of the treatment modalities mentioned above. There were 9 retrospective cohort studies, 53 case reports, 1 case series, and 2 prospective cohort studies. Articles were organized based on skin cancer subtype.

Melanoma

Melanoma is the most commonly fatal form of skin cancer, resulting in approximately 64,000 deaths worldwide each year. In the US, melanoma is the fifth most common cancer in men and seventh most common in women, with a worldwide incidence of approximately 160,000 new cases per year. Due to an increase in natural and artificial ultraviolet radiation exposure, the incidence of melanoma is rising faster than that of any other solid tumor. Cutaneous melanomas can occur anywhere on the epidermal surface but are frequently located in areas that may be easy to miss with self-inspection, such as the back or lower extremities.

The typical phenotype of a melanoma patient includes pale white skin, red or blond hair, and blue eyes. Early identification of melanoma involves visual examination, typically using the ABCDE rules of melanoma recognition. Melanoma is inclined to metastasize via the lymphatic system to other organs, such as lung, liver, brain, or bone. Skeletal metastases are present in 5%–17% of patients with Stage IV melanoma. Highly disseminated metastatic melanoma is almost always incurable, with a median duration of survival of 6–9 months. The standard of care for localized cutaneous lesions and regional lymph node metastases is surgical resection, but surgery is much less effective in metastatic disease. Recently, immunomodulation with agents such as ipilimumab and therapeutics targeting specific mutations, such as the BRAF inhibitors vemurafenib and dabrafenib, have shown favorable increases in progression-free survival in patients with metastatic melanoma.

Results Summary

A total of 22 studies meeting the inclusion criteria were found, reporting on a total of 563 patients with spine metastasis secondary to a primary cutaneous melanoma. The studies included 9 retrospective cohort studies, 10 case reports, 1 case series, and 2 prospective cohort studies.

Of the 563 patients, 319 (56.7%) were male; sex was not reported in 3 studies. The patients’ median age at diagnosis of the primary tumor was 43 years (interquartile range [IQR] 34–48 years), and the median age at presentation of spinal metastasis was 50 years (IQR 42–55 years). Of note, age at primary diagnosis for melanoma was not reported in 6 studies, and age at melanoma spine metastasis was not reported in 7 studies. The median time to spine metastasis from the primary diagnosis was 3 years (IQR 0.4–5 years). The most common locations for metastasis were the thoracic (n = 331, 58.8%) and lumbar (n = 295, 52.4%) spine. Treatment was known for 278 (49.4%) patients, with the most common treatment being radiotherapy and/or chemotherapy (n = 175, 31.1%) (Table 2). Reporting of functional outcome after treatment was highly variable across studies as seen in Supplemental Table 2. A total of 103 (18.3%) patients underwent surgery, with 46 (8.2%) patients receiving surgery alone and 57 (10.1%) undergoing a combination of surgery and adjuvant therapy. Thirteen (2.3%) patients had known tumor recurrence; however, the presence of recurrence was not reported in the majority of patients (n = 385, 68.4%). The median overall survival was 4.0 months (IQR 2.8–6 months). Survival data were reported for 466 cases (82.8%), and based on these data, survival at 3 months, 6 months, 1 year, 2 years, and 5 years was 65.0%, 29.6%, 1.5%, 0.2%, and 0.0%, respectively.

Basal Cell Carcinoma

Basal cell carcinoma (BCC) is the most common human carcinoma, accounting for 20% of carcinomas in men and 10%–15% of all carcinomas in women. The majority of patients diagnosed with a primary BCC (75%–86%) have a lesion in the head or neck, and the nasal tip is the most common location. BCC metastasis is extremely rare, with an estimated rate of approximately 0.03%. BCC most commonly metastasizes, in order of frequency, to the regional lymph nodes, lungs, bones, and skin. The risk factors for development of metastatic BCC include persistent tumor (many years), increased depth of invasion, prior radiotherapy, BCC refractory to treatment, defective cellular immunity, and larger tumor size (> 5 cm in diameter), with a rate of 1.9% in tumors greater than 3 cm in diameter, approximately 50% for tumors greater than 10 cm in diameter, and 100% in BCC with a volume
greater than 400 cm². Metastatic disease carries a poor prognosis; the mean duration of survival ranges from 8 months to 3.6 years. Treatment of localized BCC is highly dependent on patient- and lesion-specific factors, including lesion size and location. Common and effective treatment options for BCC include electrodessication and curettage, surgical excision, radiation, and photodynamic therapy. Despite a lack of high-quality evidence (CoE I), targeted systemic therapies such as vismodegib, a sonic hedgehog pathway inhibitor, may improve survival in patients with metastatic BCC.

