Original paper

Computed tomography-based flap brachytherapy for non-melanoma skin cancers of the face

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Abstract

Purpose: Non-melanoma skin cancers of the face are at high-risk for local recurrence and metastatic spread. While surgical interventions such as Mohs microsurgery are considered the standard of care, this modality has the potential for high rates of toxicity in sensitive areas of the face. Catheter flap high-dose-rate (HDR) brachytherapy has shown promising results, with high rates of local control and acceptable cosmetic outcomes.

Material and methods: Patients with non-melanoma skin cancers (NMSC) located on the face were treated with 40 Gy in 8 fractions, given twice weekly via catheter flap HDR brachytherapy. Clinical target volume (CTV) included the visible tumor plus a margin of 5 mm in all directions, with no additional planning target volume (PTV) margin.

Results: Fifty patients with 53 lesions on the face were included, with a median follow-up of 15 months. All were considered high-risk based on NCCN guidelines. Median tumor size and thickness were 18 mm and 5 mm, respectively. Median PTV volume and D_{90} were 1.7 cc and 92%, respectively. Estimated rate of local control at twelve months was 92%. Three patients (5%) experienced acute grade 2 toxicity. Two patients (4%) continued to suffer from chronic grade 1 skin toxicity at 12 months post-radiotherapy (RT), with an additional two patients (4%) experiencing chronic grade 2 skin toxicity. Forty-nine lesions (92%) were found to have a good or excellent cosmetic outcome with complete tumor remission.

Conclusions: CT-based flap applicator brachytherapy is a valid treatment option for patients with NMSC of the face. This modality offers high rates of local control with acceptable cosmetic outcomes and low rates of toxicity.

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Key words: skin cancer, non-melanoma, brachytherapy, flap, face, HDR, radiation, catheter flap.

Purpose

The incidence of non-melanoma skin cancer (NMSC) in the United States was 5.4 million new cases in 2012 alone [1]. NMSC includes squamous cell carcinoma (SCC), basal cell carcinoma (BCC), and non-epithelial skin cancers. The location of skin cancer is a critical factor for prognosis. Cancers in "area H" or "mask area" of the face, including those involving the ear, central face, periorbital, eyebrows, mandible, nose, eyelids, periauricular skin/sulci, and lips, have a higher rate of recurrence due to their close proximity to critical structures and surface irregularity of these locations (Figure 1) [2,3,4]. The National Comprehensive Cancer Network (NCCN) guidelines have listed "area H" as a high-risk location, with higher potential for tumor relapse and worse prognosis [5,6], with multiple studies providing corresponding evidence [7,8].

Therefore, finding a treatment modality that treats superficial skin cancer, which can limit the rate of recurrence and complications is imperative. Current treatment options for NMSC of the face include local excision, Mohs micrographic surgery (MMS), and radiation therapy (RT) [9,10,11,12,13,14,15,16]. Radiation can be delivered via external beam with megavoltage (MV) electrons, kilovoltage and MV photons, or using brachytherapy with low-dose-rate (LDR), high-dose-rate (HDR), and electronic HDR applicators [17,18,19,20].

Mohs micrographic surgery is an appropriate treatment for NMSC in the mask area of face [3,11,12,13,21], especially for deeply infiltrating tumors or when depth is difficult to estimate [22]. RT is also an effective treatment for NMSC, with local control rates exceeding 90% even when treating tumors, which recurred following initial surgery [23,24,25,26,27,28].

Radiation therapy alone is the preferred treatment for patients, in whom surgery is contraindicated because of age, comorbidities, or poor performance status, and for patients at risk for disfigurement or post-operative scarring due to tumor location. This is in part due to the less invasive nature of RT, which may improve cosmetic out-

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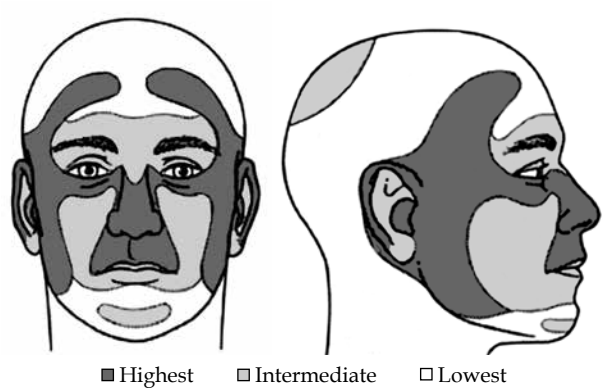

