

# High-dose-rate skin brachytherapy with interstitial, surface, or a combination of interstitial and surface mold technique

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## Abstract

**Purpose:** In order to demonstrate capabilities of brachytherapy in skin cancer treatment, we reviewed clinical outcomes of patients with non-melanoma skin cancer (NMSC) treated with high-dose-rate brachytherapy (HDR-BT) at a single-institution.

**Material and methods:** A surface custom mold (SC), interstitial (IS), or a combination of IS and SC applicator (IS + SC) was used for treatment based on depth of tumor invasion. Contoured growth tumor volume plus a 0.5 cm margin for basal cell carcinomas (BCC) and a 1-1.5 cm margin for squamous cell carcinomas (SCC) was considered a target. A prescription dose of 41.6 Gy in 8 fractions was delivered to BCC, and 46.8 Gy in 9 fractions to SCC.

**Results:** From 2013 to 2018, a total of 751 NMSC patients (534 BCCs and 217 SCCs) were treated with HDR-BT (518 with IS, 225 with SC, and 8 with IS + SC technique). Thirty patients (4%) partially responded to treatment, and 721 patients (96%) had complete responses. Only 3 patients (0.4%) displayed local recurrences. Grade 1, 2, and 3 acute toxicities were observed in 28.0%, 46.7%, and 1.2% of patients, respectively. Grade 1, 2, and 3 late toxicities were observed in 3.3%, 1.3%, and 0.1% of cases. Cosmetic results were excellent in 79.9%, good in 17.8%, fair in 1.7%, and poor in 0.5% of patients.

**Conclusions:** HDR-BT using SC, IS, or IS + SC is an effective treatment for NMSC with good outcomes and cosmetic results in both BCC and SCC.

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**Key words:** brachytherapy, skin cancer, surface, HDR, interstitial.

## Purpose

Malignant skin tumors can be differentiated into non-melanoma skin cancer (NMSC) and malignant melanoma. NMSC is the most common malignancy with increasing incidence. Two main forms of NMSC are basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), and about 70% are BCC and 30% SCC. Surgery remains a standard of care, but radiation therapy is often used in non-surgical candidates, areas of poor wound healing, and in the head and neck region, if a tumor is very large or is located in an area of the skin that makes it difficult to remove with surgery. Cryotherapy is generally used to treat precancerous skin lesions, but it is rarely used as monotherapy to treat skin cancer. Although cryotherapy is not recommended as a standard treatment of NMSC due to high-rates of recurrences [1], this method is still commonly used in countries, such as Ukraine. BCC is perfectly suitable for high-dose-rate brachytherapy

(HDR-BT) monotherapy since BCCs are typically locally invasive and rarely spread beyond the original tumor site. However, for some cases of SCC in our practice, external beam radiotherapy (EBRT) was required to irradiate regional lymph nodes. In order to provide guidelines for superficial and interstitial (IS) skin brachytherapy treatments for NMSC, there were series of papers published by the American Brachytherapy Society (ABS), including the ABS working group report for aspects of dosimetry and clinical practice [2], a survey of contemporary practice patterns [3], and the ABS consensus statement.

Based on the recommendations, surface custom-made mold (SC) applications were used if the depth of tumor invasion was less than 5 mm. If the depth of tumor invasion was deeper than 5 mm, IS implants were applied to treat NMSC. To increase the dose at the surface of the skin while maintaining acceptable hot spots from IS in the skin, a combination of IS and SC (IS + SC) was used.

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The main purpose of this work was to review the clinical outcomes of patients with NMSC, including those who were treated previously with cryotherapy and had recurrences, with HDR-BT using SC, IS, and IS + SC treated at a single-institution.

## Material and methods

### Patients and data collection

From 2013 to 2018, a total of 751 patients treated for non-melanoma skin cancer with IS and SC HDR-BT at our institution were retrospectively evaluated. Age, sex, tumor type, and localization characteristics were analyzed (Table 1). Both mono-BT and post-cryotherapy BT cases were included in this study. All patients were staged according to the eighth edition of TNM staging classification for skin cancer.

### Implant technique

If the invasion of a tumor was less than 5 mm in depth, SC applicators were used (Fig. 1). If the invasion of a tumor was 5 mm in depth or more, IS implants were used (Figs. 2-6). In order to determine the number of catheters, spacing between them, and number of planes, Paris system [4] was applied for IS-BT implant.

