Review article

Non-melanoma skin cancer treated with high-dose-rate brachytherapy: a review of literature

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Abstract

Purpose: The incidence of non-melanoma skin cancer (NMSC) has been increasing over the past 30 years. There are different treatment options and surgical excision is the most frequent treatment due to its low rates of recurrence. Radiotherapy is an effective alternative of surgery, and brachytherapy (BT) might be a better therapeutic option due to high radiation dose concentration to the tumor with rapid dose fall-off resulting in normal tissues sparing. The aim of this review was to evaluate the local control, toxicity, and cosmetic outcomes in NMSC treated with high-dose-rate BT (HDR-BT).

Material and methods: In May 2016, a systematic search of bibliographic database of PubMed, Web of Science, Scopus, and Cochrane Library with a combination of key words of "skin cancer", "high dose rate brachytherapy", "squamous cell carcinoma", "basal cell carcinoma", and "non melanoma skin cancer" was performed. In this systematic review, we included randomized trials, non-randomized trials, prospective and retrospective studies in patients affected by NMSC treated with HDR-BT.

Results: Our searches generated a total of 85 results, and through a process of screening, 10 publications were selected for the review. Brachytherapy was well tolerated with acceptable toxicity and high local control rates (median: 97%). Cosmetic outcome was reported in seven study and consisted in an excellent and good cosmetic results in 94.8% of cases.

Conclusions: Based on the review data, we can conclude that the treatment of NMSC with HDR-BT is effective with excellent and good cosmetics results, even in elderly patients. The hypofractionated course appears effective with very good local disease control. More data with large-scale randomized controlled trials are needed to assess the efficacy and safety of brachytherapy.

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Key words: HDR brachytherapy, radiotherapy, skin cancer, skin brachytherapy.

Purpose

The incidence of skin cancer has been increasing over the past 30 years and currently 2-3 million new cases are diagnosed worldwide every year. Non-melanoma skin cancer (NMSC) is the most common skin malignancy (95%) and in recent years its incidence has been increasing rapidly, even in young populations [1,2]. The development of NMSC is due to a combination of environmental, genetic, and phenotypic factors [3,4]. Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) are the two most common subtypes: about 75-80% of all NMSC are characterized by the presence of BCC, 15-20% of these malignancies present SCCs, while 1% show a mixed phenotype [5]. There are different treatment options for NMSC such as surgery, cryotherapy, laser therapy (recommended only for shallow and early SCC), topical chemotherapy, photodynamic therapy, and radiotherapy (RT). Surgical excision is the most frequent treatment due to its low rates of recurrence, reported less than 5% [6,7,8,9,10]. In addition, RT is often used to treat NMSC and, specifically, different techniques can be used such as superficial X-rays, electron beams, megavoltage photons, and low-dose-rate (LDR) or high-dose-rate (HDR) brachytherapy (BT). Usually, the treatment options are chosen based on the institutional resources and the specialist's experiences.

Electronic brachytherapy (EBT) is a new technique of radiotherapy, which delivers low-energy radiation

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at a high-dose-rate through an applicator placed on the skin. Due to introduction of new devices that are compatible for use with the equipment of EBT (such as Xoft® Axxent®, Zeiss® INTRABEAM® and Elekta® Esteya®) and the commercialization of electronic BT, has attracted considerable interest in the BT treatment of small skin tumors in last years.

Compared to the other radiotherapy technique, HDR-BT might be a better therapeutic option due to essential advantages such as high radiation dose concentration into the clinical target volumes (CTV), rapid dose fall-off at target periphery, optimal sparing of normal tissues in sensitive structures, shorter treatment time, and the use of hypofractionated course [11,12,13,14,15,16,17].

High-dose-rate BT is often delivered in the form of a surface mold but can also be delivered through use of a custom mold, Leipzig applicator, Valencia applicator, or a variety of other techniques. Moreover, HDR brachytherapy technique allows to treat with curative doses some localizations (such as cancer on face skin, near eyes and nose) with excellent and good cosmetic outcomes [18,19,20,21,22,23,24,25,26].

The role of HDR brachytherapy using ^{192}Ir source and surface applicators

The development in the late 1960s of the HDR brachytherapy afterloader, a robotic controller for automated insertion and removal of the radioactive source through catheters placed in or near the tumor, greatly improved radiation protection and simplified the delivery of the source. Most of NMSC brachytherapy today is delivered with HDR brachytherapy afterloaders using ^{192}Ir. While there is little level I evidence for traditional radiotherapy in the management of NMSC, there is no level I evidence for HDR brachytherapy. However, several retrospective and prospective studies with excellent results and adequate follow-up have been reported [19,20,21,22,23,24,25,26].