Fig. 1. Mask areas of face. Area M: forehead, scalp, cheek, and neck. Area H: periorbital, eyelids, periauricular, temple, ears, central face, lips, and nose. Photo courtesy of Stein *et al*. [4]

comes [29,30]. A primary limitation of external beam radiation therapy (EBRT) when treating tumors of the face is the difficulty in covering small or irregular fields with dose homogeneity.

Brachytherapy (BT) may be a superior treatment modality due to inherent advantages, such as high-dose concentration in the region of interest with a steep gradient of dose fall off beyond the target, providing the means to spare surrounding normal tissue. Skin high-dose-rate brachytherapy (HDR-BT) utilizing surface applicators has enhanced the ability to treat small fields [31,32].

The catheter flap (Varian Medical Systems, Palo Alto, USA) is a CT-compatible medical-grade silicone flap, with treatment catheters embedded in the material 5 mm from the surface and 10 mm apart from each other. Its design creates a gap between the source channels and between the tissue and source. Its flexibility is optimal for irregularly shaped locations. Catheter channels are positioned on the flap's middle axis, each with a diameter of 2 mm. The applicator can be cut to any size and shape in order to suit the region of interest. This has the potential to minimize some of the dose inhomogeneity that can occur when treating uneven surfaces, such as the eyes, ears, and nose, with HDR-BT surface applicator [31,32,33].

The aim of this retrospective review was to assess the efficacy and toxicity profile of a 3D CT-based HDR brachytherapy with the flap applicator in treatment of superficial NMSC of the face.

Material and methods

Patient characteristics

From January 2007 to December 2018, patients with superficial NMSC of the face were treated with HDR-BT utilizing the catheter flap. Patients were selected for HDR skin brachytherapy on a case-by-case basis at the discretion of a multidisciplinary dermatology clinic, most commonly based on concerns for inability to tolerate or refusal of surgery. Patients included into this retrospective analysis were those with histopathologically confirmed BCC or SCC, stage T1 disease according to the American Joint Committee on Cancer (AJCC) 8th Edition, and follow-up of at least six months. Depth of extension was assessed clinically by the treating physician by palpation. In cases where additional information was available, such as a detailed pathologic assessment from core biopsy that included layers of skin extension, this was also taken into consideration by the treating physician when determining depth of invasion.

Patient set-up, treatment planning, and dose

Computed tomography simulation was obtained with the patient in a supine position, during which physicians drew the treatment region of interest (ROI) that included the visible tumor plus a 5 mm margin in all directions to cover microscopic tumor extension [34,35]. CT contrasting wire was placed on the ROI to allow visualization after simulation. The flap applicator extended 10 mm beyond the ROI margins. To limit radiation doses to organs at risk (OARs), a 5 mm plastic spacer was placed intranasally in nasal cases, under the eyelid for eyelid lesions, or at the gingivolabial sulcus for skin tumors of the lip. This spacer was placed by the treating physician before CT simulation and each day before treatment delivery.

To ensure contact between the skin and applicator, the flap was secured in a thermoplastic mask (Figure 2). The flap was attached to the mask by glue in order to allow accurate reproducibility. CT simulation with the flap in place was obtained, with 1 mm thick slices. The clinical target volume (CTV) consisted of the area marked by the CT contrasting wire. The planning target volume (PTV) included the CTV without additional margin. OARs were contoured when the PTV was in close proximity to these structures, such as the eyes, lacrimal glands, and lips. The Varian BrachyVision treatment planning system was used to create a treatment plan with graphical optimization tools to achieve optimum 3D dose distributions. Iridium-192 was utilized as an HDR source, delivered via the GammaMed remote afterloader. Dosimetric goals were at the discretion of the treating physician for D_{90}, V_{100}, and conformity index (≥ 70% was considered acceptable). 40 Gy in 8 fractions delivered twice per week was prescribed to cover at least 95% of the PTV while meeting OARs constraints, which were created from the biologically effective dose (BED) equivalent of those specified by Emami *et al*. [36]. The dose fractionation scheme was based on our departmental policy, adopted from the original Leipzig protocol [37].

