ORIGINAL REPORT

Clinical Features and Outcomes of Locally Advanced and Metastatic Basal Cell Carcinoma

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Cutaneous basal cell carcinoma is a primarily indolent tumour that is easily cured. However, locally advanced BCC (laBCC) and metastatic BCC can have a poor prognosis. This retrospective cohort study, conducted at a single cancer centre over a 32-year period, reports the characteristics and clinical course of 51 patients with laBCC or metastatic basal cell carcinoma. Thirty-five patients were men (69%), with a mean age of 72 years. Most primary basal cell carcinomas were located in the head and neck (59%), and were treated with surgery (78%). Thirty-four patients had laBCC; 6 of those developed subsequent metastasis. Twenty-three metastatic basal cell carcinomas were included. The median size of laBCC was 73 mm (interquartile range 110; range 15–400 mm), with 71% measuring 5 cm or larger. Tumour infiltration beyond the subcutaneous fat was present in 59% of laBCC and bone infiltration in 12%. Of laBCC, 44% experienced local recurrence after resection, which was seen in 35% of local tumours later developing metastasis. Median time to metastasis was 33 months. Most patients developed nodal metastases only (70%), but 26% developed distant metastases. Fifteen patients died during follow-up (29%). Three patients died of their laBCC with a 5-year disease-specific survival of 79%. Five-year disease-specific survival for metastatic basal cell carcinoma was 30%. Patients with laBCC in this cohort were at high risk of local recurrence and metastasis, and 12% died of their laBCC. These findings highlight the need for intensified follow-up for this relatively rare population, especially since Hedgehog inhibitors and PD1 inhibitors might be available for these patients.

Key words: basal cell carcinoma; dermatology; oncology; advanced BCC; giant BCC.

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SIGNIFICANCE

This study reports on the outcomes of 51 patients with large cutaneous basal cell carcinoma or metastasized basal cell carcinoma. It was found that when diagnosed with a large cutaneous basal cell carcinoma, local recurrence, metastasis, and disease-specific death become more prevalent. Identifying basal cell carcinomas at high risk of adverse outcomes remains challenging, as most basal cell carcinomas are indolent tumours and are easily treated by simple excision. This study suggests that large tumour size, tumour recurrence, and histologic evolution may indicate aggressive tumour behaviour. Patients with BCC with any of these characteristics might benefit from intensified follow-up, especially as new potential treatments, like Hedgehog-inhibitors and PD1-inhibitors, might be available.

Cutaneous basal cell carcinoma (BCC) is the most common malignancy worldwide (1). Typically, this slow-growing indolent tumour can be cured with a simple surgical procedure (2, 3). Other primary treatment options include imiquimod, photodynamic therapy, or radiotherapy. However, if left untreated, a BCC may grow, become locally invasive, cause severe damage to surrounding structures, and, in rare cases, metastasize.

Advanced BCCs, including large tumours referred to as giant BCCs (gBCCs) when measuring ≥ 5 cm, and unresectable cases classified as locally advanced BCC (laBCCs) both pose a significant challenge in identifying effective treatment strategies (4). These rare presentations of BCCs are primarily documented in small-to-moderate-sized case-series focusing on selected cases with aggressive histologic subtypes (5, 6), recurrent BCCs, or cases with prolonged patient delay (7). Interestingly, the local characteristics of BCCs do not necessarily correlate with regional or distant metastasis. For example, a study of 37 gBCC cases found no evidence of metastases (8), while another series involving 43 laBCC patients reported only 1 case of metastatic disease (9). Beyond the physical burden, patients with advanced disease often experience reduced emotional well-being and impaired ability to perform daily activities (10).

While locally aggressive behaviour is not uncommon in BCCs, the risk of metastatic spread remains extremely low (0.003–0.55%) (11, 12). To date, only about 400 metastatic BCC (mBCC) cases have been reported in the literature (11–19). Once the tumour has metastasized the prognosis is poor, with a median survival of 8–14 months (20).