**Results Summary**

A total of 30 unique cases of BCC metastatic to the spine were found. Eighteen (60%) of these cases involved male patients. The median age of the patients at primary tumor diagnosis was 51 years (IQR 36–60 years), whereas the median age at presentation of spinal metastasis was 57 years (IQR 49–65 years). The median time to diagnosis of spinal metastasis from the primary diagnosis was 6 years (IQR 3–10 years). The most common locations for spinal metastasis were the lumbar (n = 17, 56.7%) and thoracic (n = 13, 43.3%) regions. Twenty-five patients underwent treatment; the most common treatments were radiotherapy alone (n = 10, 33.3%), chemotherapy alone (n = 7, 23.3%), and chemoradiation (n = 4, 13.3%). Two patients did not undergo treatment, and in 3 cases, the metastatic lesions were treated but the treatment type was not specified. Surgical treatment was reported in only 4 cases (13.3%), with all 4 patients also receiving adjuvant therapy (Table 2). Reporting of functional outcome after treatment was highly variable across studies as seen in Supplemental Table 3. One patient (3.3%) had tumor recurrence. The median overall survival was 12.5 months (IQR 6.3–29.5 months), and 6 patients were alive at last follow-up. Survival data were reported for 26 cases (86.7%), and based on these data, survival at 3 months, 6 months, 1 year, 2 years, and 5 years was 96.2%, 80.8%, 53.8%, 38.5%, and 3.8%, respectively.

**Merkel Cell Carcinoma**

Merkel cell carcinoma (MCC) is a rare neuroendocrine primary skin cancer, named from the neurosecretory granules in the tumor cells that probably originate from a neural crest derivative of Merkel cells. The disease was initially named after Friedrich Merkel in 1875, but the true histopathology was defined as a “trabecular carcinoma of the skin” in 1972 by Cyril Toker. The incidence of MCC is 44 per 100,000, and it is more common in Caucasians, males, and individuals greater than 65 years of age (average age ~72 years). Similar to other primary skin cancers, this lesion is most commonly located in the head and neck region. Nearly half of the patients have regional lymph node involvement at initial diagnosis, and one-third of patients have distant metastases. The 5-year survival rate for a patient diagnosed with MCC is 75%, 59%, and 25%, for localized, regional, and distant disease, respectively, with an overall mortality rate that is twice that of metastatic melanoma. Wide local excision and/or radiation is recommended for localized disease, with careful exploration of the regional lymphatics due to MCC’s high propensity for lymphatic spread. Systemic chemotherapy, most commonly with combined etoposide and cisplatin, is generally employed for metastatic disease.

**Squamous Cell Carcinoma**

Cutaneous squamous cell carcinoma (SCC) is a malignant primary skin cancer that arises from epithelial keratinocytes. Cutaneous squamous cell carcinoma accounts for 20% of the nonmelanoma skin cancers and is considered the second most common skin cancer in whites. This lesion most commonly arises from sun-exposed areas (head and neck region) with high cumulative chronic ultraviolet light exposure, but this carcinoma has low metastatic potential. Risk factors for high metastatic potential include recurrent SCC, SCC arising in nonexposed sites (such as the perineum, sacrum, or sole of the foot), SCC arising in radiation or thermal scars, chronic ulcers or inflammation, lesion size greater than 20 mm in diameter, increased depth of invasion, histopathology that is moderately or poorly differentiated, presence of perineural/perivascular invasion, de novo formation without a precursor lesion, chronic immune suppression or defective immunity, and incomplete excision. The mortality rate for patients diagnosed with a primary skin SCC metastasis is estimated to be approximately 75%. Similar to BCC, loco-regional therapies, including topical treatments (e.g., 5-FU [fluorouracil]), electrodessication and curettage, and surgery are highly effective in the majority of patients with localized SCC. However, systemic therapy may be required for metastatic SCC, with platinum-based chemotherapeutics and the EGFR (epidermal growth factor receptor) inhibitor cetuximab showing positive results in isolated case reports and a few small case series.