Paris system, one plane implantations should be used if the target thickness (T) is less than or equal to 12 mm. If  $T > 12$  mm, square or triangle catheter implantations would be used. Spacing between catheters was calculated also from T parameter, including  $T/0.5$  for two catheters in one plane,  $T/0.6$  for more than two catheters in one plane,  $T/1.3$  for two planes in triangle placement, and  $T/1.6$  for two planes in square placement. Active length was calculated from lesion length parameter (L) as  $L/0.7$ . Single- and double-plane implants were used to treat 5-12 mm and 12-25 mm thick tumors, respectively. Although some implantations were sub-optimal, planning optimization could be used to meet target coverage goal and OARs constraints. Occasionally, SC implants were used together with IS to increase dose to the skin surface while treating invasion of a tumor of 5 mm deep or more.

### Planning and treatment

Clinical target volume (CTV) was determined by adding visible lesion (gross tumor volume [GTV]) and a 0.5 cm margin for BCCs or 1.0-1.5 cm margin for SCCs. Planning goal was that the prescribed dose covered CTV. For IS-BT planning, CTV was equal to planning target volume (PTV). When SC was used, a 3-4 mm margin was added to CTV to create PTV to consider uncertainty of mold

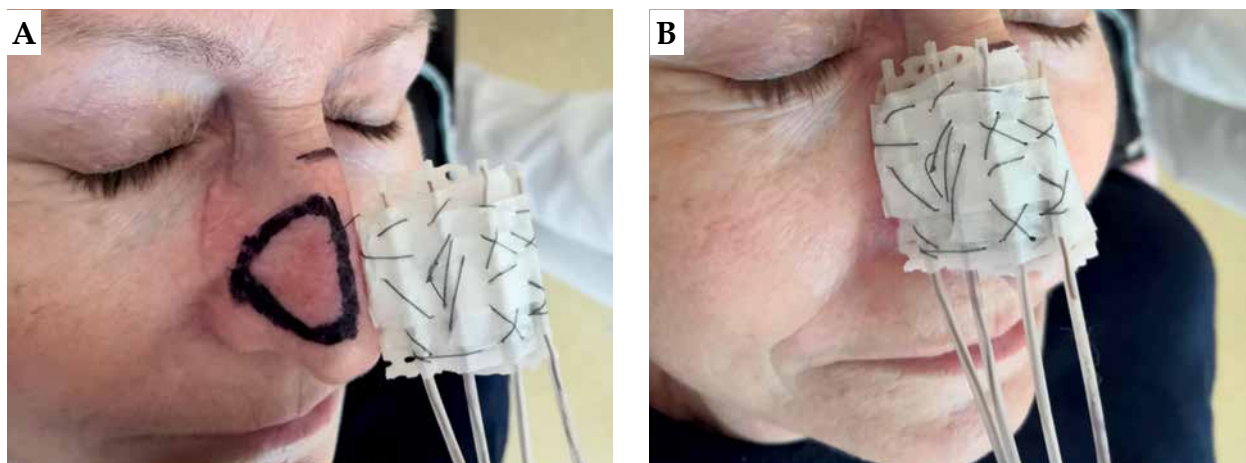


Fig. 1. A 62-year-old patient with basal cell carcinoma (BCC), superficial treatment. A, B) On first day of treatment



Fig. 2. A 78-year-old patient with squamous cell carcinomas (SCC). Local control of primary tumor, but lymph node failure after 1 year. A) Before BT, B) one month after BT, and (C) lymph node failure after 1 year



**Fig. 3.** A 76-year-old patient with squamous cell carcinomas (SCC). **A)** First day of treatment, **B)** one month after BT, and **C)** photograph taken three months after BT



**Fig. 4.** A 80-year-old patient with basal cell carcinoma (BCC), interstitial treatment of two localizations. **A)** First day of treatment, **B, C)** one month after BT, and **D, E)** three months after BT

placement. Organs at risk (OARs), including the lenses and mandibles for the head and neck lesions and bones for the extremities were contoured.