To better identify BCC patients who may benefit from intensified follow-up, including radiological imaging, or who may be eligible for clinical trials or treatment with Hedgehog inhibitors or newly registered PD1 inhibitors, a deeper understanding of the characteristics, progression, and prognosis of gBCC, laBCC, and mBCC is essential. Equally important is a more extensive insight into treatment outcomes for these relatively rare disease presentations. This retrospective cohort study aims to report on the presentation, clinical course, and treatment outcomes for patients with laBCC or mBCC in a single tertiary referral centre over a 32-year period.

METHODS

Study design and patient selection

This historical cohort study was conducted at the Department of Dermatology of the Netherlands Cancer Institute (NKI), a tertiary cancer centre in Amsterdam, the Netherlands.

All patients with histologically proven locally advanced BCCs (laBCCs) and metastatic BCCs (mBCCs) from January 1990 until February 2022 with a minimal follow-up time of 12 months were included. LaBCC is typically defined as a BCC that is not amenable to curative treatment with surgery and/or radiotherapy. In this study, we expanded the definition to include giant BCCs (gBCCs) measuring ≥ 5 cm or larger, classifying laBCC in this study as either a locally inoperable BCC or a giant BCC (gBCC) measuring ≥ 5 cm in diameter. BCCs were classified as inoperable BCCs if this conclusion was noted after multidisciplinary consultation held in our medical centre. Patients with suspected mBCC were excluded if there was no histological confirmation of metastasis, or if there was significant uncertainty regarding the primary origin of the metastasis.

Data collection

Patient, tumour, and treatment characteristics were recorded from the patient files, as well as oncological outcomes. Tumour characteristics were obtained from the primary tumour, including information on the primary treatment. In any case where this information was absent, the earliest available characteristics of the residual or recurrent tumour were recorded. In such cases, follow-up started at the date of the described tumour. Henceforth, both variations are referred to as primary tumour in this study.

Because pathology reports often lacked detailed information on tumour depth, contrary to current Dutch pathology guidelines (2, 3), both pathological and radiological information on the extent of tissue invasion was collected. Reports on tissue invasion on radiological imaging of the primary tumours were reviewed in addition to the histological data. Outcome characteristics included follow-up time, local recurrence, metastasis type and location, time to recurrence and metastasis, last treatment before recurrence or metastasis, and overall and disease-specific survival information.

Statistics

All descriptive statistics and Kaplan–Meier competing risk survival analyses were performed using R Studio version 1.2.5033 (R Foundation for Statistical Computing, Vienna, Austria). All reported time-related variables were calculated from the date of primary tumour diagnosis, unless otherwise stated.

The study was approved by the local institutional review board (IRBd21-033) and performed in compliance with the World Medical Association Declaration of Helsinki. All cases were de-identified through an assigned case number.

RESULTS

Patient and tumour characteristics

Of the 51 patients included in the study, 34 were diagnosed with laBCC, of whom 6 developed metastases. In addition, 17 patients with non-laBCC were included with metastatic disease. In total, 23 patients with mBCC were analysable (**Fig. 1**). Median follow-up was 34 months (IQR 99, range 12–343) from diagnosis of the primary tumour.

Clinical features of the patients and primary tumours are summarized in **Table I**. The majority of included

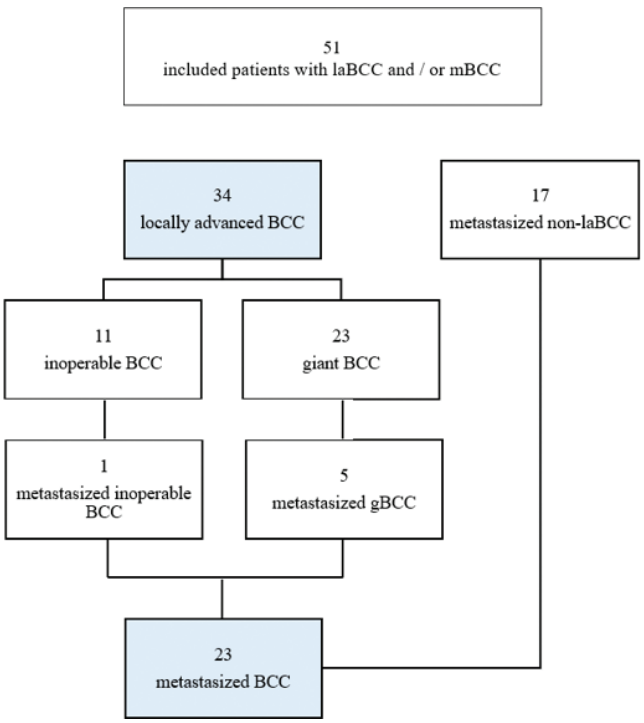

Fig. 1. Consort diagram of included patients.