At first, Svoboda *et al*. [18] in 1995 published a data of 106 lesions (76 patients) treated with high-dose-rate microselectron afterloader using expanded silicone rubber molds and ^{192}Ir source.

In the study, were used different hypofractionated regimens (12-22 Gy given in a single fractions, 27-30 Gy/3 fractions, 30 Gy/5 fractions, 40 Gy/10 fractions, 46 Gy/10 fractions, and 50 Gy given in 15 fractions), and no recurrences were observed after a median follow-up of 9.6 months. Only G1-G2 acute and late toxicity was observed, and 94.4% of lesions had an excellent and good cosmetic outcome.

In 1999, Köhler-Brock *et al*. [19] described the outcome of 520 lesions treated with HDR-BT using Leipzig applicators. The dose prescribed was 30-40 Gy in 5-10 fractions with a local control of 92% after 10 years' of follow-up. One year later, Guix *et al*. [20] described a standardized surface mold technique prospectively utilizing HDR brachytherapy in 236 NMSC lesions, and achieved 5-year local control of 98% with excellent treatment tolerance and no severe early or late complications. Similar results were reported by other authors [19,20,21,22,23,24,25,26,27,28,29,30] in their retrospective studies. Despite the potential interest in BT for the treatment of non-melanoma skin cancer, there are not a lot of randomized controlled trials, systematic reviews, and/or metanalyses in literature.

The aim of this review was to systematically evaluate the available literature data regarding the local control, toxicity, and cosmetic outcomes in patients affected by non-melanoma skin cancer and treated with HDR-BT.

Material and methods

Search strategy

In May 2016, we conducted a comprehensive literature search of the following electronic databases: PubMed, Web of Science, Scopus, and Cochrane library. The databases were searched with a combination of key words for non-melanoma-skin cancer treated with HDR-BT; "skin cancer", "high dose rate brachytherapy", "squamous cell carcinoma", "basal cell carcinoma", and "non melanoma skin cancer ".

Study selection

In this systematic review, we included randomized trials, non-randomized trials, prospective studies, retrospective studies, and case series in patients affected by NMSC treated with HDR-BT. Single case reports and small case series with less than 20 cases were excluded. Moreover, we excluded studies reporting on patients with diagnoses different from NMSC skin cancer and studies reporting only palliative intent of skin cancer. In case of duplicated datasets (e.g. multiple articles from the same study group or institution, related to the same treatment on the same cohort of patient), we included only the work with the longest follow-up and the greatest number of patients.

Data extraction and analysis

Data extraction was performed by one reviewer and checked by a second reviewer. Two reviewers independently studied the abstracts and full text of all retrieved papers to select suitable articles for the assessment; disagreement about study to be included in this review were resolved by discussion between two reviewers who selected independently the publications for the evaluation.

We obtained the following information from each report: author identification, year of publication, medical center, study design characteristics, study population, number of patients, age, sex, histological diagnoses, BT technique, total dose, dose for fraction, delivered dose, local control, toxicity, functional cosmetic outcome, and follow-up time. Finally, in order to compare clinical outcome of different modalities of fractionated regimens used (total dose and dose for fraction), the biological effective dose (BED) was calculated.

Regarding late and acute toxicities or cosmetic events, all studies selected for this review used CTCAE v4.0 (Common Terminology Criteria for Adverse Events) toxicity scales [27], or Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organi-

zation for Research and Treatment of Cancer (EORTC) scales [31].

Statistical analysis

Before data performing, an exploration phase of the data was carried out; the categorical data were described by frequency and percentage, whereas continuous data by mean, median, and range. If necessary, after data exploration, analysis and calculation of frequencies, median, and range was performed due to description of endpoints of the review.

All analyses were performed using the SPSS 22 technology.

Results

Our searches generated a total of 85 results, and through a process of screening, 10 publications were selected for the review. Of 65 studies excluded for this review, 22 were excluded due to duplicate data, 30 were excluded because they were not clinical trials but consisted in review (24), letter to editor (1) or book chapter (5). Finally, 23 studies were excluded because they did not fulfil the inclusion criteria: different treatment technique (such as use of low dose rate BT, interstitial BCT, EBRT with LINAC), little number of patients, palliative treatment, and diagnoses of melanoma skin cancer in majority of patients. Therefore, 10 studies fulfilled the inclusion criteria and were included in our review. The flowchart of systematic literature search process is shown in Figure 1.