Local response

Local response was assessed via clinical examination by the treating physician during all follow-up visits.

Toxicity

Acute toxicity was monitored on a weekly basis while on treatment via the modified Radiation Therapy Oncology Group (RTOG) morbidity criteria. Late skin toxicity was evaluated in all patients and graded by the European Organization for Research and Treatment of Cancer (EORTC) skin late radiation morbidity scoring every six months following treatment completion. Cosmetic outcomes were graded based on Harris scale scoring system [38].

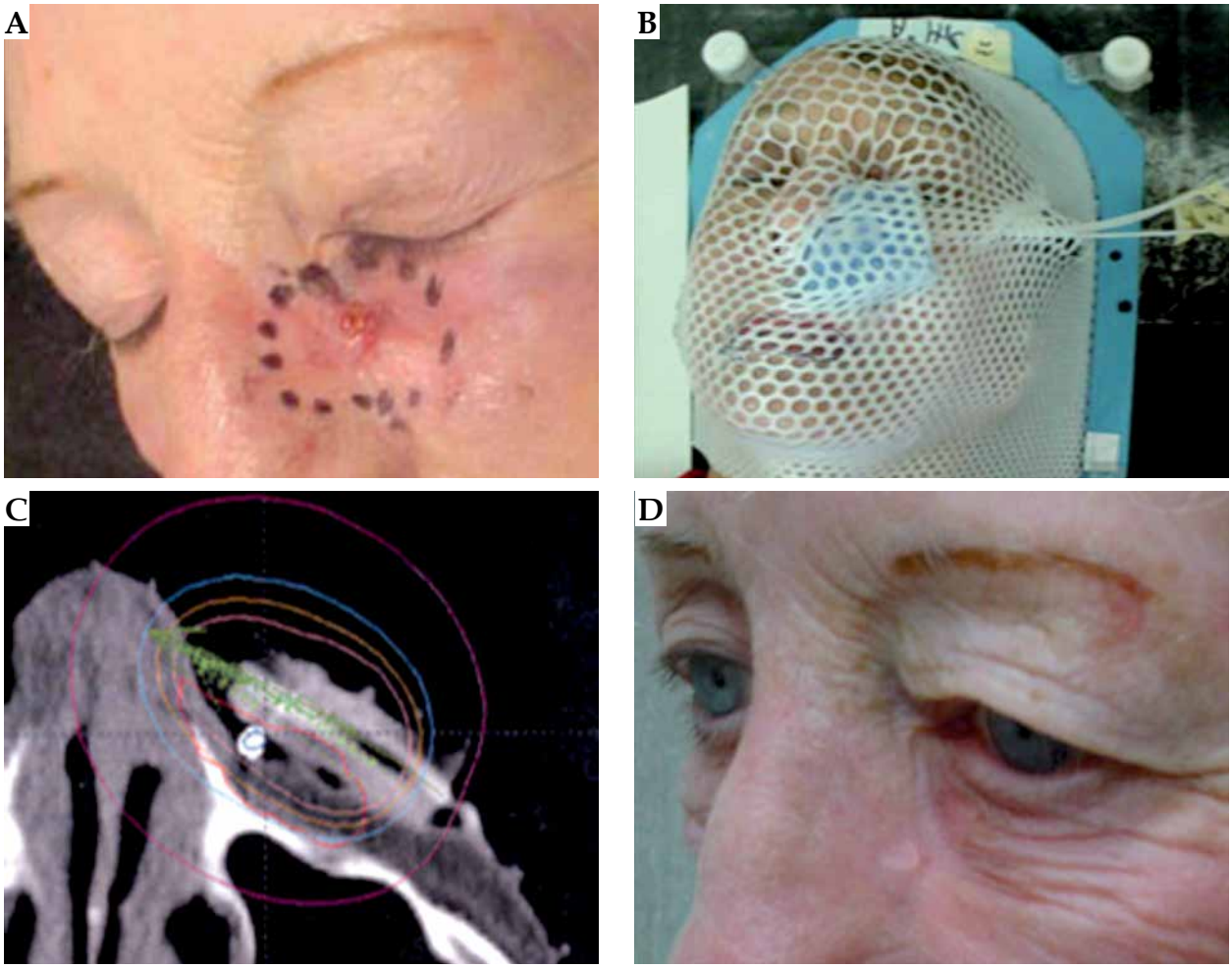

Fig. 2. An example of an 82-year-old female patient, who presented with a lesion of the medial inferior eyelid (**A**). Flap applicator was placed, and thermoplastic mask was created to secure its position (**B**). Simulation CT was obtained (**C**). 40 Gy in 8 twice weekly fractions was delivered using HDR-brachytherapy. During the final week of treatment, she developed grade 1 conjunctivitis, which was treated with a two-day course of antibiotic/steroid eye suspension. On initial follow-up one-month post-treatment, her conjunctivitis had resolved, and the lesion had diminished in size. By follow-up at seven months, her lesion had completely resolved, with minimal hypopigmentation or scarring (**D**)

Statistical considerations

Continuous variables were expressed using sample medians, while categorical variables were expressed as percentages. Kaplan-Meier method was used to estimate local control. SPSS (IBM, Armonk, NY, USA) version 21 was used for all statistical analyses.

Results

Patient characteristics are presented in Table 1. Fifty patients with 53 lesions were included for analysis with a median follow-up of 15 months (range, 6-27 months). Forty-eight (91%) lesions were primary tumors and 5 (9%) were recurrences, which included 3 post-operative recurrences and 2 recurrences after photodynamic therapy. All were considered high-risk based on the NCCN guidelines, where they were classified either as located in "area H" or in "area M", and were ≥ 10 mm [5,6].