Table I. Patient and primary tumour characteristics

Item	All patients (*n* = 51)	laBCC (*n* = 34)	mBCC (*n* = 23)
Age at diagnosis, years, mean (range)	72 (38–94)	77 (40–94)	66 (38–94)
Sex, male, *n* (%)	35 (69)	24 (71)	15 (65)
Skin type (Fitzpatrick), *n* (%)			
I	12 (23.5)	7 (21)	7 (30)
II	25 (49)	21 (62)	8 (35)
Unknown	14 (27.5)	6 (17)	8 (35)
Time to primary tumour diagnosis, months, median (IQR)	18 (51)	22 (2-240)	36 (102)
Tumour site, *n* (%)			
Head and neck area	30 (59)	19 (56)	13 (56.5)
Trunk	16 (31)	10 (29)	8 (34.8)
Lower extremities	3 (6)	2 (6)	2 (8.7)
Genital area	2 (4)	2 (6)	0 (0)
Primary tumour diameter, mm, median (IQR)	45 (85.25)	73 (110)	30 (90)
Tumour depth, *n* (%)			
Dermis	5 (9.8)	5 (15)	0 (0)
Subcutaneous fat	12 (23.5)	6 (18)	7 (30)
Beyond fat	20 (39.2)	16 (47)	5 (22)
Bone	5 (9.8)	4 (12)	3 (13)
Not available	9 (17.7)	3 (8)	8 (35)
Histological subtype, *n* (%)			
Nodular	8 (15.7)	6 (18)	3 (13)
Superficial	1 (2)	1 (3)	0 (0)
Infiltrative	7 (13.7)	2 (6)	5(22)
Basosquamous	10 (19.6)	5 (15)	5 (22)
Micronodular	1 (2)	1 (3)	1 (4)
Nodular + infiltrative	19 (37.2)	15 (44)	7 (30)
Nodular + basosquamous	4 (7.8)	3 (8)	2 (9)
Unknown	1 (2)	1 (3)	0 (0)
Recurrent tumour, *n* (%)	14 (27.5)	12 (35)	3 (13)
Initial treatment primary tumour, *n* (%)			
Surgery	40 (78)	22 (65)	20 (86.9)
Adjuvant radiotherapy	3 (6)	2 (6)	1 (4.33)
Imiquimod	2 (4)	0 (0)	1 (4.33)
Photodynamic therapy	2 (4)	2 (6)	0 (0)
Cryotherapy	1 (2)	1 (3)	0 (0)
Hedgehog inhibitors	3 (6)	3 (9)	1 (4.33)
Primary radiotherapy	1 (2)	1 (3)	0 (0)
None	2 (4)	3 (9)	1 (4.33)

patients were men (69%), with light skin (Fitzpatrick skin type I: 23.5%, skin type II: 49%) and a mean age of 72 years (range 38–94) at primary diagnosis. In 14 of the 51 patients (27.5%), the described BCC was a locally recurrent tumour. The described tumours of all included patients were mostly located in the head and neck area (*n* = 30, 59%). Some were found on the trunk (*n* = 16, 31%), lower extremities (*n* = 3, 6%), and genital area (*n* = 2, 4%). The primary tumour was limited to the subcutaneous fat in 23.5%, infiltrated beyond the subcutaneous fat in 39.2%, and infiltrated bone in 9.8%. The most common histological subtype was the nodular and infiltrative combination (37.2%), followed by the basosquamous subtype (19.6%), the nodular subtype (15.7%), and the infiltrative subtype (13.7%).