**Results Summary**

A total of 4 unique cases of SCC metastatic to the spine were found. All 4 patients (100%) were male. (Because of
### TABLE 2. Summary of patients’ demographic and clinical characteristics and outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Melanoma (n = 563)</th>
<th>BCC (n = 30)</th>
<th>MCC (n = 9)</th>
<th>SCC (n = 4)</th>
<th>Pilomatrix (n = 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex: male, n (%)†</strong></td>
<td>319 (56.7)</td>
<td>18 (60.0)</td>
<td>6 (66.7)</td>
<td>4 (100.0)</td>
<td>2 (100.0)</td>
</tr>
<tr>
<td><strong>Age at spine met, yrs‡</strong></td>
<td>50</td>
<td>57</td>
<td>63</td>
<td>65</td>
<td>64</td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td>23–67</td>
<td>32–79</td>
<td>23–77</td>
<td>50–83</td>
<td>53–74</td>
</tr>
<tr>
<td><strong>IQR</strong></td>
<td>42–55</td>
<td>49–65</td>
<td>55–73</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><strong>Age at primary, yrs</strong></td>
<td>43</td>
<td>51</td>
<td>60</td>
<td>62</td>
<td>63</td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td>18–63</td>
<td>26–67</td>
<td>23–77</td>
<td>48–73</td>
<td>51–74</td>
</tr>
<tr>
<td><strong>IQR</strong></td>
<td>34–48</td>
<td>36–60</td>
<td>46–73</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><strong>Time to spine met, yrs</strong></td>
<td>3</td>
<td>6</td>
<td>0.5</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td>0–25</td>
<td>0–30</td>
<td>0–4</td>
<td>2–12</td>
<td>0.3–2</td>
</tr>
<tr>
<td><strong>IQR</strong></td>
<td>0.4–5</td>
<td>3–10</td>
<td>0–0.9</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><strong>Location, n (%)§</strong></td>
<td>Cervical 64 (11.4)</td>
<td>9 (30.0)</td>
<td>1 (11.1)</td>
<td>1 (25.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td><strong>Thoracic</strong></td>
<td>331 (58.8)</td>
<td>13 (43.3)</td>
<td>6 (66.7)</td>
<td>2 (50.0)</td>
<td>2 (100.0)</td>
</tr>
<tr>
<td><strong>Lumbar</strong></td>
<td>295 (52.4)</td>
<td>17 (56.7)</td>
<td>3 (33.3)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td><strong>Sacral</strong></td>
<td>92 (16.3)</td>
<td>1 (3.3)</td>
<td>3 (33.3)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td><strong>Unknown</strong></td>
<td>47 (8.3)</td>
<td>3 (10.0)</td>
<td>0 (0.0)</td>
<td>1 (25.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td><strong>Treatment, n (%)</strong></td>
<td>Surgery alone 46 (8.2)</td>
<td>0 (0.0)</td>
<td>3 (33.3)</td>
<td>0 (0.0)</td>
<td>1 (50.0)</td>
</tr>
<tr>
<td><strong>RT &amp;/or chemo</strong></td>
<td>175 (31.1)</td>
<td>21 (70.0)</td>
<td>3 (33.3)</td>
<td>1 (25.0)</td>
<td>1 (50.0)</td>
</tr>
<tr>
<td><strong>Surgery &amp; adjuvant therapy</strong></td>
<td>57 (10.1)</td>
<td>4 (13.3)</td>
<td>3 (33.3)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td><strong>No treatment/unknown</strong></td>
<td>285 (56.6)</td>
<td>5 (16.7)</td>
<td>0 (0.0)</td>
<td>3 (75.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td><strong>Known progression/recurrence, n (%)¶</strong></td>
<td>Disease progression 217 (38.5)</td>
<td>17 (56.7)</td>
<td>8 (88.9)</td>
<td>1 (25.0)</td>
<td>1 (50.0)</td>
</tr>
<tr>
<td><strong>Primary recurrence</strong></td>
<td>1 (0.2)</td>
<td>14 (46.7)</td>
<td>2 (22.2)</td>
<td>2 (50.0)</td>
<td>2 (100.0)</td>
</tr>
<tr>
<td><strong>Spine met recurrence</strong></td>
<td>13 (2.3)</td>
<td>1 (3.3)</td>
<td>3 (33.3)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td><strong>Survival, n (%)</strong></td>
