



GEC-ESTRO ACROP Guideline

GEC-ESTRO ACROP recommendations in skin brachytherapy

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ABSTRACT

Purpose: The aim of this publication is to compile available literature data and expert experience regarding skin brachytherapy (BT) in order to produce general recommendations on behalf of the GEC-ESTRO Group.

Methods: We have done an exhaustive review of published articles to look for general recommendations. **Results:** Randomized controlled trials, systemic reviews and meta-analysis are lacking in literature and there is wide variety of prescription techniques successfully used across the radiotherapy centers. BT can be delivered as superficial application (also called contact BT or plesiotherapy) or as interstitial for tumours thicker than 5 mm within any surface, including very irregular. In selected cases, particularly in tumours located within curved surfaces, BT can be advantageous modality from dosimetric and planning point of view when compared to external beam radiotherapy. The general rule in skin BT is that the smaller the target volume, the highest dose per fraction and the shortest overall length of treatment can be used.

Conclusion: Skin cancer incidence is rising worldwide. BT offers an effective non-invasive or minimally invasive and relative short treatment that particularly appeals to elder and frail population.

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The incidence of skin cancer has been rising over the past decades. World Health Organization (WHO) estimates that currently 2–3 million non-melanoma skin cancers (NMSC) occur globally each year with one in every three cancers diagnosed being a skin cancer [1]. These data are most likely underestimated. The incidence rates in Europe varied between 40–130/100,000 person-years for basal cell carcinoma (BCC) and 8–30/100,000 person-years for squamous cell carcinoma (SCC) respectively [2]. A trend in increasing incidence in older population has been confirmed [3]. It is expected that NMSC may soon start to represent a major public health problem and pose a significant burden to any health care system. Many patients with NMSC referred for radiotherapy are older, frail, have unresectable tumours or contradictions to surgery due to advanced age or co-morbidities. This issue already introduces a bias in data analysis and comparison with other treatment methods. Various radiotherapy techniques have been developed to treat skin cancer: superficial and orthovoltage X-rays, electron and megavoltage photon treatment, and brachytherapy

(BT) in all the modalities: low dose rate (LDR), high dose rate (HDR), pulsed dose rate (PDR), and electronic BT. Due to logistics of LDR application, this modality has been gradually abandoned. The treatment choice is usually based on institutional resources and specialist experience and should consider local control, cosmetics, toxicity and convenience/expected compliance of the treatment.

BT is an appropriate and effective treatment option for selected skin cancers, mainly NMSC that are not better served by surgical removal, non-radiotherapy treatment modalities, or external beam radiotherapy (EBRT) [4]. There are several advantages of HDR and PDR BT when compared with EBRT that should be considered in the decision making process. BT is usually delivered as a hypofractionated course, three or two times a week, rather than daily, which translates into fewer treatment visits for a patient, particularly useful for elderly and frail patients. The dose is delivered in a short period of time. Computer-based treatment planning allows for an optimized dose distribution. A rapid fall in dose beyond

radioactive source makes it possible for increased tumour control while sparing the surrounding tissue and shorter overall treatment duration reduces risk of tumour cell repopulation. There are no randomized controlled trials, systemic reviews and meta-analysis in literature regarding skin BT and there is wide variety of prescription techniques successfully used across the radiotherapy centers [5]. All the recommendations in this paper have a level of evidence IV (LOE IV: based in retrospective cohort studies, no prospective studies); and grade of recommendation B (GOR B: Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended) [6].

Modalities of BT applications in skin

Current skin applications in brachytherapy can be classified in two modalities [7,8]:

- Superficial, also called contact brachytherapy or plesiotherapy.
- Interstitial, with the insertion of plastic tubes or rigid needles.

Superficial modalities involve moulds and flaps for larger lesions, and radionuclide based shielded applicators and electronic based shielded applicators for small volume lesions. Interstitial BT is applied to deeper located and/or very irregular tumours.