Overall, in 10 studies analyzed in this review, 1977 lesions (1870 patients) were treated; of them, the majority of lesions 65% consisted in BCC, 32.5% were SCC, and the reaming 2.5% consisted in mixed phenotype such as Kaposi's sarcoma, lymphomas, melanomas, and Bowen's disease. The median age of patients treated was 72 years old, and 61% (1141) of patients were male and 39% (729) were female. The characteristics of these studies included in the review are summarized in Table 1 and Table 2.

Doses and fractionation

Comparing with external beam radiation, HDR-BT has an advantage regarding deep and superficial doses. In fact, during HDR-BT, the dose remains on the surface and does not penetrate deeply with optimal sparing of normal tissues due to dose concentration into the clinical target volumes (CTV) and rapid dose fall-off at target periphery [10,11,12,13,14,15,16,17]. Published studies have mainly reported standard fractionation and hypofractionated brachytherapy regimens in patients treated with HDR-BT, and the biological effective dose (BED) was often calculated due to define the total dose and dose for fractions regimen for a better local control and acceptable late and acute toxicity [19,20,21,22,23,24,25,26,33,34,35,36,37].

Biological effective dose is an inherent part of the linear quadratic (LQ) model of radiation effects and estimates the true biological dose delivered by a particular combination of dose per fraction and total dose to a given tissue characterized by a specific a/b ratio. It is calculated by the equation BED = nd [1 + d(α/β)] where n – the number of fractions, d – the dose/fraction, and α/β – radio-sensitivity coefficients at the dose at which the linear and quadratic components (for early or late cell damage, respectively) of cells killed are equal [38,39]. The a/b ratios vary based on the tumor type. For example, squamous cell cancers with high cell proliferation are characterized by 10-30 α/β ratio, while breast cancer shows lower values (4-5 Gy) as well in prostate cancer (0.8-2.5 Gy) and melanoma malignancies [39,40]. For NMSC, the alpha/beta ratios are approximately 10 Gy [39]; for SCC lesions, the α/β value is lower and it is reported at a value of 8.5 in different data in literature [41]. From the previous equation, it is evident that the BED will increase proportionally to the dose per fraction and inversely proportional to the α/β ratio. If the total dose is kept constant, the BED will increase if the dose per fraction is increased. For these reasons, it is important to perform BED calculations before clinical decisions since different histological classes of cancers have different a/b ratios, leading to different clinical responses, despite not changing the total dose.

Conventional fractionated regimes were reported by Guix *et al*. [20] data of 136 patients affected by NMSC and received a total dose of 60-65 Gy in 33 to 36 fractions. In this study, the mean age of patients was 67 years old (range, 23-91), 5 years local control for all patients was 98%.

Hypofractionated HDR brachytherapy regimens, which reduce the number of treatment fractions, compared with the conventional regimen that involves around 30 and 35 fractions, have been shown to achieve very good local control without increased side effects or

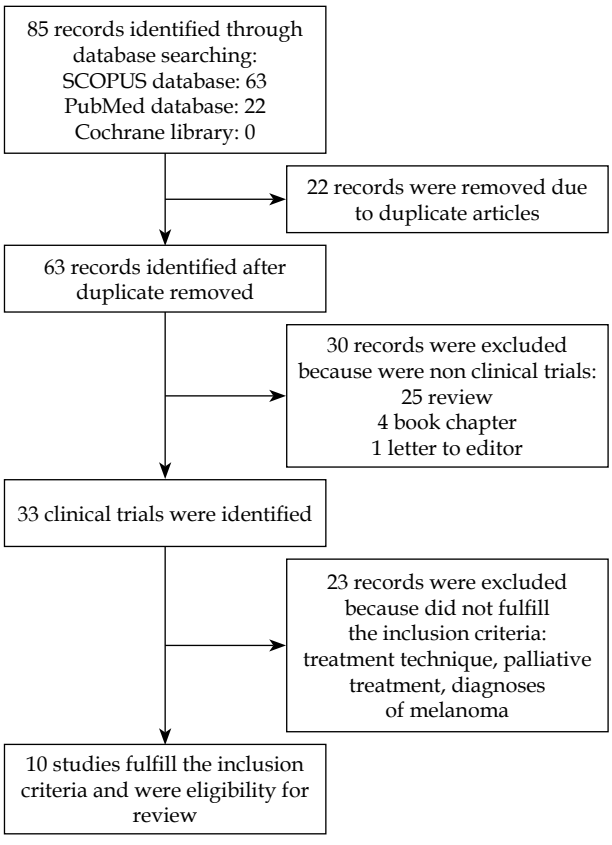

Fig. 1. Flow chart of systematic literature search process

Table 1. Summary of studies where high-dose-rate brachytherapy was used for the treatment of non-melanoma skin cancer – part I