Surgery was the most common initial treatment for the primary tumour (*n* = 40, 78%), including 1 patient treated with Mohs surgery. Incomplete primary resection was reported in 16 surgically treated cases (44%), and of those patients, 12 received re-excision, 1 received re-excision with adjuvant radiotherapy, and 3 patients received adjuvant radiotherapy alone. The remaining 22% non-surgically treated patients were primarily treated with other methods, such as vismodegib (6%), imiquimod (4%), photodynamic therapy (4%), cryotherapy (2%), primary radiotherapy (2%), or no initial treatment (4%).

Locally advanced basal cell carcinoma

Of the 34 laBCCs in this study, 23 patients (68%) had a giant BCC (gBCC) of ³5 cm in diameter and 11 patients (32%) had a non-giant inoperable BCC. Median tumour diameter of the 34 laBCCs was 73 mm (IQR 110, range 15–400 mm). Among the gBCCs, 14 were 9 cm or larger. The majority of all laBCCs were located on the head-and-neck area (56%). For the gBCC subgroup, 41% of tumours were located on the head-and-neck area and 41% on the trunk. Tumour infiltration was beyond the subcutaneous fat in 59% (*n* = 20), with 12% infiltrating bone. Of these 20 tumours with deep tumour infiltration beyond the subcutaneous fat, 73% were located in the head-and-neck area. Patient and primary tumour characteristics are further specified in Table I.

Among all patients with laBCCs, 15 patients developed local recurrence, 8 with inoperable primary BCCs and 7 with primary giant BCCs. Of these 15 recurrent patients, 5 (33%) experienced their first local recurrence after surgery (including 2 following incomplete surgery), 4 (27%) during or after treatment with Hedgehog inhibitors, 4 after imiquimod therapy, and 2 after primary radiotherapy. The median time to recurrence was 13.6 months (IQR 8.8–13.8).

Of all laBCC patients, 6 patients (18%) developed metastases, 5 of whom had a primary gBCC. These 6 patients were included in the mBCC subgroup. During follow-up, 10 patients (29%) died, including 4 patients (12%) whose death was attributed to their locally advanced BCC. Of those, 2 patients had a primary inoperable BCC and neither of them developed metastases. Median disease-specific survival (DSS) from primary diagnosis was 122 months for laBCC (**Fig. 2**), with a 5-year OS of 79% from primary tumour diagnosis. The patient outcomes are summarized in **Table II**. At the time of writing up the study, 15 patients (44%) were still in active follow-up.

Metastatic basal cell carcinoma

Twenty-three patients with metastases were included in this study, with a median time to metastasis of 33 months (IQR 62) after the primary BCC diagnosis. In 6 mBCC cases, the primary tumour was a laBCC. Of all 23 mBCCs, 78% of patients initially developed metastasis in the locoregional lymph nodes, sometimes accompanied by subcutaneous or distant metastasis. Three patients (13%) developed subcutaneous metastasis first, of which 1 progressed to hematogenous metastases. Two patients (9%) displayed an immediate onset of hematogenous metastases, while the radiological reports did not record any nodal metastases. After follow-up, a total of 6 patients (26%) developed hematogenous metastasis,