For BCC cases in Table 2, a total dose (TD) of 41.6 Gy in 8 fractions (5.2 Gy per fraction) was delivered. For

SCC cases, 46.8 Gy in 9 fractions (5.2 Gy per fraction) was prescribed. Each fraction was delivered daily. With an  $\alpha/\beta$  ratios of 6-7 Gy for BCC and 10 Gy for SCC [5-7], an equivalent dose of 2 Gy fractions (EQD<sub>2</sub>) was estimated as 58-60 Gy for both groups. Given the same  $\alpha/\beta$  ratios,

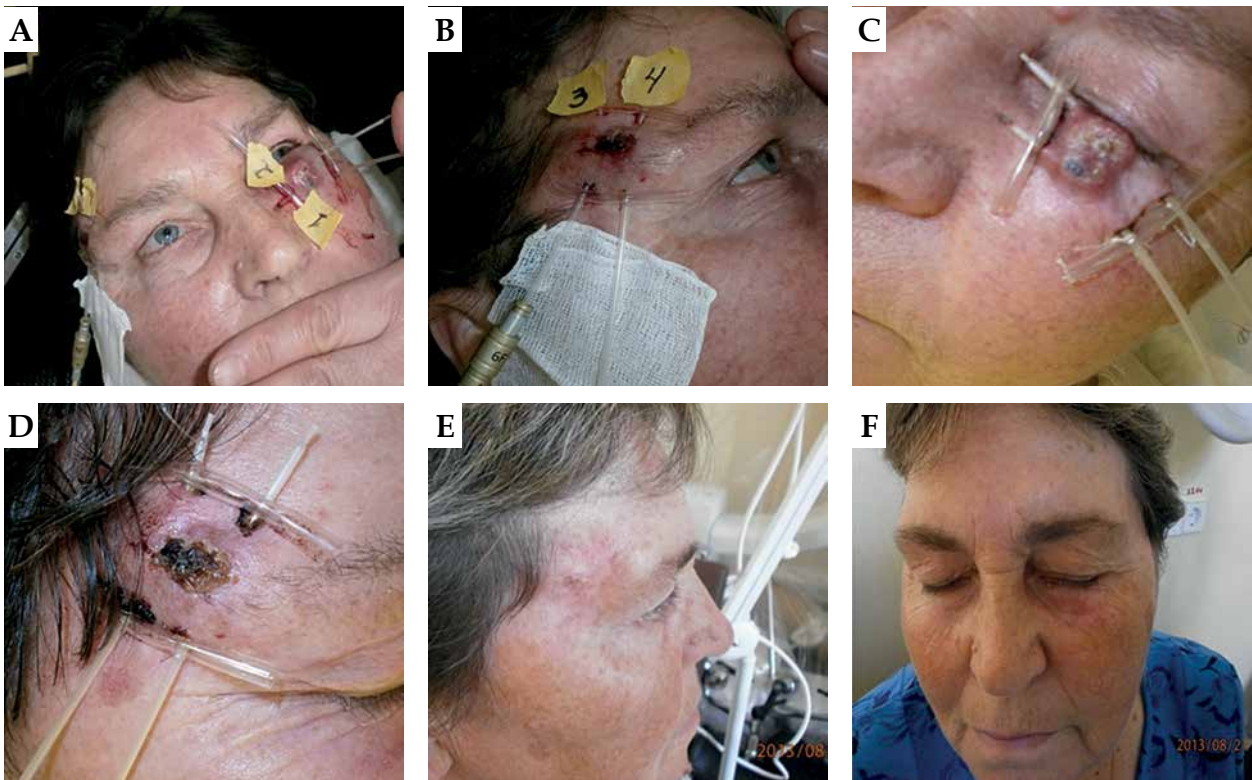


Fig. 5. A 63-year-old patient with BCC, interstitial treatment of two localizations. A, B) First day of treatment, C, D) six's day of treatment, and E, F) three months after BT