Study (year)	Modality	Source	No of lesions	Lesion type (No)	No of patients	Mean age	Gender	Dose (Gy)	Fractions	Bed	Frequency
Svoboda *et al.* [18] (1995)	HDR-BT using custom-made surface molds	^{192}I	106	BCC (76) SCC (11) Lymphomas (2) Bowen's disease (9) Other (8)	76	72	45 M 31 F	12-22 27-50	1 3-15	51.3-66.7	Weekly/ daily/twice day
Köhler-Brock *et al.* [19] (1999)	HDR-BT using Leipzig applicator	^{192}I	520	BCC SCC Kaposi's sarcoma Lymphomas Melanomas	520	–	–	30-40	5-10	48-56	1-2 times a week
Guix *et al.* [20] (2000)	HDR-BT using custom-made surface molds	^{192}I	136	BCC (102) SCC (34)	136	67	84 M 52 F	60-65	33-36	72-76.7	Daily
Skowronek *et al.* [21] (2005)	HDR-BT using Freiburg flap applicator and custom-made surface molds	^{192}I	179	BCC (52) SCC (102) Other (25)	179	70.8	93 M 86 F	50-60	5-6	75-120	1-2 times a week
Ghaly *et al.* [22] (2008)	HDR-BT using Leipzig applicator	^{192}I	67	BCC (36) SCC (29) Keloids (2)	56	69	26 M 30 F	40	8	60	Twice a week
Kanikowski *et al.* [24] (2008)	HDR-BT using surface applicators or custom-made surface molds	^{192}I	497	BCC (233) SCC (118)	497	72	257 M 240 F	50-60 30-40	10 8	60-96	–
Gauden *et al.* [23] (2013)	HDR-BT using Leipzig applicator	^{192}I	236	BCC (121) SCC (115)	200	76	136 M 64 F	36	12	46	Daily
Tormo *et al.* [25] (2014)	HDR-BT using Valencia applicator	^{192}I	45	BCC (45)	33	78	18 M 15 F	42	6-7	70	Twice a week
Delishaj *et al.* [26] (2015)	HDR-BT using Valencia applicator	^{192}I	57	BCC (44) SCC (12) Kaposi's sarcoma (1)	39	84	24 M 15 F	40-50	8-10	60-75	2-3 times a week
Arenas *et al.* [42] (2015)	HDR plesiotherapy using a fixed applicator or a customized mold	^{192}I	134	BCC (92) SCC (42)	134	77.9	83 M 51 F	45-57	15-19	58.5-74.1	3 times a week

HDR-BT – high-dose-rate brachytherapy, BCC – basal cell carcinoma, SCC – squamous cell carcinoma, M – male, F – female, ^{192}I – Iridium 192

Table 2. Summary of studies where high-dose-rate brachytherapy was used for the treatment of non-melanoma skin cancer – part II

Study (year)	Prescription	Follow-up (median)	Local control (%)	Recurrence rate	Acute toxicity	Late toxicity	Cosmetic results
Svoboda *et al*. [18] (1995)	–	9.2 months	100	No recurrence	G1-G2 (25.4%)	G1-G2 (5.7%)	Excellent 50% Good 44.4% Poor 5.6%
Köhler-Brock *et al*. [19] (1999)	6-8 mm	10 years	92	8%	G1-G2	G1-G2	–
Guix *et al*. [20] (2000)	5 mm	5 years	98	2%	G1-2 (57.6%)	G1-G2 (0.84%)	Excellent 98% Good 2%
Skowronek *et al*. [21] (2005)	5 mm	12 months	91.1	8.9%	G1-G2 (87.7%) G3 (12.3%)	G1-G2 (54%) G3 (3.4%)	–
Ghaly *et al*. [22] (2008)	Leipzig appropriate depth	18 months	100	No recurrence (3 lesions persisted)	G1-G2 (82%)	G1-G2	Excellent
Kanikowski [24] (2008)	Depth based on CT or 3 mm	12 months	83.3	16.7%	G1-G2 (91.1%) G3 (8.9%)	G2 (17.1%) G3 (4.9%)	Not observed
Gauden *et al*. [23] (2013)	Leipzig appropriate depth	66 months	98	2%	G1-G2 (80%)	G1-G2 (20%)	Poor 5.5% Fair 6.5% Good 26% Excellent 62%
Tormo *et al*. [25] (2014)	4 mm	47 months	97.8	2.2%	G1	G1	Excellent
Delishaj *et al*. [26] (2015)	4 mm	12 months	96.2	No recurrence (2 lesions persisted)	G1-G2 (63.2%)	G1-G2 (19.3%)	Excellent 86% Good 12.6% Fair 1.7%
Arenas *et al*. [42] (2015)	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% Fair 13% Not available 5%

reduced cosmetic results. Moreover, conventional fractionated regimens have different disadvantages such us higher number of sessions, overall treatment duration, moving the patient to the hospital, which can lead to an increase of overall costs effective therapy.