An excellent review of those different modalities and details on the applicators from physics point of view have been published by the American Brachytherapy Society (ABS), with an updated review of relevant papers on skin BT [9].

Superficial brachytherapy

Surface moulds

Mould BT is a technique of delivering BT by an applicator that is usually custom made and designed to provide a more constant and reproducible frame for source positioning. Mould can be used for flat surfaces and irregular shapes. A customized mould can be constructed from specialized polymers, acrylic resin, wax (such as those used in dentistry) or a thermoplastic material or similar in which the catheters are embedded [10,11] (Fig. 1). Moulds fit to the external patient surface and the catheters must remain in the exact position as closely as possible to tumour surface to provide adequate dose coverage of tumour volume and increase the distance to other normal surrounding structures. In postoperative BT the gradient can overdose the skin, therefore the catheters must

be placed at a few mm of distance from the skin, preferably 5 mm. Conformal custom moulds are often utilized for complex shapes and irregular surfaces like the earlobe or nose. An irreversible hydrocolloid can be used for making impression. Cerrobend alloy or thin lead is chosen for shielding purposes [12]. A thermoplastic mask with catheters embedded in wax or resin is useful for an accurate reproducibility for extensive lesions of the scalp. Low-cost 3D printers are a promising solution for the customization of the HDR BT applicators but regulatory materials' approval is required for clinical application [13]. Published studies involving mould technique have shown good local control and cosmesis [14–20] (see separate file for table).

The dose prescription point with moulds is usually 3–5 mm under the skin surface but in case of advanced tumours with deep ulcer or deep dermis infiltration, it should be at least 3–5 mm under the deepest point of a given tumour, defined by an appropriate imaging, therefore interstitial BT or EBRT should be considered in such cases.

The ABS in 2001 made specific recommendations for head-and-neck cancer patients [21]:

1. Superficial (<5 mm thick) tumours can be treated with fractionated HDR using moulds.
2. Suitable sites for mould therapy include scalp, face, pinna, lip, buccal mucosa, maxillary antrum, hard palate, oral cavity, external auditory canal, and the orbital cavity after exenteration.
3. A total HDR dose equivalent to about 60 Gy LDR (prescribed at 5 mm depth) is recommended. The actual HDR dose per fraction and number of fractions can be varied to suit individual situation (site and treatment volume). HDR can be used as a boost to 45–50 Gy EBRT (LDR equivalent doses of 15–30 Gy).

Surface flaps

In case of non-excessive surface irregularity, commercially available flaps may be used. These consist of regular layers of silicon-based material or linked pellets of 10 mm in thickness or diameter in which the catheters are embedded. Ten mm inter-catheter distance and a minimum of 5 mm distance to the skin are assured. Typical prescription depth with flaps is less than 5 mm under the skin. The available flaps are the Freiburg™ flap (Elekta Instrument AB, Stockholm, Sweden), the H.A.M.™ (Mick Radio-Nuclear Instruments and Eckert & Ziegler BEBIG, Berlin, Germany), and the Catheter Flap set™ (Varian Medical Systems, Palo



Fig. 1. 53 year old with 12 months non-healing ulceration on the left middle finger. Biopsy confirmed SCC. No bony invasion. Prior unsuccessful treatment with cryotherapy. On examination: 2.1 cm × 3.1 cm lesion. Skin US 1.9 mm total tumour depth, 3.6 mm from the top of the tumour to bone. Treatment: Skin HDR brachytherapy 37.5 Gy in 8 fractions, treatment twice a day over 4 days. Results at 18 month follow-up. (Example of surface moulds and flaps).

Alto, CA, USA). Parallel equidistant plastic tubes can be taped to a bolus to obtain a hand-made flap that is fixed to the skin or scalp in every fraction.

- Surface moulds and flaps are indicated on regular surfaces. Flaps are convenient in larger volume lesions.
- Customized moulds can be adapted to irregular surfaces like nose, pinna, hand and fingers.
- Dose is prescribed to 3–5mm under the skin surface.
- A distance from the source to the skin of 5mm is recommended to obtain homogeneity on the surface of the skin, and avoid an overdosage.