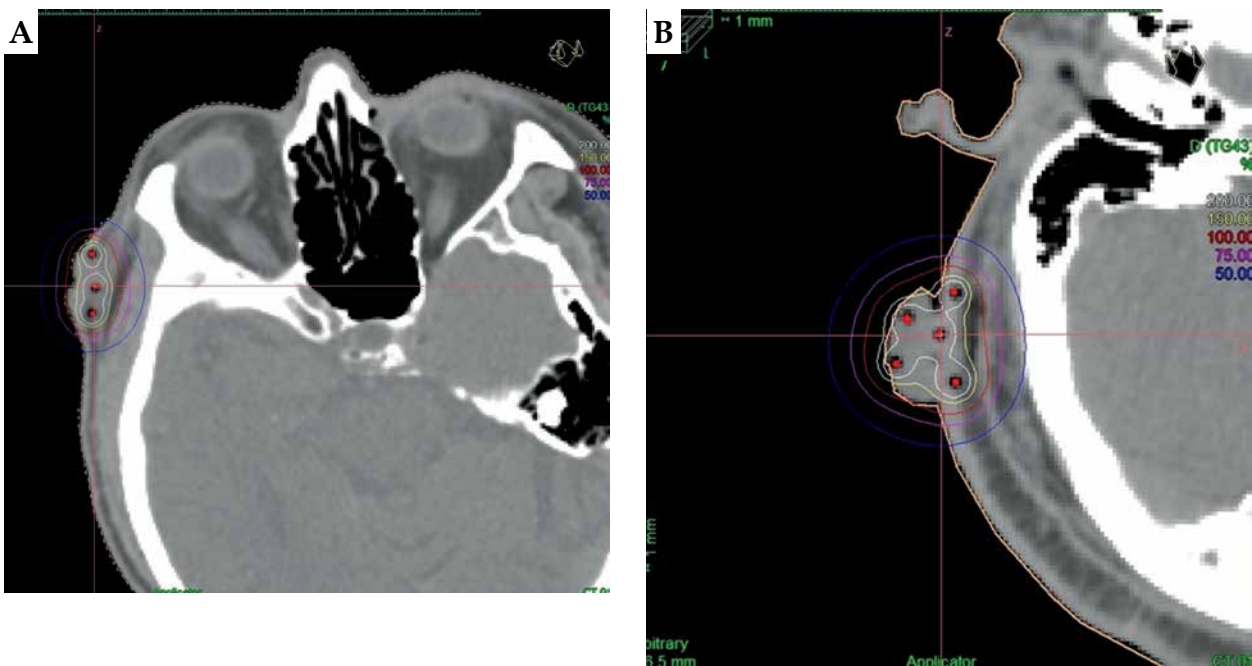


Fig. 6. Clinical examples of interstitial implants and CT-based treatment planning

the biologically effective dose (BED) was 77 Gy for the group diagnosed with BCC, and 71 Gy for the SCC group.

Treatment planning was performed on computed tomography (CT) images. Forward planning with uniform dwell time loading, followed by graphical or manual

optimization was used to adjust isodose distributions (Fig. 6). CTV ratio that received 150% of prescribed dose ( $V_{150}$ ) to  $V_{100}$  was kept below 0.45 ( $V_{150}/V_{100} < 0.45$ ). This constraint could be achieved when the spacing between IS catheters was about 1-1.2 cm.

Radiation dose was delivered with an HDR Elekta afterloader (MicroSelectron v3) using  $^{192}\text{Ir}$  radioactive source.

### Endpoints

Treatment responses (local control, toxicity, and cosmetics results) were evaluated during and early after dose delivery. Treatment responses were determined according to time of tumor resorption and epithelization of skin defects occurring, and patients' status localis (any comments or complaints during routine follow-ups). A partial response was defined in a patient, in whom the tumor was still partially present in the irradiated lesion at 1 and 3 months after treatment. Patients with partial responses had no disease-free period since the tumors were likely to grow and spread.

Local control was evaluated at 5 years after treatment. Usually, follow-up occurred at each month, every three months, and every six months after first year of treatment. Early toxicities were evaluated with skin hyperemia close to irradiated volume, swelling, and patients' complaints. These acute effects were characterized by erythema, edema, rash dermatitis, pruritus, desquamation, and in rare cases, ulceration. These acute effects were graded as G0 for no change over baseline; G1 for follicular, faint or dull erythema, epilation, dry desquamation, or decreased sweating; G2 for tender or bright erythema, patch moist desquamation, or moderate edema; G3 for confluent, moist desquamation other than skin folds, or pitting edema; and G4 for ulceration, hemorrhage, or necrosis [8].

Late side effects appear with atrophy, pigmentation change, hair loss, telangiectasia fibrosis, and in rare cases, ulceration at six months after HDR-BT [9]. Late toxicities were graded as follows: G0 - none, G1 - slight atrophy, pigmentation change, or some hair loss, induration, G2 - patch atrophy, moderate, telangiectasia, total air loss, or induration, G3 - market atrophy, gross telangiectasia, fibrosis, G4 - ulceration or necrosis [8].

Cosmetic results were also evaluated by physicians according to RTOG grading system [8]. Slight changes in pigmentation or slight indurations were regarded as excellent, and moderate telangiectasia and fibrosis were considered good. Atrophy, gross telangiectasia, and severe induration were deemed fair, and ulceration or necrosis were considered poor cosmetic results.

