Metastatic basal cell carcinoma: Prognosis dependent on anatomic site and spread of disease

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was 54 months (95% confidence interval (CI), 24–72), with shorter survival in DM (24 months; 95% CI, 12–35) versus RM cases (87 months; 95% CI, 63–not evaluable).

**Conclusion:** Cases with RM and DM mBCC may have different clinical courses and outcomes. Based on published reports, DM cases were younger at mBCC diagnosis, with shorter median survival than RM cases. This study provides a historical context for emerging mBCC treatments.

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1. Introduction

Basal cell carcinoma (BCC) is the most commonly diagnosed skin cancer. Although most BCCs are indolent, metastases occur in rare cases [1,2]. Because metastatic BCC (mBCC) is uncommon, its incidence and disease course are poorly characterised. Since the first description by Beadles [3] of mBCC in 1894, fewer than 400 cases have been reported [2]. Estimates of mBCC incidence vary widely, ranging from 0.0028% to 0.55% of all BCCs [2,4].

Metastatic BCC spreads by lymphatic and haematogenous routes [2,5,6]. For cases with lymph node metastases only, average survival is reported to be 3.6 years after metastatic diagnosis [2]. Among cases with haematogenous spread to sites such as bone, liver and lung, average survival is reported to be 8–14 months [5,6].

Most articles describing mBCC cases cite criteria proposed by Lattes and Kessler [7] (1951) to define true mBCC cases: primary BCC located on skin, not a mucus membrane; primary tumour described as BCC with histological confirmation of metastasis; and direct spread of primary tumour ruled out. These criteria have been used historically to distinguish mBCC cases from second primary tumours and locally advanced BCC.

The emergence of novel therapies to treat metastatic or locally advanced BCC marks the beginning of a new era in treatment options for patients and underlines the need to understand disease characteristics and course [8]. To that end, this report provides a comprehensive analysis of mBCC cases reported after the von Domarus and Stevens [6] 1984 review of 170 previously published cases. The objective of this analysis is to describe the association between the extent of disease spread and survival among mBCC cases reported from 1981 to 2011.

2. Methods

A PubMed-based search of the MEDLINE database identified 1016 English-language mBCC case reports published from January 1981 to October 2011 using the terms ‘basal cell’ or ‘basal cell carcinoma’; ‘metastatic’, ‘metastases’ or ‘metastasis’ and ‘skin’. Articles were manually searched to identify mBCC cases based on the criteria by Lattes and Kessler [7]. Publications were also identified from article bibliographies in an effort to include all relevant sources. Meeting abstracts were excluded because the analysis required detailed information about individual cases, both to determine survival and to confirm mBCC diagnosis, which was typically not available from abstracts.

Date of metastasis was defined for each case by the authors of the primary publications. In some cases, the diagnosis was incidental; in others, the diagnosis occurred as a part of routine follow-up. The differences between cases in how the metastatic diagnosis was made may affect the survival estimates and reflect how mBCC cases are likely to be diagnosed in routine clinical practice.

To determine survival after mBCC diagnosis, either total duration of follow-up reported in months or years or chronologic information sufficient to calculate total follow-up time after mBCC diagnosis was abstracted for each case. For cases with chronologic information only, month and year of mBCC diagnosis were subtracted from month and year of death or last known follow-up to determine total survival time. Cases were excluded for which only year was stated for date of metastatic diagnosis, death or last reported follow-up.

Most cases with lymph node spread lacked sufficient information on size of lymph node metastasises to apply specific staging criteria. Instead, cases were categorised based on extent of disease spread as either regional metastases (RM) or distant metastases (DM). These categories were intended to align with tumour staging systems that differentiate RM from DM based on current understanding of cancer biology. RM cases had spread to regional lymph nodes, soft tissue (including subcutaneous tissue or skin), salivary glands or ipsilateral muscle in the same anatomic region (e.g. head and neck primary and metastasis), DM cases had spread to distant lymph nodes, viscera, bone, brain or meninges. A consort diagram of mBCC cases assessed for inclusion in survival analysis is provided in supplemental Fig. 1.

Anatomic location of the primary tumour was classified into five categories: head and neck, trunk, genitals, limbs and multiple locations. Tumours located on the shoulder, axilla, back, chest or abdomen were classified as trunk. Cases with two or more primary sites were included in the multiple-locations category.