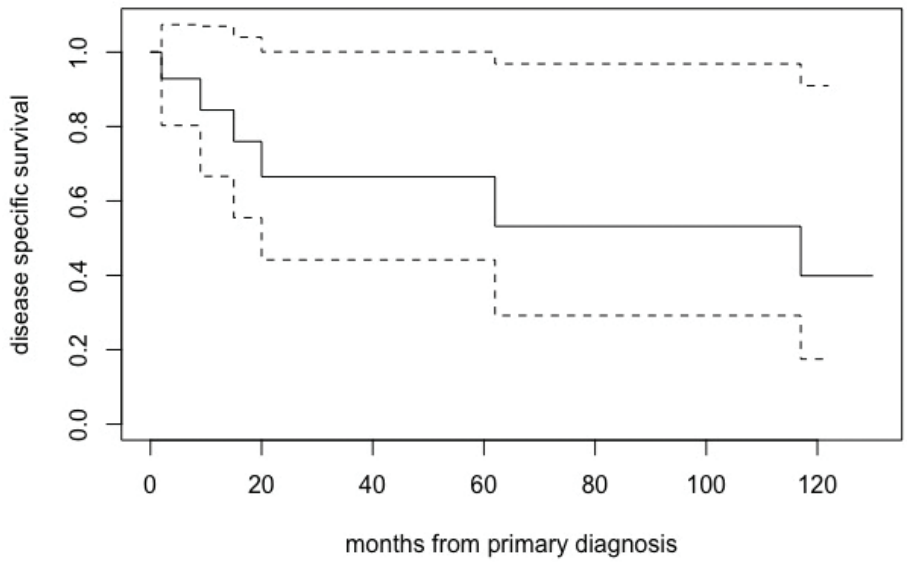

Fig. 2. Disease-specific survival of all advanced BCC patients. *Time from diagnosis of primary tumour.

mainly to the lungs, bones, or both. Most metastases were treated with surgery ($n=14$, 61%), either with ($n=8$) or without ($n=6$) adjuvant radiotherapy. One patient was treated with radiotherapy (4%) alone. In cases where unresectable disease was diagnosed, patients were treated with chemotherapy ($n=2$), Hedgehog (Hh) inhibitors ($n=2$), or immunotherapy (IT) ($n=2$). One patient with progressive disease under IT after 2 years showed regression of all metastases after switching to Hh inhibitors. The other patient who received IT progressed and had extensive curative surgery in another hospital, while previously being assessed with unresectable disease. Both patients on chemotherapy died of BCC, and both Hh patients progressed, of whom 1 switched to IT and the other chose to discontinue treatment. Two mBCC patients opted for best supportive care, of whom 1 was alive at the end of follow-up. Six of 23 mBCC patients died, 4 of whom of their BCC. Three patients with hematogenous metastases died of BCC during follow-up (50%). Of the 5 patients with subcutaneous metastasis, 2 died during follow-up (40%). The disease-specific survival rates starting from diagnosis of the primary tumour were 60% after 2 years and 30% after 5 years. Median survival time from the diagnosis of metastasis was 15 months (**Fig. 3**).

Table II. Clinical outcomes

Item	All patients ($n=51$)	laBCC ($n=34$)	mBCC ($n=23$)
Local recurrence, *n* (%)	22 (43)	15 (44)	8 (35)
Time to recurrence, months, median (IQR)	24.6 (30.6)	13.6 (5)	29.2 (18.2)
Metastasis, *n* (%)	23 (45)	6 (18)	23 (100)
Time to metastasis, months, median (IQR)	33 (62)	*	33 (62)
Metastasis type (first), *n* (%)			
Nodal	16 (31)	*	16 (70)
Subcutaneous	3 (6)		3 (13)
Visceral/bone	2 (4)		2 (9)
Nodal + visceral/bone	1 (2)		1 (4)
Nodal + subcutaneous	1 (2)		1 (4)
Metastasis type (all), *n* (%)			
Nodal only	13 (25)	*	13 (56)
Subcutaneous only	2 (4)		2 (9)
Visceral/bone only	2 (4)		2 (9)
Nodal + visceral/bone	3 (4)		3 (13)
Nodal + subcutaneous	2 (4)		2 (9)
Subcutaneous + visceral/bone	1 (2)		1 (4)
Overall survival**			
Died, *n* (%)	15 (29)	10 (29)	6 (26)
2 year OS, %	84%	82%	87%
5 year OS, %	80%	79%	83%
Disease-specific survival**			
Died of BCC, *n* (%)	7 (14)	4 (12)	4 (17)

*laBCC metastases are included and described in the mBCC subgroup. **Survival data are measured from diagnosis of primary tumour.

DISCUSSION

In this retrospective cohort study on the characteristics and oncological outcomes of patients with laBCC and mBCC, we found that a significant number of laBCC cases developed local recurrence and metastasis. Specifically, 44% of laBCC cases developed local recurrence in a median time of 13.6 months, while 18% developed metastasis in a median time of 33 months from primary tumour diagnosis. It was also noted that 12% of laBCC patients ultimately died from their BCC. This indicates that patients with laBCC are at high risk of adverse outcomes, and that intensified follow-up is strongly advised for at least 3 years.