Different hypofractionated regimens with very good local control has been reported in literature [19,20,21,22, 23,24,25,26,27,28,37,41,42]. Most commonly hypofractionated course described consist in a total dose of 30-40 Gy, delivered in 5-10 fractions once/twice per week (Köhler-Brock *et al*. [19]), 36 Gy in 12 fractions (Gauden *et al*. [23]), 47-57 Gy delivered in 3 times weekly (Arenas *et al*. [42]), 40-50 Gy delivered in 7-8 fractions 2/3 time at week (Ghaly *et al*. [22], Delishaj *et al*. [26]), 42 Gy in 6 fractions delivered twice weekly (Tormo *et al*. [25]). Other hypofractionated regimes reported in some studies consist in 50-60 Gy given in 8-10 fractions and 50-60 Gy delivered in 5-6 fractions two time a week (Skowronek *et al*. [21]).

Local control

An excellent local control in patients with NMSC and treated with HDR-BT has been shown in different studies, and the local control rate is variable reported with a wide range from 83.3% [24] to 98-100% [18,22,25,26]. The main factors that may influence local control consist of total dose prescription, doses for fractions, dimension and depth of lesion, and histological type. Kanikowski [24] reported a recurrences rate of 16.7% after a median follow-up of 12 months in 497 patients with skin cancer treated by brachytherapy between November 1999 till April 2008 (Table 1 and 2). However, this study included patients who received palliative brachytherapy and patients previously treated with external beam radiation, which reported recurrences after treatment. The data reported by Skowronek *et al*. [21] showed a recurrences rate of 8.9% (179 lesions treated) after a median follow-up of 12 months but this study included 8 patients with skin metastases and receiving BT with palliative intent.

Köhler-Brock *et al*. [19] reported a recurrence rate of 8% of 520 lesions treated with HDR-BT using Leipzig applicators at the doses of 30-40 Gy in 5-10 after, 10 years follow-up. The study included Kaposi's sarcoma, melanomas, and skin metastases. Finally, other studies [20,22,23,25,26] including patients affected by NMSC treated with definitive HDR-BT, reported excellent local control rate of 98-100%.

Table 3. Radiation Therapy Oncology Group (RTOG) morbidity scoring criteria [31]

Grading	Acute toxicity	Late toxicity
G0	No change over baseline	None
G1	Follicular, faint or dull erythema, epilation, dry desquamation, decreased sweating	Slight atrophy, pigmentation change, some hair loss
G2	Tender or bright erythema, patchy moist desquamation, moderate edema	Patch atrophy, moderate, telangiectasia, total hair loss, induration
G3	Confluent, moist desquamation other than skin folds, pitting edema	Market atrophy, gross telangiectasia, fibrosis
G4	Ulceration, hemorrhage, necrosis	Ulceration or necrosis

Overall, the median of local control rate after HDR brachytherapy in 10 studies analyzed was 97%.

Adverse events and cosmetic results

As reported in the literature, HDR brachytherapy treatment is very well tolerated with excellent cosmetic results despite applicators used (Lippizing applicators, Valencia applicators or custom made surface molds), total doses, and dose for fractions. Moreover, excellent cosmetic outcomes and acceptable acute and late side events were observed even in elderly patients using hypofractionated regimen of 40-50 Gy delivered in 8-10 fractions 2-3 time weekly [19]. As shown in Table 3, the most common early side-effects due to HDR-BT treatment are erythema, edema, rash dermatitis, pruritus, desquamation, and in rare cases ulceration. Late side effects appear, as per definition, 6 months after HDR-BT treatment and often consist of atrophy, pigmentation change, hair loss, telangiectasia fibrosis, and in rare cases ulceration (Table 3). RTOG morbidity scoring criteria [31].

According to toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC), scale G1-G2 acute toxicities after HDR-BT varies widely from 24.5% [18] to 91.1% [24]. G3 RTOG/EORT acute toxicities has been reported in several studies in literature and they differ from 0% [19,20,22,23,25,26] to 40.3%, as reported by Arenas *et al*. [42]. Acute G4 toxicity was reported only in one study with a frequency of 2.2% [42]. The incidence of late toxicity reported in literature is lower than the incidence of acute toxicity. G1-G2 late toxicities differ from a minimum of 0.84% [20] to a maximum of 54% [21].