## Results

### Patients and tumor characteristics

Between 2013 and 2018, a total of 751 non-melanoma skin cancer patients were treated with HDR-BT (Table 1). One hundred and forty-five patients (19.3%) were previously treated with cryotherapy for the same lesions. Six hundred and six patients (80.7%) were treated with exclusive BT. The median age of the patients was 71 years (range, 43-90 years). Sixty percent of the patients were males, and forty percent were females. Between the two main non-melanoma forms, BCC accounted for nearly 71%, and SCCs were about 29%. By using TNM staging classification for skin cancer, there were 298 stage I

**Table 1.** Total of 751 non-melanoma skin cancer (NMSC) cases treated from 2013 to 2018

Patients	Number	Percentage (%)		
Age (years)				
Median	71			
Max	90			
Min	43			
Sex				
Male	450	60.0		
Female	301	40.0		
Histology				
Basal cell carcinoma	534	71.1		
Squamous cell carcinoma	217	28.9		
Staging				
	All	BCC	SCC	
I (less than 2 cm)	298	211	87	39.7
II (2 to 4 cm)	437	311	126	58.2
III (more than 4 cm)	12	9	3	1.6
IV (gross cortical invasion)	4	1	4	0.5
Lesion location				
Neck	45			6.0
Scalp	195			26.0
Face	280			37.3
Nose	120			16.0
Ear	36			4.8
Trunk	45			6.0
Extremity	30			4.0
BT indication				
Recurrence after cryotherapy	145			19.3
Exclusive	606			80.7

(39.7%), 434 stage II (58.2%), 12 stage III (1.6%), and 4 stage IV (0.5%) skin cancers. In this study, 90% (676 cases) of skin tumors were located in the head and neck region (6% neck, 26% scalp, 37% face, 16% nose, and 5% ear), where high conformity is extremely important. Ten percent of tumors were located on the trunk and other extremities. Out of total number of 751 patients, 225 patients (30%) were treated with SC technique, 518 patients (69%) with IS implantation, and 8 patients (1%) with IS + SC.

### Clinical outcomes

After a median follow-up of 36 months (range, 12 months to 5 years), seven hundred and twenty-one patients (96%) treated with HDR-BT had complete responses to the treatment, including 513 patients in the BCC group and 205 patients in the SCC group. Also, 30 patients (4%) partially responded to the treatment, with

**Table 2.** Treatment response, acute and late toxicities, and cosmetic results of the patients

	Number (%)	BCC group (41.6 Gy in 8 fractions) n (%)	SCC group (46.8 Gy in 9 fractions) n (%)
	751 patients	531 patients	220 patients
Response to treatment			
Complete	721 (96.0)	513 (96.6)	205 (93.2)
Partial	30 (4.0)	18 (3.4)	15 (6.8)
Recurrence	3 (0.4)	3 (0.6)	0 (0.0)
Acute toxicity			
Grade 1	210 (28.0)	116 (21.8)	94 (42.7)
Grade 2	351 (46.7)	282 (53.1)	69 (31.4)
Grade 3	9 (1.2)	5 (0.9)	4 (1.8)
Late toxicities			
Grade 1	25 (3.3)	5 (0.9)	20 (9.1)
Grade 2	10 (1.3)	5 (0.9)	5 (2.3)
Grade 3	1 (0.1)	0 (0.0)	1 (0.5)
Cosmetic results			
Excellent	600 (79.9)	434 (81.7)	166 (75.5)
Good	134 (17.8)	89 (16.7)	45 (20.5)
Fair	13 (1.7)	8 (1.5)	5 (2.3)
Poor	4 (0.5)	0 (0.0)	4 (1.8)

18 from the BCC group and 15 from the SCC group. Only 3 patients (0.4%) had local recurrences of the disease. All 3 local recurrences occurred in the BCC group. Overall, the local control rate was 95.6%. One patient from the SCC group shown in Figure 2, despite displaying good results from local treatment, was diagnosed with lymph node relapse one year later. The presence of regional lymph node metastasis was found in 3 patients from the SCC group. No patient had regional lymph node metastasis in the BCC group. The loco-regional control rates were 98.2% in the SCC group and 99.5% overall.