<td>Patients w/ known survival 466 (82.8)</td>
<td>26 (86.7)</td>
<td>6 (66.7)</td>
<td>2 (50.0)</td>
<td>1 (50.0)</td>
</tr>
<tr>
<td><strong>Patients w/ unknown survival</strong></td>
<td>97 (17.2)</td>
<td>4 (13.3)</td>
<td>3 (33.3)</td>
<td>2 (50.0)</td>
<td>1 (50.0)</td>
</tr>
<tr>
<td><strong>&lt;3 mos median survival</strong></td>
<td>163 (35.0)</td>
<td>1 (3.8)</td>
<td>5 (83.3)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td><strong>3–5.9 mos median survival</strong></td>
<td>165 (35.4)</td>
<td>4 (15.4)</td>
<td>0 (0.0)</td>
<td>2 (100.0)</td>
<td>1 (100.0)</td>
</tr>
<tr>
<td><strong>6–11.9 mos median survival</strong></td>
<td>131 (28.1)</td>
<td>7 (26.9)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td><strong>12–23.9 mos median survival</strong></td>
<td>6 (1.3)</td>
<td>4 (15.4)</td>
<td>1 (16.7)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td><strong>24–59.9 mos median survival</strong></td>
<td>1 (0.2)</td>
<td>9 (34.6)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td><strong>&gt;60 mos median survival</strong></td>
<td>0 (0.0)</td>
<td>1 (3.8)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td><strong>Overall survival from spine met Dx, mos</strong></td>
<td>Median 4.0</td>
<td>12.5</td>
<td>1.5</td>
<td>4.0</td>
<td>3.0</td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td>0.7–48</td>
<td>1–72</td>
<td>1–23</td>
<td>4–4</td>
<td>3–3</td>
</tr>
<tr>
<td><strong>IQR</strong></td>
<td>2.8–6.3</td>
<td>6.3–29.5</td>
<td>1–2.2</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Chemo = chemotherapy; Dx = diagnosis; met = metastasis; RT = radiotherapy.
* Percentages are based on the total number of patients for each skin cancer subtype, except for survival percentages, which are based on the number of patients with known survival status.
† Sex was not reported in 3 studies for melanoma.
‡ Age at spine metastasis was not reported in 7 studies for melanoma.
§ Spinal location is shown by any level of involvement.
¶ Known progression/recurrence based on the number of patients mentioned with overall disease progression after treatment of spine metastasis, with local recurrence of their primary skin cancer lesion at any point during follow-up, and with known local recurrence of their spinal metastasis after treatment. Of note, data regarding disease progression and/or recurrence were not available in the majority of studies, and these data are likely significant underestimations, given the poor survival of patients with skin cancer spine metastasis.
the small number of cases in this category, the full range is presented rather than IQR.) The patients’ median age at diagnosis of the primary tumor was 62 years (range 48–73 years), and their median age at presentation of spinal metastasis was 65 years (IQR 50–83 years). The median time to spine metastasis from the primary diagnosis was 3 years (IQR 3 years). Two patients had metastases in the thoracic spine, 1 patient had a lesion in the cervical spine, and 1 patient had a lesion of unknown location. One patient underwent chemoradiation, 1 patient received only palliative treatment, and the other 2 patients had unknown treatment plans. No patient underwent surgery. The median overall survival was 4.0 months, with only 1 patient alive at last follow-up. Survival data were reported for 2 cases, and based on these data survival at 3 months and 6 months were 100.0% and 0.0%, respectively (Table 2 and Supplemental Table 5).