Histology descriptions were recorded for both primary tumour and metastasis. Cases without specific histology details were classified as BCC. Cases with
squamous differentiation were included in the same category as basosquamous and metatypical tumours.

Disease characteristic differences between groups (RM versus DM) were assessed with t tests and χ² tests. Kaplan–Meier estimates of 1-year survival probability, median survival time and 95% confidence intervals (CIs), were provided. Overall survival differences by site of spread, age (<65 versus ≥ 65 years), sex, publication date (1981–1990, 1991–2000 and 2001–2011) and treatment (chemotherapy, radiation therapy or surgery) were evaluated with the log-rank test. Data were analysed with JMP (version 9.0; Cary, NC) and validated with SAS (version 9.2; Cary, NC). Alpha was set at 0.05, and all P values were two sided.

3. Results

From 172 mBCC cases published from January 1981 through October 2011 that met initial evaluation criteria, 100 cases with clear survival information after metastatic diagnosis were included in the analysis [4,6,9–90]. Sixty cases were reported from North America, 20 from Europe, 10 from Asia, seven from Australia and New Zealand, two from Africa and one from South America. Among 50 cases for whom race was reported, 43 (86%) were Caucasian. Among seven cases with both mBCC and Gorlin syndrome identified during this time period, one had sufficient survival information to be included in this analysis [12,91–96].

Table 1 shows selected characteristics for the 100 mBCC cases by site of disease spread. Nine cases had metastases to more than two locations. Among RM cases, one had spread to three sites (auditory meatus, oral cavity and subcutaneous neck) [49]. Four DM cases had metastases to three sites, and four had spread to four sites. There was no significant difference in time from primary BCC to mBCC diagnosis between RM and DM cases.

Among 93 cases with clear documentation of treatment for metastases, 36 (39%) received more than one type of treatment. Among 20 cases who received chemotherapy, 12 (60%) received more than one chemotherapy agent; cases were treated with a median of two agents (Table 2). Four cases who received chemotherapy had no evidence of disease after treatment, three had stable disease, 11 had progressive disease or recurrence, one

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All cases (n = 100)</th>
<th>Distant metastases (n = 50)</th>
<th>Regional metastases (n = 50)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at BCC diagnosis, years a</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SE)</td>
<td>57.1 (1.8)</td>
<td>53.6 (2.1)</td>
<td>61.1 (2.8)</td>
<td>.037</td>
</tr>
<tr>
<td>Median</td>
<td>58.0</td>
<td>54.5</td>
<td>65.0</td>
<td></td>
</tr>
<tr>
<td>Years from BCC to mBCC diagnosis b</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SE)</td>
<td>8.0 (0.8)</td>
<td>7.4 (1.1)</td>
<td>8.6 (1.2)</td>
<td>.48</td>
</tr>
<tr>
<td>Median</td>
<td>6.0</td>
<td>6.0</td>
<td>6.0</td>
<td></td>
</tr>
<tr>
<td>Age at mBCC diagnosis, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SE)</td>
<td>62.1 (1.3)</td>
<td>58.0 (1.7)</td>
<td>66.3 (1.8)</td>
<td>.0013</td>
</tr>
<tr>
<td>Median</td>
<td>62.0</td>
<td>58.5</td>
<td>69.0</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td>.52</td>
</tr>
<tr>
<td>Female</td>
<td>31 (31.0)</td>
<td>14 (28.0)</td>
<td>17 (34.0)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>69 (69.0)</td>
<td>36 (72.0)</td>
<td>33 (66.0)</td>
<td></td>
</tr>
<tr>
<td>Location of primary BCC</td>
<td></td>
<td></td>
<td></td>
<td>.32</td>
</tr>
<tr>
<td>Head and neck</td>
<td>56 (56.0)</td>
<td>30 (60.0)</td>
<td>26 (52.0)</td>
<td></td>
</tr>
<tr>
<td>Trunk</td>
<td>26 (26.0)</td>
<td>15 (30.0)</td>
<td>11 (22.0)</td>
<td></td>
</tr>
<tr>
<td>Genitals</td>
<td>7 (7.0)</td>
<td>2 (4.0)</td>
<td>5 (10.0)</td>
<td></td>
</tr>
<tr>
<td>Limbs</td>
<td>5 (5.0)</td>
<td>1 (2.0)</td>
<td>4 (8.0)</td>
<td></td>
</tr>
<tr>
<td>Multiple locations</td>
<td>6 (6.0)</td>
<td>2 (4.0)</td>
<td>4 (8.0)</td>
<td></td>
</tr>
<tr>
<td>Vital status at last follow-up</td>
<td></td>
<td></td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Alive</td>
<td>52 (52.0)</td>
<td>15 (30.0)</td>
<td>37 (74.0)</td>
<td></td>
</tr>
<tr>
<td>Dead</td>
<td>48 (48.0)</td>
<td>35 (70.0)</td>
<td>13 (26.0)</td>
<td></td>
</tr>
<tr>
<td>Treatment for metastases c</td>
<td>n = 93</td>
<td>n = 47</td>
<td>n = 46</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>20 (21.5)</td>
<td>17 (36.2)</td>
<td>3 (6.5)</td>
<td>.0005</td>
</tr>
<tr>
<td>Radiation therapy</td>
<td>40 (43.0)</td>
<td>20 (42.6)</td>
<td>20 (43.5)</td>
<td>.93</td>
</tr>
<tr>
<td>Surgery</td>
<td>59 (63.4)</td>
<td>19 (40.4)</td>
<td>40 (87.0)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>None</td>
<td>16 (17.2)</td>
<td>13 (27.7)</td>
<td>3 (6.5)</td>
<td>.0069</td>
</tr>
</tbody>
</table>

