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Palliative treatment for in-transit cutaneous metastases of Merkel cell carcinoma using surface-mold computer-optimized high-dose-rate brachytherapy

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Abstract

PURPOSE—To evaluate the palliative treatment benefit of surface-mold computer-optimized high-dose-rate brachytherapy (SMBT) for in-transit cutaneous metastases of Merkel cell carcinoma (MCC).

PATIENTS & METHODS—Ten patients with in-transit cutaneous MCC metastases were treated with SMBT at the Dana-Farber/Brigham & Women's Cancer Center (DFBWCC) between 2006 and 2012.

RESULTS—The median age at diagnosis was 76 years (range 63–87 years). Seven patients had in-transit metastases on the lower extremities (70%), 2 patients on the head & neck (20%), and 1 patient on an upper extremity (10%). A total of 152 metastatic MCC lesions were treated with SMBT. All SMBT treated lesions resolved clinically within a few weeks of therapy. The median follow-up was 34 months (range 22–85 months). Two of 152 treated lesions recurred during the study period for a local control rate of 99%. Eight patients (80%) developed additional in-transit metastases outside the original SMBT fields. Five of these 8 patients underwent additional SMBT.

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CONFLICT OF INTEREST

None

PRIOR PRESENTATION

None

At study conclusion, 3 patients (30%) are alive without disease, 3 patients (30%) are alive with disease, and 4 patients (40%) died of MCC.

DISCUSSION—SMBT offers effective and durable palliation for cutaneous metastases of MCC, although it does not appear to alter disease course.

Keywords

Merkel cell carcinoma; in-transit cutaneous metastases; brachytherapy

Merkel cell carcinoma (MCC) is a rare (~ 1500 case per year) and aggressive (~ 33% mortality) cutaneous neuroendocrine carcinoma that favors UV-exposed skin of the head and neck as well as the extremities in older white patients [1, 2]. The incidence of MCC is increased in immunosuppressed patients with organ transplantation, chronic lymphocytic leukemia, and human immunodeficiency virus.[1, 3] Although the molecular pathogenesis remains largely unknown, a novel Merkel cell polyomavirus was identified in 100% of tumors [4, 5]. MCC exhibits a propensity for early regional involvement and distant relapse [6]. Survival is dependent on disease stage at diagnosis with the 5-year disease-specific survival at 97% for skin-limited disease, 52% for regional lymph node disease and 11% for distant metastatic disease [7]. Although treatment is dependent on stage, radiation therapy is favored as MCC is a highly radiosensitive tumor [8].

Despite aggressive management with wide local excision and radiation therapy (RT) [9–12], locoregional recurrence and metastatic progression are nonetheless common.[6] In-transit metastases are common on the lower extremities, and are more rarely seen on the head and neck. Untreated, in-transit cutaneous metastases often amalgamate into large malodorous ulcerated tumors that can cover an entire limb (Figure 1). As such, they can become cosmetically disfiguring, pose a wound care challenge for patients and their caregivers, and present impairments to the patient's quality of life. Treatment may be challenging as in-transit metastases are often multifocal, tend to be located on the curved surfaces of the extremities making conventional external beam radiation therapy (EBRT) technically challenging, and may appear adjacent to previously treated fields with poor tolerance for additional therapy (Figure 3). In-transit lesions are often too numerous for clear margin excision, and resection carries risks of poor wound healing in the setting or pre-existing or evolving lymphedema. Response to chemotherapy is variable and rarely durable [13]. Isolated limb perfusion/infusion may be complicated by tissue necrosis, muscle injury, compartment syndrome, vascular thrombosis, paresthesias & nerve palsies as well as systemic toxicities [14, 15]. Palliative surface-mold computer-optimized high-dose-rate (HDR) brachytherapy (SMBT) overcomes these limitations and offers a well-tolerated treatment with effective and durable local control.

Previously, we published the first case report describing the use of SMBT for palliation of in-transit cutaneous metastases of MCC on the lower extremity [16]. Here, we describe treatment outcomes and disease course in 9 additional patients treated with SMBT.

METHODS

PATIENTS

We obtained approval from the Institutional Review Board (IRB) at the Dana-Farber/Brigham & Women's Cancer Center (DF/BWCC) for our study. From our MCC patient database, we identified 10 patients with in-transit cutaneous metastases treated with SMBT at the DF/BWCC between January 2006 and November 2012. All patients were diagnosed with MCC that was confirmed by histology. Patient demographics and treatment response were extracted from electronic medical records.

SMBT TREATMENT PROTOCOL

As described in our previous publication, radioopaque markers were placed over in-transit cutaneous metastases and CT guide wires outlined the treatment field that, in most cases, extended 2 cm around all metastases (Figure 4A). A moldable applicator, composed of a thermoplastic cast and hollow HDR treatment catheters spaced at 1 cm intervals, was applied to the skin surface (Figure 4B). A single 1 × 3 mm radioactive seed of the gamma emitter Iridium-192 was then directed to separate positions (e.g., “dwell” positions) within the hollow catheters. The location of the dwell positions and the amount of time the radioactive source rested at each position were computer optimized to provide the most uniform radiation dose to the targeted lesions (Figure 4C). Typically, a total prescribed dose of 12 Gy was delivered in 2 equal fractions, 1 or 2 days apart, to a target depth of 5–10 mm based on clinical and radiographic findings.