Pilomatrix Carcinoma

Pilomatrix carcinoma was described initially by Mahlerbe in 1880 as a calcifying epithelioma presumed to be derived from a sebaceous gland.65 Forbis and Helwig provided the name of “pilomatrixoma” in 1961 when they reviewed 228 case of this lesion.39 Lopansri and Mihm in 1980 proposed the hair matrix as the site of origin.63 Pilomatrix carcinoma commonly presents in the head or neck region as a slow-growing dermal or subcutaneous mass less than 3 cm in diameter. The peak incidence is estimated to occur between 8 and 13 years of age with tumors being identified before the 3rd decade of life in more than 60% of cases.11,63 Pilomatrix carcinoma shows a predilection for females and is associated with various clinical syndromes.63 The exact rate of metastases is unknown and reports estimate that the metastases probability is approximately 12% with rare bone metastases.11 Pilomatrix carcinoma is poorly responsive to chemoradiation, and is most often treated with wide surgical excision.11

Results Summary

A total of 2 unique cases of pilomatrix carcinoma metastatic to the spine were found. Both patients (100.0%) were male. (Because of the small number of cases in this category, the full range is presented rather than IQR.) The patients’ median age at primary tumor diagnosis was 63 years (range 51–74 years) and median age at presentation of spinal metastasis was 64 years (range 53–74 years). The median time to spine metastasis from the primary diagnosis was 1 year (range 0.3–2 years). Both patients (100.0%) had lesions in the thoracic spine. One patient was treated with chemoradiation and the other with surgery (only). Neither patient had tumor recurrence, but 1 patient died 3.0 months after treatment. The other patient was alive at last follow-up (duration not reported), although further treatment was not undertaken due to his poor clinical condition (Table 2 and Supplemental Table 6).

Overall Survival and Tumor Recurrence

The median overall survival for a patient diagnosed with a spinal metastasis from a primary skin malignancy is 4.0 months (IQR 2.8–6.3 months) from diagnosis of the metastatic lesion (Fig. 2 upper). Stratified by tumor subtype, the median duration of survival is 12.5 months for BCC, 4.0 months for melanoma, 4.0 months for SCC, 3.0 months for pilomatrix carcinoma, and 1.5 months for MCC (p < 0.0001) (Fig. 2 lower). The percentage of known continued disease progression after spine metastasis diagnosis was 40.1% (244/608, range 25.0%–88.9%), the rate of known recurrence of primary skin cancer lesion was 3.5% (21/608, range 0.2%–100.0%), and the rate of known spine metastasis recurrence despite treatment for all skin malignancies was 2.8% (17/608, range 0.0%–33.3%).

Operative Result Summaries

A total of 25 operative studies (including 189 patients) and 40 nonoperative studies (including 419 patients) were found suitable for analysis. In the surgical group, decompression procedures were performed via a posterior approach in 186 cases, an anterior approach in 2 cases, and a combined approach in 1 case.

Irrespective of skin cancer subtype, in patients who received surgical intervention alone, medical management alone (chemotherapy and/or radiation without surgery), or the combination of surgery and medical management (chemotherapy and/or radiation), the mean duration of survival was 4.6 ± 0.3 months, 6.9 ± 0.7 months, and 9.1 ± 1.2 months from diagnosis of spinal metastasis, respectively. In patients who received medical management (chemo-
therapy and/or radiation without surgery), the median duration of survival after diagnosis of spine metastasis was 6.3 months (IQR 3–6.3 months). In patients who received surgical intervention alone, the median duration of survival after diagnosis of spine metastasis was 6.3 months (IQR 2.8–6.3 months). In patients who received surgical intervention in combination with medical management (chemotherapy and/or radiation), the median duration of survival after diagnosis of spine metastasis was 6.3 months (IQR 2.5–6.3 months). These postoperative survival rates for surgical and nonsurgical studies are shown in Fig. 3.