All patients completed treatment without interruption to total dose of 40 Gy in 8 fractions given twice weekly (BED of 60 Gy, assuming α/β of 10 Gy). Median PTV volume, D_{90}, and V_{100} were 1.7 cc (95% confidence interval [CI]: 0.9-2.3), 92% (95% CI: 82-99), and 85% (95% CI: 80-92), respectively.

All acute skin toxicities that occurred were observed after the 5th fraction. Thirty-two patients (60%) developed grade 1 toxicity (skin erythema). Nineteen patients (35%) experienced grade 2 toxicity (bright erythema, patchy moist desquamation, or moderate edema). Three patients (5%) suffered from grade 3 toxicity (acute dermatitis with patches and moist desquamation). All eight patients with eyelid or peri-orbital lesions developed ipsilateral grade 1 acute conjunctivitis by the last week of their treatment course, which responded to an antibiotic/steroid combination eye suspension, given for two days after the treatment completion.

Five patients (10%) experienced chronic grade 1 skin toxicity at 6 months post-RT, which included slight atrophy or pigmentation change. Two patients (4%) continued to suffer from chronic grade 1 hypopigmentation and

Table 1. Patient characteristics (n = 50 patients, 53 lesions)

	n (%)
Age (years), median (range)	80 (73-101)
Gender	
Male	23 (46)
Female	27 (54)
Histology	
Basal cell carcinoma	35 (66)
Squamous cell carcinoma	18 (34)
Tumor size (mm), median (range)	18 (5-20)
Tumor thickness (mm), median (range)	5 (3-7)
Location	
Area H	40 (75)
Nose	17 (32)
Temple	8 (15)
Eyelid	6 (11)
Ear	4 (8)
Lip	3 (6)
Peri-orbital	2 (4)
Area M	13 (25)
Scalp	5 (9)
Forehead	4 (8)
Cheek	2 (4)
Neck	2 (4)

two patients (4%) continued to experience grade 2 telangiectasias at 12 months post-RT. There were no chronic grade ≥ 3 toxicities. No patient required hospitalization secondary to treatment-related toxicity.

Estimated local control at one year was 92% using the Kaplan-Meier method. There were four local recurrences at final follow-up, including two nasal SCC lesions, one eyelid BCC lesion, and one lip BCC lesion. Forty-nine lesions (92%) were found to have a good or excellent cosmetic outcome with complete tumor remission.