RESULTS

The median age at diagnosis was 76 years (range 63–87 years). All patients (100%) were white. There were 6 men (60%) and 4 women (40%). At diagnosis, 2 patients were stage IB (20%), 2 were stage IIA (20%), 3 were stage IIIA (30%), and 3 were stage IIIB (30%). Seven patients had in-transit metastases on the lower extremities (70%), 2 patients on the head & neck (20%), and 1 patient on an upper extremity (10%). Initial treatment consisted of wide local excision (WLE) alone in 3 patients (30%) WLE and locoregional RT in 2 patients (20%), WLE, locoregional RT and chemotherapy in 3 patients (30%) and regional RT and chemotherapy in a single patient (10%). The initial site of relapse for all 10 patients (100%) was in-transit on the skin at a median time of 9 months after diagnosis (range 1–45 months). Two patients received salvage chemotherapy for in-transit cutaneous metastases prior to referral to the DF/BWCC (Table 1).

A total of 152 metastatic MCC lesions were treated with SMBT with each patient receiving treatment for anywhere from 2 to 36 lesions. Most patients received 1200 cGy in 2 equal fractions to a target depth of 5–10 mm based on their physical examination as well as findings on imaging studies. Two patients (20%) received 1000 cGy in 2 equal fractions, due to significant lymphedema at presentation. The median follow-up was 34 months (range 22–85 months) (Table 1). All in-transit cutaneous metastases treated with SMBT resolved within a few weeks of treatment. Treatment response was durable as 149 of 152 of lesions did not recur during the study period (99% control rate). Two patients (20%) experienced

recurrence of a single lesion in the previous SMBT field, 1 at 25 months post-SMBT in the setting of diffuse metastatic disease, and the other at 2 months post-SMBT in a lesion that was underdosed by 33%. Treatment side effects included mild erythema in all patients (100%) and ulceration in 2 patients (20%), both of whom were treated in the setting of significant lymphedema.

Two patients (20%) who underwent more than one course of SMBT treatment are alive without evidence of local or distant disease (AWOD). Eight patients (80%) developed additional in-transit cutaneous metastases outside of their original SMBT field on the affected extremity (median 2 episodes, range 1–5). Five of these 8 patients had further SMBT resulting in resolution of these additional in-transit cutaneous metastases. Three of these 5 patients who underwent additional SMBT treatments are AWOD. All of the patients (100%) had outside of SMBT field recurrence with 80% having in-transit metastases. Overall, 3 (30%) patients are AWOD, 3 (30%) are alive with disease, and 4 (40%) died of MCC (Table 1).

DISCUSSION

In keeping with the literature, our study population was white (100%), older (median age of 76 years) with a slight male to female preponderance (1.5:1) [1, 2]. In-transit cutaneous metastases were most commonly seen on the extremities (80%) where lymphatic drainage is more predictable. This is not surprising as locoregional control rates for lower extremities MCCs have been reported to be as low as 15% [13, 17]. Interestingly, 2 patients with a history of polio developed in-transit cutaneous metastases in the affected limb. One of these patients also had elephantiasis nostras verrucosa complicated by severe lymphedema (Figure 2). We also observed in-transit cutaneous metastases on the head & neck (20%), which were less common. The risk for the development of in-transit cutaneous metastases appeared to be associated more with the anatomic location of the primary tumor (e.g., lower extremities) than with the stage of disease at presentation. Indeed, in-transit cutaneous metastases were observed in both local disease for primary tumors (stage IB) and > 2 cm (stage IIA), as well as regional lymph node disease (stage IIIA & B). In our patients, in-transit cutaneous metastases tended to be multifocal (median of 10 lesions (range 2–36)), located between the primary site and regional lymph nodes as well as retrograde to the primary tumor bed. Indeed, 1 patient presented to the DF/BWCC with a recommendation for limb amputation due to the multifocality of in-transit cutaneous metastases (Figure 2). In-transit metastases presented as both violaceous nodules on the surface of the skin (Figure 2) as well as palpable subcutaneous nodules with no overlying skin changes (Figure 3). SMBT was selected over conventional therapy as in-transit cutaneous metastases tended to be in close proximity to surgical sites or previously irradiated fields (100%) and unresponsive to previous chemotherapy given as part of the initial management (4/10 (40%)) or salvage treatment (2/10 (20%)).