Prognostic Factors

Of the studies on primary skin cancer spinal metastases, only 47 unique studies (involving a total of 339 patients) reported at least 1 of the prognostic factors analyzed, including, age, sex, pain at presentation, neurological deficit, ambulatory status, recurrence of primary lesion at any point, level of spinal lesion, and survival. The median overall survival for a patient older than 65 years and diagnosed with a spinal metastasis from a primary skin malignancy was 4.0 months compared with 12.0 months for a patient younger than 65 years (p = 0.0263). In terms of spinal level involved, the median duration of survival after diagnosis of a spine metastasis was 4 months for cervical, thoracic, and lumbar lesions, and 2.8 months for sacral (p < 0.0001). The median overall survival for a patient who presented with a neurological deficit was 4.0 months compared with 12 months for a patient with no neurological deficit on presentation (p = 0.0152 on Gehan-Breslow-Wilcoxon test). The median overall survival for a patient who was ambulatory on presentation was 12 months compared with 3 months for a nonambulatory patient (p = 0.0050). Pain at presentation, and recurrence of primary lesion did not have a significant impact on survival (Fig. 4).

Study Quality and Overall Strength of Literature

All 65 studies were case reports, case series, or cohort studies without control groups. Hence, the majority of papers had a baseline CoE of IV, with few papers having a CoE of III. Based on the CoE and the quality and consistency of data, the overall strength of findings is “moderate” to “insufficient.”

Discussion

Few studies have examined the influence of primary skin cancer metastasis to the spinal column, and thus there is a lack of information for clinicians and patients alike. In the current study, we performed a systematic review of the literature for studies and reports detailing the treatment options, clinical outcomes, and survival following the diagnosis of a skin cancer spinal metastasis stratified by skin cancer subtype. We demonstrate that the mean overall survival for patients diagnosed with a primary skin cancer spinal metastasis is 5.2 ± 0.28 months. The median overall duration of survival for a patient diagnosed with a spinal metastasis from a primary skin malignancy is 4 months, and the median duration of survival stratified by tumor subtype is 12.5 months for BCC, 4 months for melanoma, 4 months for squamous cell carcinoma, 3 months for pilomatrix carcinoma, and 1.5 months for MCC (p < 0.0001). Clinicians commonly use a life expectancy of greater than 3 months to determine whether surgical intervention should be offered, whereas some surgeons advocate for greater than 6-month life expectancy. Our study demonstrates that with the exception of BCC, patients who experience spinal metastasis from primary skin cancers commonly do not meet these cutoffs. Studies on the effect of primary skin cancer metastasis to the spinal column are limited to case reports with few retrospective studies, and thus we aim in this study to provide clinicians with information to effectively counsel and/or treat this patient population.