Discussion

Patients with NMSC in areas, which are cosmetically sensitive, are not ideal candidates for resection, particularly in cases where an extensive surgical defect may result or if a complex reconstruction is required. Preservation of tissue may be more achievable by radiotherapy for these patients, leading to improved cosmetic outcomes without increasing the risk of local failure [39,40]. A large-scale systematic review and pooled analysis found no statistically significant difference between local recurrence rates of SCC of the skin after Mohs micrographic surgery, external beam radiotherapy, and brachytherapy [41].

Thus far, there has only been one randomized controlled trial for patients with BCC of the face comparing surgery versus radiation. Three RT techniques were utilized, including interstitial BT (55% of patients), superficial contact therapy (33% of patients), and conventionally fractionated EBRT (12% of patients). Rate of failure at four years was higher with RT than surgery (7.5% vs. 0.7%). Cosmetic results were also found to be significantly better after surgery than after RT. However, no outcome analysis was conducted comparing treatment sites or RT techniques [42,43].

Despite technological advancements, studies assessing outcomes of NMSC treated with HDR-BT have been sparse. Furthermore, hypofractionation has shown excellent rates of local control, toxicity, and cosmetic results in the treatment of NMSC [44].

We found rates of local control (92%) comparable to those reported in the literature. Other retrospective studies using HDR-BT with surface molds for NMSC reported local control rates between 87% and 100% [45,46,47,48,49,50].

In our study, 49 patients (92%) had good/excellent cosmetic outcomes with complete tumor remission. Three patients (5%) experienced grade 3 acute dermatitis with patches and moist desquamation. Two patients developed mild skin telangiectasia and 2 developed skin hypopigmentation one-year post-radiation. Similar studies using HDR-BT or electronic BT reported equivalent results, with high rates of acceptable cosmetic outcomes in follow-up [31,51,52,53,54,55,56,57].

There are several established differences between BCC and SCC, such as their natural history, patterns of spread, and recurrence rates [58,59,60,61,62,63]. Therefore, management strategies for SCC and BCC vary in terms of imaging and local and systemic therapy [5,6].

One factor to consider when assessing an ideal radiation fractionation is a tumor's α/β ratio, which is a measure of its radiosensitivity, with higher ratios suggesting less susceptibility to the sparing effect of fractionation. While the α/β ratio of NMSC is generally accepted as being higher than that of melanoma, there has been no established consensus on comparison of the α/β ratios of BCC and SCC, with most studies combining the two together [64,65].

This leads to the question of whether radiation fractionation should differ between BCC and SCC. While indications for post-operative radiation and treatment of regional lymphatic stations change depending on histology, the NCCN guidelines list identical doses and fractionation schema for BCC and SCC when treating definitively with radiation [5,6]. This similarity is also reflected in the 2020 American Society for Radiation Oncology (ASTRO) guidelines and the 2019 American Brachytherapy Society (ABS) consensus statement for skin brachytherapy, which do not separate by histology [66,67]. The 2020 ABS consensus statement for skin brachytherapy suggests that there may be differences in radiosensitivity between the two entities and that different equivalent doses may be targeted for each. However, the data supporting this con-

Table 2. Summary of studies on high-dose-rate brachytherapy (custom made/flap) for the treatment of non-melanoma skin cancer