In this study, we defined locally advanced basal cell carcinoma (laBCC) as a collective term encompassing both giant BCCs (gBCCs) > 5 cm in diameter and BCCs deemed inoperable or not suitable for curative radiotherapy. Although variable definitions and terminology for laBCC are not uncommon (32–34), clinical outcomes varied slightly between inoperable BCCs and giant BCCs. Inoperable BCCs demonstrated the higher rates of local recurrence (73%, 8/11), compared with an overall recurrence rate of 44% in the laBCC cohort. This finding

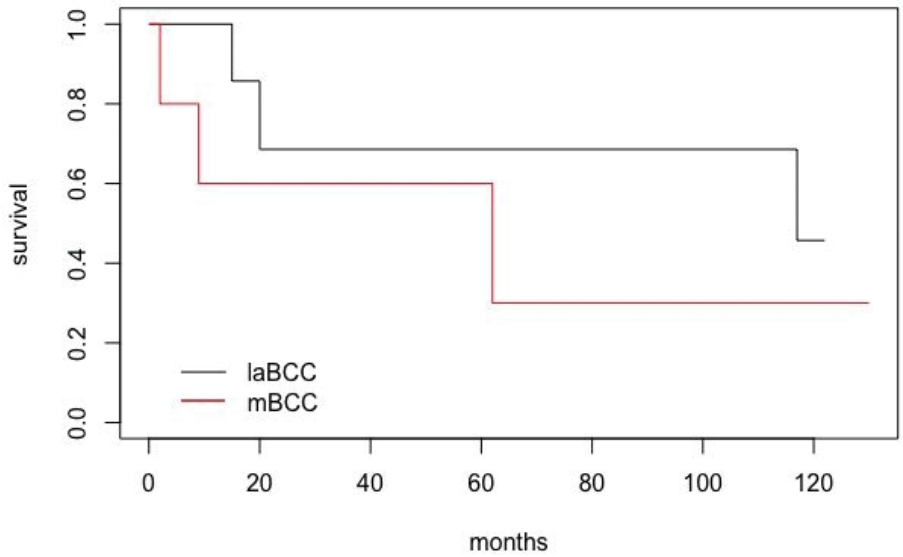

Fig. 3. Disease specific survival of laBCC and mBCC. *Time from diagnosis of primary tumour.

may reflect the reliance on alternative, often less definitive, treatment modalities (35). Additionally, inoperable BCCs, although not large in diameter, may be more prone to local recurrence due to their infiltrative histological characteristics (36). Among the 11 inoperable cases, 55% showed an infiltrative histological subtype and 65% extended beyond the subcutaneous fat, compared with 50% and 47% respectively in the general laBCC cohort. Furthermore, bone invasion was more frequent in inoperable cases (27% vs 12%). Despite their aggressive local behaviour, inoperable BCCs showed a lower incidence of metastasis (1 of 11 patients) compared with gBCCs (5 of 23 patients), while, interestingly, we found a 35% local recurrence rate before metastasis in our mBCC population, indicating that patients with recurrent BCCs are indeed at risk for metastasis.

In various studies, tumour recurrence is a common occurrence in laBCC. For example, an American study found that 68% of giant BCC were recurrent (7), while an Australian case series reported 16% recurrence (9, 21). The latter study's findings are consistent with the overall recurrence rate of BCC of around 15.2% in this study. Local tumour recurrence in BCC is typically associated with incomplete resection, but the current data suggest that local tumour recurrence could also be an indication of aggressive behaviour.

This study found that out of the 34 laBCCs included, 24 (71%) were classified as giant, meaning that they had a diameter of 5 cm or larger. Moreover, this study included 14 giant BCC (gBCC) larger than 9 cm. This is the largest group of such large gBCCs described to date. Extensive patient delay is common in patients with gBCC (7, 9, 22), and played a significant role in the development of such large tumours in this study. The median time to diagnosis for all laBCCs was 18 months, while it was 60 months for gBCC cases alone. Furthermore, of 24 gBCCs 41% were located on the trunk, while this was 29% for all laBCCs. Rather than having aggressive tumours, these patients might have difficulty in seeking healthcare, resulting in the manifestation of exceptionally large tumours on easily concealable areas of their bodies. In addition, 26% of the patients with BCC metastasis had a primary giant BCC in this study. Of those, 83% were larger than 9 cm. In contrast to other studies on laBCC and gBCC (8–10), in this cohort, patient delay and large tumour size might indeed be risk factors for developing metastasis.