Although decompressive surgical intervention plus radiation is demonstrated to be the preferred treatment for patients with solitary spinal metastases with symptomatic epidural spinal cord compression, the utility of this intervention may not be appropriate for all tumor subtypes. In our study, the median duration of survival for patients diagnosed with a spinal metastasis from a primary skin cancer was 6.3 months whether patients received surgery alone, medical treatment (chemotherapy and/or radiation) alone, or surgery with adjuvant medical treatment, whereas the mean survival was 4.6 months, 6.9 months, and 9.1 months from diagnosis of spinal metastasis, in each group respectively. These results indicate that surgical intervention by itself does not increase survival substantially, with no significant difference in mean duration of survival between the surgically treated and medically treated groups (p = 0.2867). The methodology of this review did not allow for the direct comparison of treatment modalities in a head-to-head fashion, so no conclusions or recommendations regarding appropriate treatment for primary skin cancer metastases to the spine can be made from these observational data. However, there were more long-term survivors in the medically managed group and the group treated with surgery and chemotherapy with or without adjuvant radiation suggesting that patients who survived beyond the median had an increased likelihood of having a longer life expectancy. Given the limited sample size, further analysis...
Fig. 4. Survival stratified by the prognostic factors of age greater than 65 years (A), ambulatory status (B), pain at presentation (C), involved spinal level (D), neurological deficit on presentation (E), and recurrence of the primary skin lesion (F). The difference in survival was statistically significant for age greater than 65 years (p = 0.0263), nonambulatory status (p = 0.0050), and sacral spinal involvement (p < 0.0001) on Mantel-Cox testing. Presence of a neurological deficit was significant on Gehan-Breslow-Wilcoxon testing (p = 0.0152). Presence of pain at presentation and recurrence of the primary lesion were nonsignificant. Figure is available in color online only.
of each subgroup will have to be performed in a prospective manner to determine whether these findings hold true.

To address our second objective, we attempted to identify prognostic factors, other than tumor subtype and treatment option employed, that predict survival in this patient population. An adequate understanding of the effect of prognostic variables on clinical outcomes and overall survival is critical in deciding the appropriate treatment options for a given patient. We found that age greater than 65 years (p = 0.0263), sacral spinal involvement (p < 0.0001), presence of a neurological deficit (p = 0.0152), and nonambulatory status (p = 0.0050) were associated with decreased survival in patients diagnosed with a primary skin cancer spinal metastasis. These findings are consistent with the results of Patchel et al. and Chaichana et al. that demonstrate that metastatic epidural spinal cord compression (MESC) is a common and debilitating process associated with spinal metastases that can cause neurological deficit and compromise ambulation, in addition to being associated with poorer overall prognoses.20,38 Pain at presentation and recurrence of the primary lesion did not have a significant impact on survival. Gokaslan et al. reported that 82% of patients had pain on presentation and 17% had a neurological deficit, whereas 74% of patients had pain and 21% had a neurological deficit in the study performed by Spiegel et al. Given the paucity of high-quality studies and preponderance of case reports and studies with inadequate sample size or a substantial degree of selection bias, certain prognostic factors could not be evaluated due to unavailability (nonreporting) or were not found to be statistically significant.

As our understanding of the molecular background of primary skin cancers increases, it is expected that a preponderance of novel biomarkers will be available to fully characterize and provide prognostic criteria for patients with Stage IV disease. For instance, the BRAF inhibitors vemurafenib and dabrafenib and immunotherapies such as ipilimumab, an anti–CTLA-4 monoclonal antibody, have shown promising initial results for patients with Stage IV melanoma.94 Although the studies of these agents that have been completed to date do not stratify the subpopulation of melanoma patients and treatments options. Additionally, many of the studies included did not contain enough information concerning variables that could have been used, when combined with other studies, to adequately evaluate their impact on survival and/or clinical outcomes. Finally, as with other systematic reviews and meta-analyses, a major limitation is publication bias. As such, further studies are needed to compare the impact of surgery, radiotherapy, chemotherapy, immunotherapy or the combination on the survival of patients diagnosed with primary skin cancer metastasis to the spine. Larger retrospective studies and preferably prospective randomized controlled trials are needed to further guide management in this specific patient population.

Conclusions

Patients diagnosed with a primary skin cancer metastasis to the spine have poor overall survival with the exception of BCC. The median duration of survival for patients who underwent surgical intervention alone, medical management (chemotherapy and/or radiation) alone or the combination was similar across interventions. Age greater than 65 years, sacral spinal involvement, presence of a neurological deficit, and nonambulatory status were associated with decreased survival in patients diagnosed with a primary skin cancer spinal metastasis.

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References

15. Beer RE, Alcalay J, Goldberg LH: Multiple bone metastases

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Skin cancer spinal metastasis survival


38. Findlay GF: Adverse effects of the management of malignant spinal cord compression. **J Neurol Neurosurg Psychiatry** 47:761–768, 1984


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