All data are n (%) unless stated otherwise.

BCC, basal cell carcinoma; mBCC, metastatic basal cell carcinoma; SE, standard error.

a n = 79.

b n = 95.

c n = 36 cases received >1 type of treatment.
Table 2
Treatment administered to mBCC patients who received chemotherapy (n = 20), a 1981–2011.

<table>
<thead>
<tr>
<th>Drug/Drug class</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platinum-based</td>
<td>16</td>
<td>80</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>7</td>
<td>35</td>
</tr>
<tr>
<td>5-Fluorouracil</td>
<td>6</td>
<td>30</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>Vincristine/vinblastine</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Taxane</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Other/ unspecifiedb</td>
<td>6</td>
<td>30</td>
</tr>
</tbody>
</table>

mBCC, metastatic basal cell carcinoma.

a Twelve of 20 (60%) received >1 type of chemotherapy.

b Other drugs were amygdalin, cyclophosphamide, etoposide, gemcitabine and rituximab. Drug was unspecified for one case.

Table 3
Histology of primary BCC in mBCC cases, 1981–2011.

<table>
<thead>
<tr>
<th>Histology</th>
<th>All cases, n (%)</th>
<th>Distant metastases, n (%)</th>
<th>Regional metastases, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basosquamous or metatypical</td>
<td>10 (10.0)</td>
<td>6 (12.0)</td>
<td>4 (8.0)</td>
</tr>
<tr>
<td>Infiltrative</td>
<td>14 (14.0)</td>
<td>9 (18.0)</td>
<td>5 (10.0)</td>
</tr>
<tr>
<td>Morpheaform</td>
<td>10 (10.0)</td>
<td>5 (10.0)</td>
<td>5 (10.0)</td>
</tr>
<tr>
<td>Other</td>
<td>14 (14.0)</td>
<td>6 (12.0)</td>
<td>8 (16.0)</td>
</tr>
<tr>
<td>BCC, no subtype specified</td>
<td>52 (52.0)</td>
<td>24 (48.0)</td>
<td>28 (56.0)</td>
</tr>
</tbody>
</table>

BCC, basal cell carcinoma; mBCC, metastatic basal cell carcinoma.

a One case described as metatypical and morpheaform.

b Other cases described as infiltrative and nodular.

c One case described as morpheaform and nodular.

d Other histologies: adenoid, adenoid cystic, and keratotic, clear cell, keratotic, nodular, and solid.

had no response and one had no response information. Details for these cases are provided in the supplemental Table 1.

Table 3 shows the distribution of RM and DM cases by histology. Forty-eight cases had detailed histology information for primary BCC and 38 cases had information on mBCC histology. Seventy-seven cases had the same histology description for primary tumour and mBCC both (of which 31 were the same named histological subtype) and 16 cases had a histology description for the primary tumour but not for mBCC. Differences in site of spread or survival based on histology could not be adequately assessed because 52% of cases lacked specific histology descriptions. Details for all cases are provided in supplemental Table 2.