### Toxicities

A total of 181 patients (128 patients in the BCC group and 53 patients in the SCC group) had grade 0 acute toxicity. The percentages of grade 0 toxicity in both the groups were nearly equal (24.1% in the BCC group and 24.1% in the SCC group).

A total of 570 patients (75.6%), 403 patients in the BCC group and 167 patients in the SCC group, had acute toxicity evaluated during 1- and 3-month routine check after the treatment (Table 2). According to toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC) [8], 210 patients (28.0%) had grade 1, 351 patients (46.7%) had grade 2, and 9 patients (1.2%) had grade 3 early reaction to the radiation.

While the percentage of patients with grade 1 acute toxicity was higher in the SCC group treated with a higher prescription dose (42.7% in the SCC group vs. 21.8% in the BCC group), a larger number of patients ( $n = 282$ ,

53.1%) had grade 2 early reactions in the BCC group, in which although a relatively lower dose was delivered, lesion volumes were larger in general.

Late toxicities were observed (Table 2) in 36 patients (10 cases in the BCC group and 26 cases in the SCC group). Grade 1 toxicity developed in 3.3% of patients, grade 2 toxicity occurred in 1.3% of patients, and grade 3 toxicity were observed in 0.1% of patients. All of these were detected at 6-month post-treatment or later.

### Cosmetic results

Excellent cosmetic results were achieved in 79.9% of cases (600 patients: 434 in the BCC group and 166 in the SCC group; Table 2). Good cosmetic results were observed in 17.8% (134 patients: 89 and 45 from the BCC and the SCC groups, respectively), fair in 1.7% (13 patients: 8 and 5 from the BCC group and the SCC group, respectively), and poor in 0.5% of cases (4 patients from the SCC group).

### Discussion

In this study, we described outcomes and toxicities of HDR interstitial and superficial treatments of 751 patients treated between 2013 and 2018. Several comparable results previously published are summarized in Table 3 [10-18]. Very good local control (LC) of 100% was reported by Svoboda *et al.* [10] (1995), 97.8% by Tormo *et al.* [11], 98% by Guix *et al.* [12] (2000), and 97.9% (87.2% after 5 years) by Pellizzon *et al.* [13] (2020). Median follow-up was 5 months and more of the first two groups, and

**Table 3.** Summary of studies for skin cancer treatment with high-dose-rate brachytherapy (HDR-BT)

Study (year) [Ref.]	Prescription	No. of patients/lesions	Prescription depth	Follow-up (median)	Local control	Recurrence rate	Acute toxicity	Late toxicity	Cosmetic results
Svoboda <i>et al.</i> (1995) [10]	18-22 Gy one fraction, 9-10 Gy per fraction, TD = 27-30 Gy (weekly), 4 Gy per fraction, TD = 40 Gy	76/106	Surface	5 and more months	100.0%	No recurrence	G1-G2 (25.4%)	G1-G2 (5.7%)	Excellent (50.0%) Good (44.4%) Poor (5.6%)
Kohler-Brock <i>et al.</i> (1999) [18]	5-10 Gy per fraction, TD = 30-40 Gy (one or two times per week)	520/520	6-8 mm	10 years	92.0%	8.0%	G1-G2	G1-G2	Excellent
Guix <i>et al.</i> (2000) [12]	1.8 Gy per fraction, TD = 60-65 Gy. Boost 10-15 Gy after 3 weeks	136/136	5 mm	5 years	98.0%	2.0%	G1-G2 (57.6%) G4 (10.0%)	G1-G2 (0.84%)	Excellent (98.0%) Good (2.0%)
Pelizzon <i>et al.</i> (2020) [13]	Most 4 Gy per fraction, TD = 40 Gy (daily)	71/101	3-5 mm	3 years 5 years	97.9% 87.2%	2.1% 12.8%	G1-G2 G3 (8.9%)	G3 (3.9%)	Excellent
Skowronek <i>et al.</i> (2005) [17]	3 Gy per fraction, TD = 48-51 Gy (BID)	179/179	5 mm	12 months	91.1%	8.9%	G1-G2 (87.7%) G3 (12.3%)	G1-G2 (54.0%) G3 (3.4%)	Excellent or good
Tormo <i>et al.</i> (2014) [11]	6-7 Gy per fraction, TD = 42 Gy (twice a week)	33/45	4 mm	47 months	97.8%	2.2%	G1	G1	Excellent
Arenas <i>et al.</i> (2015) [14]	3 Gy per fraction, TD = 54 Gy (3 times per week)	134/134	5 mm	33 months	95.12%	4.88%	G1-G2 (57.5%) G3 (40.3%) G4 (2.2%)	G1-G2 (3.1%) G3 (2.2%) G4 (0.8%)	Excellent/good (82.0%) Fair (13.0%) Not available (5.0%)
Delishaj <i>et al.</i> (2015) [15]	5 Gy per fraction, TD = 40-50 Gy (2-3 times per week)	39/57	4 mm	12 months	96.25%	No recurrence (2 lesions persisted)	G1-G2 (63.2%)	G1-G2 (19.3%)	Excellent (86.0%) Good (11.7%) Fair (2.3%)
Olek <i>et al.</i> (2018) [16]	5 Gy per fraction, TD = 40 Gy (twice per week), 3 Gy per fraction, TD = 48 Gy (daily)	172/273	3 mm	25 months	95.2%	4.8%	G0 (0.4%) G1 (33.3%) G2 (48.7%) G3 (12.1%) G4 (5.1%)	G1 (2.2%) G2 (2.6%) G4 (4.4%)	
Present study (2022)	5.2 Gy per fraction, TD = 41.6 Gy for BCC, TD = 46.8 Gy for SCC (daily)	751/751 (534 BCCs, 217 SCCs)	3-5 mm (SC), 5-25 mm (IS, IS + SC)	36 months (12 months - 5 years)	95.6%	4.4%	G1 (28.0%) G2 (46.7%) G3 (1.2%)	G1 (3.3%) G2 (1.3%) G3 (0.1%)	Excellent (79.9%) Good (17.8%) Fair (1.7%) Poor (0.5%)