Table 4. Cosmetic rating scale [31]

Excellent	No changes to slight atrophy or pigment change, or slight hair loss or no changes to slight induration or loss of subcutaneous fat
Good	Patch atrophy, moderate telangiectasia, and total hair loss; moderate fibrosis but asymptomatic; slight field contracture with less than 10% linear reduction
Fair	Marked atrophy and gross telangiectasia; severe induration or loss of subcutaneous tissue; field contracture greater than 10% linear measurement
Poor	Ulceration or necrosis

Overall, three studies [21,24,42] reported G3 late toxicity with frequencies of 2.2%, 3.4%, and 4.9%, respectively; G4 late toxicity was described only by Arenas *et al*. [42] data in 0.8% of lesions treated as shown in Table 2. In Table 4, we present a cosmetic rating scale [31].

Finally, as reported in many studies in literature, the treatment of NMSC with HDR BT is associated with excellent cosmetic outcomes even in elderly patients, as reported in our previous study [19,20,21,22,23,24,25,26,27]. On average, an excellent cosmetic result was reported from approximately 62% [23] to 98-100% [20,22,25]; a good cosmetic result from 0-2% [20,25] to 26% [23]; a fair result from 0% [25] to 13% [27], and, finally, a poor cosmetic result was reported in a range wide from 0% [24,25,26] to 5.5% [23]. Overall, an excellent and good cosmetic outcome consisted of 94.8% of cases.

Discussion

Surgery is often the primary treatment for NMSC lesions due to low rates of recurrence reported [6,7,8,9,10]. However, surgical treatment is an invasive procedure, and in elderly patients is not always feasible because of comorbidities, performance status, or lesion location (near the eyes, nose, and on facial skin). Typically, RT is the treatment of choice in this class of patients since surgery might be accompanied with functional or cosmetic deficits. The development of new devices for small skin tumor treatment and the introduction of commercial electronic BT have attracted considerable interest for BT as a skin cancer treatment. Despite the new technologies available, few studies have focused on the treatment of NMSC with HDR-BT and hypofractionated regimes seems to be a valid option for the treatment of NMSC with very good local control, toxicity, and cosmetic result [19,20,21,22,23,24,25,26,33,34,35,36,37,43,44]. In 1999, Köhler-Brock *et al*. [19] described the outcome of 520 lesions treated with HDR-BT using Leipzig applicators. The dose prescribed was 30-40 Gy in 5-10 fractions, and after 10 years' of follow-up, local control was 92% of the cases; only G1-G2 late and acute toxicities were observed. One year later, Guix *et al*. [20] reported the results of 236 NMSC lesions treated with HDR-BT using custom-made surface molds, and after five years of follow-up, the local control was 98%. In addition, Gauden *et al*. [23] published

the data of 236 lesions, and the local control was 98% after 36 months of follow-up. The total dose prescribed was 36 Gy in 12 fractions, and no G3 or higher late or acute toxicities were observed.

Hypofractionated course appears effective with very good local disease control and have different advantages such us little number of fractions, overall shorter time of duration, reduction of times for moving the patient to the hospital, and feasible outpatient treatment regimen, which can lead to reduction of overall costs effective therapy [36]. Comparable outcomes were reported by Bhatnagar [37], Tormo *et al*. [25], and Ballester-Sánchez *et al*. [28] with the use of hypofractionated course and Valencia applicators or HDR electronic BT with surface applicators, which resulted in excellent local control, cosmetic results, and very low-grade toxicities. More recently, we reported our data [26] of 57 lesions in elderly patients receiving hypofractionated regimes at the dose of 40-50 Gy in 8-10 fractions (using Valencia applicator) with excellent local control, cosmetic results with no G3 or higher acute or late toxicity. Finally, Haseltine *et al*. [29] reported the data of 61 patients treated with HDR brachytherapy, hypofractionated external beam radiation therapy (EBRT), or standard fractionation EBRT in patients affected by NMSC. After a median follow-up of 30 months, the local control was 81% and 2-year overall survival was 89%. There was no statistical difference in local control, overall survival, cosmetic outcome, or toxicity between treatment modalities.

Conclusions

As seen in our review, HDR-BT, through use of a custom mold, Leipzig applicator, Valencia applicator, or a variety of other techniques, is an alternate radiation modality that may be valuable for treatment of selected NMSCs. Typically, HDR-BT is the treatment of choice in patients, in which surgery is not feasible because of comorbidities, performance status, or lesion location, and surgery might be accompanied with functional or cosmetic deficits. Overall, the hypofractionated course appears to be effective with very good local disease control. Moreover, this cost-effective therapy shows high compliance and a feasible outpatient treatment regimen, essential in elderly patients. Finally, more data with large-scale randomized/prospective controlled trials and longer follow-up are needed to assess the efficacy and safety of HDR-BT, and to compare it directly with external beam therapy as well as the differential cure rates of subtypes of BCC versus SCC.