Twenty-five mBCC cases had metastases to more than one location (Table 4). Among 24 cases with bone metastases, 20 had disease spread to vertebrae and nine had spread to ribs. All bone metastases were described as being distant from the primary BCC site and were not thought to be tumour invasion.

Among 15 DM cases with lymph node spread, 14 of 15 (93%) involved regional lymph nodes and a distant site such as bone or lung; one case had spread to distant lymph nodes only. Lymph node spread was described before diagnosis of distant metastases in seven of 15 cases (47%). Four of seven cases had detailed information on time from discovery of lymph node spread to diagnosis of distant metastases, with a mean of 18 months (range, 11–30 months). For these four cases, time from diagnosis of distant metastasis was used to determine survival time.

In 33 of 35 DM cases who died, cause of death was related to mBCC. In the remaining two DM cases who died, one was reported as having died from another cause, and cause of death was unknown for the other. Among 13 RM cases who died, cause of death was related to mBCC in five. In the other eight RM cases who died, four died from other causes, and cause of death was unknown for four.

Compared with RM cases, DM cases had shorter survival times, with a 1-year survival probability of 58.6% (95% CI, 44.6–72.6%) versus 87.8% (95% CI, 78.6–97.0%) for RM (Table 5). Median survival was 24 months among DM cases versus 87 months for RM (Fig. 1). A sensitivity analysis that used time from lymph node spread instead of time from distant metastasis in seven of 15 cases (47%). Four of seven cases had detailed information on time from lymph node spread to diagnosis of distant metastases, with a mean of 18 months (range, 11–30 months). For these four cases, time from distant metastasis was used to determine survival time.

In 33 of 35 DM cases who died, cause of death was related to mBCC. In the remaining two DM cases who died, one was reported as having died from another cause, and cause of death was unknown for the other. Among 13 RM cases who died, cause of death was related to mBCC in five. In the other eight RM cases who died, four died from other causes, and cause of death was unknown for four.

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Additional survival estimates were performed to determine whether other factors were related to mBCC survival time. DM cases with and without bone and lung metastases were compared because these were the two most common sites of distant metastases. Among 24 DM cases with bone metastases, median survival was 12 months (95% CI, 5–24 months), which was significantly shorter than median survival for the 26 cases...
without bone metastases (66 months; 95% CI, 24–88 months; \(P = 0.026\)). However, 14 of 24 (58%) cases with bone metastases had disease spread to two or more sites, compared with only seven of 26 (27%) cases without bone metastases.

Median survival was significantly longer among 28 DM cases with lung metastases than in 22 DM cases without lung metastases: 66 months (95% CI, 24–76 months) versus 10 months (95% CI, 3–24 months; \(P = 0.0002\)). For these cases, 12 of 28 (43%) with lung metastases had disease spread to two or more sites, compared with nine of 22 (41%) cases without lung metastases. Kaplan–Meier analyses that compared survival by number of metastatic sites (less than two versus two or more), age (<65 versus ≥65 years), sex and publication year (1981–1990 versus 1991–2000 versus 2001–2011) did not identify any significant survival differences (data not shown).

4. Discussion

This analysis provides a comprehensive description of the mBCC disease course and survival based on 100 cases reported in the peer-reviewed literature from 1981 to 2011. Based on total known follow-up times for the mBCC cases included in this analysis, Kaplan–Meier estimates of the median mBCC survival times were 24 months for DM cases and 87 months for RM. Previously reported median mBCC survival times ranged from 8 to 14 months; however, these were not