5 years of the second two groups. Equivalent dose in most of the studies was in a range of 60-75 Gy (EQD<sub>2</sub>), similar to our prescriptions. Although fractionation regimes varied quite rapidly from 1.8 Gy per fraction in Guix *et al.* [12] to 7 Gy per fraction in Tormo *et al.* [11], EQD<sub>2</sub> prescriptions were very similar to our prescribed dose of 5.2 Gy per fraction. More aggressive fractionation, such as 9-10 Gy or 18-22 Gy in one fraction were reported by Svoboda *et al.* [10], but rarely used. At the same time, Guix *et al.* [12] and Svoboda *et al.* [10] reported excellent cosmetic results of 98% and 50%, respectively. These results were evaluated after 5 months and 5 years after last fraction of treatment, respectively.

Standard fractionation approach (1.8 Gy per fraction) reported by Guix *et al.* [12] was very beneficial from radiobiological point of view, but it was not suitable for IS technique because of a long treatment period. Also, 6-7 Gy per fraction shown by Tormo *et al.* [11] or higher dose (range, 9-22 Gy) per fraction reported by Svoboda *et al.* [10], shortened the time of treatments, but may cause more severe skin reactions or some poor cosmetic results from irradiation.

In this study, NMSC patients were treated with a 60 Gy prescription. The prescriptions reported in the published studies were about 55-65 Gy EQD<sub>2</sub> using  $\alpha/\beta = 6$  Gy for LQ model. Pellizzon *et al.* [13] and Svoboda *et al.* [10] treated with lower prescription dose (50 Gy EQD<sub>2</sub> with 40 Gy in 10 fractions). From a 5-year median follow-up by Pellizzon *et al.* [13], recurrent rate of 12.8% was much higher than in other groups (range, 2-9%). With the same prescription, Svoboda *et al.* [10] reported no recurrence; however, only 27 patients (30%) were treated with this prescription rate.

All groups in Table 3 reported that G1-G2 acute toxicities were usually resolved after 6 months. The same results were observed in our patients.

Although SC and IS techniques are quite different in dose normalization and hot-spot locations, our study and those published previously showed that the results are comparable for all NMSC BT.

In general, several main factors may influence local control. The factors consisted of total dose prescription, doses for fractions, previous treatment (such as EBRT or cryotherapy), tumor dimension, depth of the lesion, and histological type. It is important to perform further detail studies to establish clinical evaluations since these factors can lead to different clinical responses.

## Conclusions

Brachytherapy can deliver the most conformal radiation dose to superficial or deep-seated NMSC. HDR-BT using SC, IS, or IS + SC is an effective treatment for NMSC with good clinical outcomes and cosmetic results in both BCCs and SCCs.

## Disclosure

The authors report no conflict of interest.

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