Disclosure

Authors report no conflict of interest.

References

1. Lomas A, Leonardi-Bee J, Bath-Hextall F. A systematic review of worldwide incidence of nonmelanoma skin cancer. *Br J Dermatol* 2012; 166: 1069-1080.
2. Eisemann N, Waldmann A, Geller AC et al. Non-melanoma skin cancer incidence and impact of skin cancer screening on incidence. *J Invest Dermatol* 2014; 134: 43-50.
3. Kricker A, Armstrong BK, English DR et al. Does intermittent sun exposure cause basal cell carcinoma. A case-control study in Western Australia. *Int J Cancer* 1995; 60: 489-494.
4. Zanetti R, Rosso S, Martinez C et al. The multicentre south European study 'Helios'. I: Skin characteristics and sunburns in basal cell and squamous cell carcinomas of the skin. *Bitr J Cancer* 1996; 73: 1440-1446.
5. Katalinic A, Kunze U, Schäfer T. Epidemiology of cutaneous melanoma and non-melanoma skin cancer in Schleswig-Holstein, Germany: incidence, clinical subtypes, tumour stages and localization (epidemiology of skin cancer). *Br J Dermatol* 2003; 149: 1200-1206.
6. Caresana G, Giardini R. Dermoscopy-guided surgery in basal cell carcinoma. *J Eur Acad Dermatol Venereol* 2010; 24: 1395-1399.
7. Smeets NW, Kuijpers DI, Nelemans P et al. Mohs' micrographic surgery for treatment of basal cell carcinoma of the face–results of a retrospective study and review of the literature. *Br J Dermatol* 2004; 151: 141-147.
8. Brodland DG, Zitelli JA. Surgical margins for excision of primary cutaneous squamous cell carcinoma *J Am Acad Dermatol* 1992; 27: 241-248.
9. Macfarlane L, Waters A, Evans A et al. Seven years' experience of Mohs micrographic surgery in a UK centre, and development of a UK minimum dataset and audit standards. *Clin Exp Dermatol* 2013; 38: 262-269.
10. Chren MM, Torres JS, Stuart SE et al. Recurrence after treatment of nonmelanoma skin cancer: A prospective cohort study. *Arch Dermatol* 2011; 147: 540-546.
11. Pérez-Calatayud J, Granero D, Ballester F et al. A dosimetric study of the Leipzig applicators. *Int J Radiat Oncol Biol Phys* 2005; 62: 579-584.
12. Niu H, Hsi WC, Chu JC et al. Dosimetric characteristics of the Leipzig surface applicators used in the high dose rate brachy radiotherapy. *Med Phys* 2004; 31: 3372-3377.
13. Kowalik L, Lyczek J, Sawicki M et al. Individual applicator for brachytherapy for various sites of superficial malignant lesions. *J Contemp Brachytherapy* 2013; 5: 45-49.
14. Granero D, Pérez-Calatayud J, Gimeno J et al. Design and evaluation of a HDR skin applicator with flattening filter. *Med Phys* 2008; 35: 495-503.
15. Granero D, Pérez-Calatayud J, Ballester F et al. Radiation leakage study for the Valencia applicators. *Phys Med* 2013; 29: 60-64.
16. Khan L, Choo R, Breen D et al. Recommendations for CTV margins in radiotherapy planning for nonmelanoma skin cancer. *Radiother Oncol* 2012; 104: 263-266.
17. Hwang IM, Lin SY, Lin LC et al. Alternative effective modality of Leipzig applicator with an electron beam for the treatment of superficial malignancies. *Nuc Inst Meth A* 2003; 508: 460-466.
18. Svoboda VH, Kovarik J, Morris F. High dose-rate microselectron molds in the treatment of skin tumors. *Int J Radiat Oncol Biol Phys* 1995; 31: 967-972.
19. Köhler-Brock A, Prager W, Pohlmann S et al. The indications for and results of HDR afterloading therapy in diseases of the skin and mucosa with standardized surface applicators (the Leipzig Applicator). *Strahlenther Onkol* 1999; 175: 170-174 [Article in German].
20. Guix B, Finestres F, Tello J et al. Treatment of skin carcinomas of the face by high dose rate brachytherapy and custom made surface molds. *Int J Radiat Oncol Biol Phys* 2000; 47: 95-102.
21. Skowronek J, Chicheł A, Piotrowski T. HDR brachytherapy of skin cancer - the Wielkopolski Cancer Centre's experience *Współcz Onkol* 2005; 9: 347-354 [Article in Polish].
22. Ghaly M, Zinkin H, Dannenberg M et al. HDR Brachytherapy with Standardized Surface Applicators in the Treatment