Table 5
Kaplan–Meier estimates of 1-year and median survival by selected characteristics among mBCC cases, 1981 to 2011.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n</th>
<th>1-year survival probability, % (95% CI)</th>
<th>Median survival (95% CI), months</th>
<th>Survival time range, months</th>
<th>(P) value(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cases</td>
<td>100</td>
<td>73.2 (64.4–82.0)</td>
<td>54 (24–72)</td>
<td>0–120+</td>
<td></td>
</tr>
<tr>
<td>Site of spread</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distant metastases</td>
<td>50</td>
<td>58.6 (44.6–72.6)</td>
<td>24 (12–35)</td>
<td>0–108</td>
<td>.0006</td>
</tr>
<tr>
<td>Regional metastases</td>
<td>50</td>
<td>87.8 (78.6–97.0)</td>
<td>87 (63–NE)</td>
<td>0–120+</td>
<td></td>
</tr>
<tr>
<td>Treatment ((n = 93))</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>20</td>
<td>69.3 (48.8–89.8)</td>
<td>30 (10–54)</td>
<td>2–66</td>
<td>.12</td>
</tr>
<tr>
<td>No chemotherapy</td>
<td>73</td>
<td>76.4 (66.5–86.2)</td>
<td>72 (24–87)</td>
<td>0–120+</td>
<td></td>
</tr>
<tr>
<td>Radiation therapy</td>
<td>40</td>
<td>87.5 (77.2–97.8)</td>
<td>54 (24–76)</td>
<td>6–120+</td>
<td>.19</td>
</tr>
<tr>
<td>No radiation therapy</td>
<td>53</td>
<td>65.2 (52.1–78.3)</td>
<td>87 (18–87)</td>
<td>0–87</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>59</td>
<td>93.1 (86.5–99.6)</td>
<td>72 (63–96)</td>
<td>1–120+</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>No surgery</td>
<td>34</td>
<td>43.8 (27.0–60.5)</td>
<td>10 (2–24)</td>
<td>0–60</td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval; mBCC, metastatic basal cell carcinoma; NE, not evaluable.

\(^a\) Between-group comparison of overall survival data.

Fig. 1. Survival after metastatic basal cell carcinoma (mBCC) diagnosis for cases with regional metastases (\(n = 50\)) compared with distant metastases (\(n = 50\)). NE, not evaluable.
estimated with Kaplan–Meier methods and seem to have been restricted to patients who died, resulting in shorter median survival times [5,6,97]. In contrast, a recent retrospective Kaplan–Meier analysis of 10 cases from a single institution reported considerably longer mBCC survival than previously published estimates [98]. This analysis included cases with distant mBCC but excluded metastases with basosquamous morphology, which are currently categorised in the National Comprehensive Cancer Network (NCCN) guidelines as squamous cell carcinoma because of a more aggressive clinical course [99].

The observed association between mBCC survival time and metastasis location is consistent with prior reports of longer survival among cases with lymphatic versus haematogenous spread [100]. RM cases had both a higher 1-year survival probability and a longer median survival time than DM cases. The survival times calculated with the extent of disease-based categories are similar to those observed in survival analyses based on lymph node–only versus non-lymph node metastases and support the use of current tumour staging systems to characterise mBCC cases [101]. The effect of treatment on survival could not be assessed because treatment choice depended on extent of disease spread (ie, chemotherapy for DM, surgery for RM) and the small number of cases in this analysis precluded use of multivariate methods.

Overall, 38 mBCC cases (five RM and 33 DM) were reported to have died of disease. Cause of death was related to complications of disease or treatment, such as cachexia, pneumonia and renal failure. Among RM cases who died, five of 13 cases (38.5%) died of disease compared with 33 of 35 (94.3%) of DM cases. This difference is consistent with the shorter survival time among DM cases observed in the survival analysis and the expectation that DM cases had mBCC-specific deaths.

Among DM cases, patients with bone metastases seemed to have significantly shorter survival times than those without bone metastases. In contrast, patients with lung metastases seemed to have significantly longer survival times than those without lung metastases. These findings suggest that longer survival may be more closely related to metastasis site than to overall disease burden. Further study is needed to evaluate whether these observations are valid.

Among all 100 mBCC cases, nine had spread to three or more sites, which made it difficult to evaluate the number of metastatic sites as an independent predictor of survival. When these nine cases were compared with 91 cases with metastases to two or fewer sites, the difference in median survival was not statistically significant. Larger case series or data from population-based sources may provide more effective evaluation of the association between disease burden and survival.

Because mBCC is rare and limited information about the disease has been reported, it can be difficult to confirm that a case is truly mBCC as opposed to a second primary skin BCC or a different tumour type altogether. To address this issue, cases described as basosquamous carcinomas in organs other than skin were excluded. Although we were limited to the author assessment of the tumours, the majority of authors justified the mBCC diagnosis based on the Lattes and Kessler [7] criteria, which require documented history of a prior BCC of skin and histological confirmation of metastasis. Several recent case reports used immunohistochemistry to confirm mBCC diagnosis by ruling out other tumour types as the source of metastasis [4,10,22,28]. In addition, one study reported an association between trisomy 6 and mBCC [31]. However, no immunohistochemical or molecular markers have emerged that reliably predict which BCCs are more likely to metastasise or that independently confirm mBCC diagnoses, and the cases included in this analysis did not contain information on the mutational status of the BCCs.