We treated a total of 152 lesions with SMBT. All lesions resolved clinically within a few weeks of treatment (Figure 4D). During a median follow-up of 34 months (range 22–85 months), there were only 2 in-SMBT-field recurrences. As described in our previous publication, 1 in-SMBT-field recurrence was histologically documented at 25 months post-

SMBT in the setting of diffuse metastatic disease to which the patient ultimately succumbed. The other was noted clinically at 2 months post-SMBT in a patient who received 33% less than the prescribed dose. Local control rates were thus superb at 99% (149/152). There was high patient acceptability as duration of treatment typically spanned 2 treatments 2 days apart in contrast to conventional EBRT which may span 3 or more weeks. Patient tolerance was excellent with only mild to moderate erythema (100%) in the treatment field. Two patients (20%) with severe lymphedema, however, developed ulceration in the SMBT field. As the prescribed dose was delivered to a target depth of 5–10 mm with a sharp dose fall-off at the edge of the treatment field, no patients experienced post treatment fibrosis, worsening lymphedema or damage to surrounding skin, muscle or bone.

The prognosis for patients who develop in-transit cutaneous metastases (stage IIIB) is poor with a relative survival of <30% at 5 years [18]. Our study cohort fared no better as only three (30%) patients who received serial SMBT for additional in-transit metastases are alive without disease. In-transit cutaneous metastases portend a grave prognosis and often herald distant progression with a fatal outcome. Indeed, the remaining 7 patients in our study (70%) have developed distant metastatic disease, with four succumbing to MCC (40%).

We conclude that SMBT offers both effective and durable palliation for MCC patients with in-transit cutaneous metastases, but does not alter disease course. While our study is limited by small numbers and further studies are warranted, SMBT should nonetheless be given due consideration in the palliation of in-transit cutaneous metastases where treatment options are limited.

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Figure 1.
Untreated in-transit MCC metastases of left arm and chest wall with lymphedema and cellulitis.

Figure 2.
Patient 10 with biopsy-proven in-transit MCC metastases on a background of lymphedema associated elephantiasis nostras verrucosa to whom a recommendation of amputation had been made.

Figure 3. Patient 5 with biopsy proven in-transit MCC metastases presenting as numerous subcutaneous nodules with no overlying skin changes at 6 months after completion of wide local excision, locoregional radiation and systemic chemotherapy. Suspicious lesions are marked with “Q”.

Figure 4.

A. Radio-opaque markers were placed over in-transit MCC metastases. Radio-opaque copper CT guide wires outlined at least 1–2 cm margins for treatment planning. **B.** Frieberg flap applicator with hollow HDR treatment catheters were applied to the skin surface. **C.** The location of the dwell positions and the amount of time the radioactive source rested at each position were computer-optimized to provide the most uniform radiation dose to the

targeted lesions, with optimal sparing of non-involved deep and surrounding tissue. **D.** Lesions completely resolved at 6 week follow-up with treatment sites demarcated in red.

Table 1

Characteristics of MCC patients treated with SMBT for in-transit cutaneous metastases

Patient No	Sex, age at diagnosis (yr)	Primary site	AJCC stage at diagnosis	Initial treatment (pre-SMBT)	Time to relapse* (mo**)	Chemo for in-transit metastases, No of chemo regimens (pre-SMBT)	SMBT (cGy)	In-field recurrence, time to recurrence (mo)	Site of other recurrence (time to recurrence (mo))	SMBT for additional in-transit metastases	Total lesions treated	Follow-up (mo**)	Status
1	M, 70	R calf	IIA	WLE, LR-RT	8	N	1200	Y, 25	In-Transit (19, 28), Distant (19)	N	11	42	DOD
2	M, 72	R groin	IIIB	Chemo, R-RT	12	Y, 2	1200	N	In-Transit (85)	Y	8	85	AWOD
3	M, 76	R forehead	IIIA	WLE, LR-RT, chemo	11	N	1200	N	Regional (25, 26), Distant (36)	N	4	36	AWD
4	M, 81	L forehead	IIIA	WLE, LR-RT	10	N	1200	N	Regional (23), Distant (27)	N	2	32	AWD
5	F, 63	L calf	IIIA	WLE, LR-RT, chemo	7	Y, 1	1200	N	In-Transit (13,15)	Y	13	39	AWOD
6	M, 63	R thigh	IIA	WLE, LR-RT, chemo	9	N	1200	Y, 2	In-Transit (16, 18, 19, 21, 24), Regional (24), Distant (24)	Y	37	31	DOD
7	F, 87	R calf	IB	WLE	6	N	1200	N	In-Transit (7, 15), Regional (12)	Y	3	26	AWOD
8	F, 83	L forearm	IB	WLE	1	N	1200	N	In-Transit (3, 5, 17, 20), Regional (20) Distant (5)	Y	29	22	DOD
9	F, 76	R foot	IIIB	WLE, LR-RT, S-RT	7	N	1200	N	In-Transit (7, 11.5, 18), Regional (12), Distant (22)	N	9	24	DOD
10	M, 79	L calf	IIIB	WLE	45	N	1000	N	In-Transit (45, 47, 49), Regional (49), Distant (58)	N	36	58	AWD

* The initial site of relapse for all patients was in-transit cutaneous metastases

** Calculated from the time of diagnosis

*** WLE, wide local excision; LR-RT, loco-regional radiation therapy; R-RT, regional radiation therapy; chemo, chemotherapy; AWOD, alive without disease; AWD, alive with disease; DOD, died of disease