of Superficial Malignant Skin Lesions. *Int J Radiat Oncol Biol Phys* 2008; 72: S505-S506.
23. Gauden R, Pracy M, Avery AM et al. HDR brachytherapy for superficial non-melanoma skin cancers. *J Med Imaging Radiat Oncol* 2013; 57: 212-217.
24. Kanikowski M. HDR brachytherapy of skin cancer in material of Greater Poland Cancer Center. *J Contemp Brachytherapy* 2009; 1: S197.
25. Tormo A, Celada F, Rodriguez S et al. Non-melanoma skin cancer treated with HDR Valencia applicator: clinical outcomes. *J Contemp Brachytherapy* 2014; 6: 167-172.
26. Delishaj D, Laliscia C, Manfredi B et al. Non-melanoma skin cancer treated with high-dose-rate brachytherapy and Valencia applicator in elderly patients: a retrospective case series. *J Contemp Brachytherapy* 2015; 7: 437-444.
27. CTCAE v4.0: NIH Publication No. 09-5410.
28. Ballester-Sánchez R, Pons-Llanas O, Candela-Juan C et al. Electronic brachytherapy for superficial and nodular basal cell carcinoma: a report of two prospective pilot trials using different doses. *J Contemp Brachytherapy* 2016; 8: 48-55.
29. Haseltine JM, Parker M, Wernicke AG et al. Clinical comparison of brachytherapy versus hypofractionated external beam radiation versus standard fractionation external beam radiation for non-melanomatous skin cancers. *J Contemp Brachytherapy* 2016; 8: 191-196.
30. Frakulli R, Galuppi A, Cammelli S et al. Brachytherapy in non-melanoma skin cancer of eyelid: a systematic review. *J Contemp Brachytherapy* 2015; 7: 497-502.
31. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Oncol Biol Phys* 1995; 31: 1341-1346.
32. Fabrini MG, Perrone F, De Liguoro M et al. High-dose-rate brachytherapy in a large squamous cell carcinoma of the hand. *Brachytherapy* 2008; 7: 270-275.
33. Ballester-Sánchez R, Pons-Llanas O, Llavador-Ros M et al. Depth determination of skin cancers treated with superficial brachytherapy: ultrasound vs. histopathology. *J Contemp Brachytherapy* 2015; 6: 356-361.
34. Montero A, Hernanz R, Capuz AB et al. High-dose-rate (HDR) plesiotherapy with custom-made molds for the treatment of non-melanoma skin cancer. *Clin Transl Oncol* 2009; 11: 760-764.
35. Maroñas M, Guinot JL, Arribas L et al. Treatment of facial cutaneous carcinoma with high dose rate contact brachytherapy with customized molds. *Brachytherapy* 2011; 10: 221-227.
36. Donaldson MR, Coldiron BM. No end in sight: the skin cancer epidemic continues. *Semin Cutan Med Surg* 2011; 30: 3-5.
37. Bhatnagar A. Nonmelanoma skin cancer treated with electronic brachytherapy: results at 1 year. *Brachytherapy* 2013; 12: 134-140.
38. Jones B, Dale RG, Deehan C et al. The role of biologically effective dose (BED) in clinical oncology. *Clin Oncol (R Coll Radiol)* 2001; 13: 71-81.
39. Jones B, Dale RG. Mathematical models of tumour and normal tissue response. *Acta Oncol* 1999; 38: 883-893.
40. Brenner DJ, Hall EJ. Fractionation and protraction for radiotherapy of prostate cancer. *Int J Radiat Oncol Biol Phys* 1999; 43: 1095-1101.
41. Trott KR, Maciejewski B, Preuss-Bayer G et al. Dose-response curve and split-dose recovery in human skin cancer. *Radiother Oncol* 1984; 2: 123-129.
42. Arenas M, Arguís M, Díez-Presa L et al. Hypofractionated high-dose-rate plesiotherapy in nonmelanoma skin cancer treatment. *Brachytherapy* 2015; 14: 859-865.
43. Kuncman Ł, Kozłowski S, Pietraszek A et al. Highly conformal CT based surface mould brachytherapy for non-melanoma skin cancers of earlobe and nose. *J Contemp Brachytherapy* 2016; 8: 195-200.
44. Skowronek J. Brachytherapy in the treatment of skin cancer: an overview. *Postepy Dermatol Alergol* 2015; 32: 362-367.