It was difficult to determine whether the histology of the primary and metastatic lesions was identical because most cases did not have specific descriptions for both. However, 31 cases had identical histology subtype descriptions for primary and metastatic lesions. Although we cannot confirm that the primary tumours described for cases included in this analysis were the actual source of the mBCC, the high proportion of cases with consistent histology descriptions among those that reported this information is reassuring. Only 10% of cases included in this analysis were described as being of a basosquamous or a metatypical subtype. While there is widespread belief that basosquamous BCCs are much more likely to metastasise, the data show that other histology subtypes also lead to mBCC.

Overall, the data reveal considerable variation in how mBCC cases are treated, which is consistent with the lack of treatment standards for this disease. Surgery and radiation therapy were the most commonly reported treatments for RM and DM cases. The higher proportion of RM cases treated with surgery and radiation therapy suggests that these treatments might have been offered with curative intent for this earlier stage of disease. Only 20 of 100 mBCC cases included in this analysis, of which 17 were DM cases, received chemotherapy to treat their metastases. Although DM cases were more likely than RM cases to receive chemotherapy, DM cases were also more likely to receive no treatment at all.

Among the 20 cases described in this report who were treated with chemotherapy, 16 (80%) received platinum-based agents and six of 16 (38%) had a favourable response to therapy. In other words, there was no evidence of disease or partial response after treatment. This finding is consistent with publications that describe...
positive responses to platinum-based chemotherapy. However, there are no randomised clinical trials that measure survival benefit or impact on quality of life for these agents in this setting [3,102].

A few limitations should be considered when interpreting the results of this analysis. First, case reports published in the literature might represent the extremes of what is seen in typical clinical practice. In other words, cases with unusually short or long survival times might be more likely to be reported. Second, this analysis is based on information reported in published articles and, therefore, depends on the authors’ clinical judgment and stated diagnoses. Several cases were excluded because they lacked information on survival time after mBCC diagnosis. In addition, some included cases were eventually lost to follow-up or were reported shortly after mBCC diagnosis, with minimal follow-up time. Finally, these data are retrospective and should be used only to generate hypotheses for further study.

Because mBCC is rare, some clinicians might be unaware that BCC can metastasise and might not recognise or correctly diagnose the disease. Therefore, although the findings from this analysis are consistent with previously published estimates that report survival differences based on site of disease spread, we cannot fully validate these results. Moreover, this analysis is limited by its small sample size and retrospective nature. Analyses of population-based data sources or prospective observational studies could provide more insight into the natural history of mBCC.

Theoretically, changes in mBCC treatment patterns and overall improvement in health care quality over time may have also affected survival. However, comparison of median survival among cases reported in 1981–1990, 1991–2000 and 2001–2011 did not demonstrate a significant survival difference between these periods, and there was no apparent trend over time. New treatments for mBCC are now being introduced. This article provides information on cases that were described before the introduction of new therapies and, therefore, can serve as a benchmark for the effect of these new treatments.

Until recently, no approved therapies for mBCC were available [8]. During a time when new treatment options are emerging, this study provides a comprehensive, updated assessment of the disease course and survival differences based on site of spread for mBCC, and the historical context of this disease.

**Conflict of interest statement**

Employment or leadership position:

J. Hou: Medical Director, Genentech  
M. McCusker: Employee, Genentech

L. Wang: Principal Epidemiologist, Genentech  
H. Yue: Senior Statistical Scientist, Genentech

Consultant or advisory role:

R. Dummer: Roche and Novartis  
K. Lewis: Roche, Genentech  
D. Schadendorf: Amgen, BMS, GSK, Leo, MSD, Novartis, Roche  
Sekulic: Roche/Genentech

Stock ownership:

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M. McCusker: Roche  
H. Yue: Roche

Honoraria:

R. Dummer: Roche and Novartis  
A. Hauschild for advisory boards, speaker bureaus: Amgen, AstraZeneca, BMS, Boehringer Ingelheim, Celgene, Eisai, GSK, IGEA, Lilly, MelaSciences, Merck Serono, MDS/Merck, Novartis, Oncosec, Roche Pharma  
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**Appendix A. Supplementary data**

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References