Squamous differentiation is a frequent topic of discussion in studies on laBCC and mBCC (23–26). In this study, the basosquamous subtype was seen in 19.6% of all primary tumours and in 22% of primary tumours that subsequently metastasized. These percentages are in line with a study by Farmer and Helwig (26), while other studies on metastatic BCC have found smaller subsets of these squamous differentiated BCCs (12–14, 27). Acquisition of a squamous differentiation might be associated with a more aggressive course of disease. In this line, 5 out of 10 basosquamous tumours in this study acquired the basosquamous subtype after local recurrence. Of these, at least 3 tumours showed an infiltrative subtype in the primary tumour. These tumours appear to lose differentiation and obtain more squamous characteristics commonly associated with metastatic potential.

Metastatic spread is extremely rare in BCC (0.003–0.55%) (3, 11). Approximately 400 cases of metastatic BCC are known worldwide (11–19), and this study adds 23 new cases. The first metastatic spread was almost exclusively locoregional (91%) and primarily nodal (78%). Six patients developed distant metastasis during follow-up. Three patients with distant metastases died of BCC during follow-up (50%). This is in line with the literature, reporting that patients with distant metastases have shorter survival than those with regional metastases

(18). Interestingly, of the 5 patients with locoregional subcutaneous metastasis, 2 died during follow-up. Therefore, the prognosis of subcutaneous metastasis only was worse than overall mBCC in this cohort (26% overall death rate). However, determining the clinical significance of this finding poses a considerable challenge with such small numbers.

Hedgehog inhibitors are a relatively new therapeutic modality with which 6 laBCC and 3 mBCC patients in this study were treated. Resistance to Hh inhibitors can develop after a median of 24.5 and 13.1 months for laBCC and mBCC respectively (28–30), as well as burdensome side effects such as muscle spasms, dysgeusia, and nausea (31). Response rate is reported to be 43% in laBCCs (31). In our cohort, complete response was seen in 50% of laBCC patients treated with Hh inhibitors. One of 3 (33%) mBCC patients showed complete response, 1 patient died, and 1 patient showed disease progression and switched to PD1 inhibitors. PD1 inhibitors are the newest EMA registered line of treatment in The Netherlands for patients with mBCC that progressed during Hh treatment.

A limitation of this study was the retrospective design and inclusion of patients from 1 single cancer centre, resulting in selection bias. Therefore, the results of this study might not be applicable to the general population or to most BCCs. Because of the rarity of laBCC and mBCC, this study design was considered most appropriate. Second, there was a lack of detailed information on tumour depth, as measured tumour depth is often not reported in pathology reports, despite Dutch pathology guidelines recommending its inclusion (2). To minimize missing data for this characteristic, nominal data on tissue invasion were collected instead of numeric tumour depth, as reported in the methods. Lastly, as this study was conducted at a tertiary oncological hospital and resection of the primary tumour was often performed in a referring hospital, data on primary tumours were seldom complete. Where necessary, tumour characteristics of the first known tumour were described.

Identifying BCCs at high risk of adverse outcomes remains challenging. This study suggests that tumour size of >5cm, tumour recurrence, and histologic evolution into basosquamous differentiation may indicate such a high-risk BCC. Furthermore, we support including both gBCCs and inoperable BCCs under the unified definition of laBCC, as both subpopulations share substantial clinical challenges and adverse prognostic features given our findings. Considering the rarity and overlapping complexity of these tumours, further subclassification of these local manifestations of BCCs might be undesirable.

Patients with BCC with any of these characteristics might benefit from regular follow-up for at least 3 years. When diagnosed with a locally advanced BCC, local recurrence, metastasis, and disease-specific death become more prevalent and intensified follow-up is strongly advised. Future studies on the value of radiological imaging in the follow-up of these advanced BCCs are needed to build evidence-based guidelines. Finally, additional data on the genomics and tumour micro-environment of both laBCC and mBCC might be helpful to further understand this rare course of disease in a common tumour with a rising incidence.

The authors have no conflicts of interest to declare.

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