Study [ref] (year)	Modality	No. of patients	No. of lesions	Histology (*n*)	Mean age	Gender	Dose (Gy)	Fractions	BED (Gy)	Frequency	Prescription	Median follow-up (Mo)	Local control (%)	Acute toxicity	Late toxicity	Cosmetic results
Svoboda *et al.* [46] (1995)	Custom-made surface molds	76	106	BCC (76) SCC (11) Other (19)	72	45 M 31 F	12-22 27-30 30-50	1 3 5-15	26.4-70.4	Weekly/ daily/twice daily	Surface of applicator	9.6 (mean)	100	G1: 30.2% G2: 24.5%	Not reported	Not reported
Guix *et al.* [48] (2000)	Standard Brock type and custom-made surface molds	136	136	BCC (102) SCC (34)	67	84 M 52 F	60-80	33-46	70.1-97.7	Daily	5 mm from applicator surface	Min. 12 mo (median not reported)	Actuarial 5 yr. DFS: 98%	G1: 86% G2: 14% G4: 10%	Not reported	Good/ excellent: 98% Unfavorable: 2%
Skowronek *et al.* [51] (2005)	Freiburg flap applicator and custom-made surface molds	179	179	BCC (102) SCC (52) Other (25)	70.8	93 M 86 F	50-60	5-6	100.0-120.0	1 or 2 times a week	5-20 mm from applicator surface	Not reported	Not reported	G1: 70.4% G2: 17.3% G3: 12.3%	G1: 36.9% G2: 11.7% G3: 3.4%	Not reported
Gauden *et al.* [53] (2013)	Leipzig surface applicator	200	236	BCC (121) SCC (115)	76 (median)	136 M 64 F	36	12	46.8	Daily	3-4 mm from applicator surface	66	98	G1: 71% G2: 34%	G1-2: ~10% (exact % not reported)	Excellent: 62% Good: 26% Fair: 6.5% Poor: 5.5%
Arenas *et al.* [56] (2015)	Leipzig surface applicator and custom-made surface molds	114	134	BCC (92) SCC (42)	77.9	83 M 51 F	45-57	15-19	58.5-74.1	3 times a week	3-5 mm from applicator surface	33	5 yr. DFS 93%	G1-2: 57.5% G3: 40.3% G4: 2.2%	G0-1: 95.2% G4: 0.8%	Good/ excellent: 82% Fair: 13% Unavailable: 5%
Olek *et al.* [50] (2018)	Topographic applicator (thermoplastic surface molds)	172	273	BCC (148) SCC (104) Other (21)	79 (median)	Not reported	40 48	8 16	60.0-62.4	2 or 4 times a week	Tumor depth or 3 mm from surface	25	25 mo 95.2%	G1: 33.3% G2: 48.7% G3: 12.1% G4: 5.1%	Erythema: 4.4% Ulceration: 4.0% Telangiectasia: 2.6% Pigment changes: 2.2%	Not reported
Current study	Catheter flap applicator	50	53	BCC (35) SCC (18)	80	21 M 29 F	40	8	60.0	2 times a week	Depth based on CT	15	92	G1: 60% G2: 35% G3: 5%	G1-2: 7.5%	Good/ excellent: 92% Fair: 8%

BED – biologically effective dose (assuming α/β of 10 Gy), Mo – months, BCC – basal cell carcinoma, SCC – squamous cell carcinoma, M – male, F – female, G1 – grade 1, G2 – grade 2, G3 – grade 3, G4 – grade 4, Min – minimum

cept remains limited at this time, and many practitioners do not change their dosing strategy based on histology [68]. There are others who modify their radiation volumes based on histology, such as the GEC-ESTRO recommendations published by Guinot *et al*. in 2018, which used different CTV margins for BCC and SCC [69]. The majority of studies treating NMSC with HDR brachytherapy did not change their prescription dose or margins based on histology [24,46,47,53,62]. It is for this reason that we treated BCC and SCC similarly.

HDR-BT was well tolerated in our cohort, with low rates of severe acute toxicity and no chronic grade ≥ 2 toxicities. There have been some studies suggesting that a large dose per fraction used during HDR-BT have high rates of late toxicity [48,51,54,70]. The data presented herein suggests that 40 Gy delivered in 8 fractions given twice per week can result in acceptable late toxicity, with mild skin telangiectasia and hypopigmentation in only 4 patients (8%). The majority of available literature reports high rates of local control and acceptable acute and chronic toxicity with the use of HDR-BT (Table 2).

A limitation of this study was the short follow-up, with a median of 15 months. It remains to be observed if continued follow-up would reveal higher rates of recurrence and/ or late toxicity. Results from Gauden *et al*., with a median follow-up of 66 months, showed that rates of chronic toxicity stabilized with longer follow-up, suggesting that the majority of toxicity may occur in the first one to two years after treatment [53].

Conclusions

Computed tomography-based flap applicator brachytherapy is a valid treatment option for patients with superficial non-melanoma skin cancer of the face when surgery is not feasible, with high rates of local control and low rates of toxicity. Large-scale prospective randomized controlled trials and longer follow-up are needed to assess the ultimate efficacy and safety of HDR-BT in comparison with other modalities.

Disclosure

The authors report no conflict of interest.

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