Superficial radionuclide based shielded applicators

In case of small lesions, on regular and plane surfaces, adequately sized applicators were developed specifically for this purpose. The Leipzig type™ applicator is cup-shaped and made of tungsten with the HDR source at its vertex [22]. Different diameters, from 10 mm to 30 or 45 mm are available (Elekta or Varian). Although the main disadvantage of these applicators can be non-flat dose distribution delivering an inhomogeneous dose on the target volume, and relatively large penumbra [23–25], several studies have shown the clinical efficacy of this approach [26–29]. The prescription depth usually depends on the depth of the skin tumour infiltration, usually no more than 4 mm.

The Valencia™ applicator (Elekta) was developed from the Leipzig™ applicator by adding a flattening filter to homogenize the dose distribution, resulting in significant improvement of the useful beam and penumbra [30,31]. It is cup-shaped and made of tungsten, with two sizes of 20 mm (VH2) and 30 mm (VH3) of diameter. The 40 mm (VH4) and 50 mm (VH5) are under development. Lesion size must not exceed 15 or 20 mm for VH2 and VH3 with a minimum of 5 mm of margin and 1–2 mm extra from CTV-PTV due to setup uncertainty. The template Ia Fe-ITIC™ has been developed specifically for marking the added Planning Target Volume (PTV) on skin and helps to avoid interfraction set-up errors [32]. Because of the filter-induced attenuation, the treatment times are higher and can take from 5 to 15 min. The typical prescription depth is 3 mm with a skin surface dose of around 135% [33–35]. Valencia™ applicators have a removable 1 mm thick plastic cover cap in close contact with the patient skin. The overtreatment without the cap for the first millimeter of skin goes up to a factor of 2.8. Depth of the area to be treated must not exceed 3–4 mm what delivers 80–90% of the dose to a depth of 5 mm, due to a gradient of 10% per mm. Skin high frequency ultrasound of the lesion or surgical bed to define the depth of PTV is recommended. Immobilization during every session of BT can be obtained with an articulated arm, tape or thermoplastic mask (see separate file for tables).

Electronic based shielded applicators

In order to reduce the treatment time and to avoid dependence on HDR equipment and a brachytherapy facility, several electronic solutions have been implemented, leading to development of electronic based applicators [8]. Currently, three major electronic applicator systems can be used for skin cancer. The Axxent™ (Xoft Inc, San Jose, USA) has a 50 kV electronic source and is used mainly for the intracavitary treatments. For skin treatments, the source needs to be mounted on special applicators with flattening filter [36]. Another device is the 50 kV Intrabeam™ (Carl Zeiss, Oberkochen, Germany), with the specifically developed skin applicator [37,38]. The third system is Esteya™ (Elekta, Stockholm, Sweden) [39,40], compact and dedicated specifically for skin BT. It has a

69.5 kV electronic source and a dose gradient that is slightly shallower (8% per mm) than with Leipzig™, Valencia™ and Axxent™ systems (12% per mm). The dose rate allows for shorter treatment times, lasting approximately one third of the Valencia applicator times. The design of Esteya™ has significantly improved radiation leakage [41–47] (see separate file for table).

- Superficial radionuclide or electronic based shielded applicators are indicated mainly for small volume lesions on regular surfaces.
- They always must be in complete contact with the surface, fixed without pressing the skin and be immobilized.
- Dose is usually prescribed to 3–4mm depth.
- Skin high frequency ultrasound of the lesion or surgical bed to define the depth of CTV is recommended in skin tumours.

Interstitial brachytherapy

Interstitial BT is indicated in cases when other radiotherapy techniques, including surface BT, are not suitable for a good dose coverage of the tumour, in particular, when the thickness is more than 5 mm and/or the tumour is in curved surfaces as in the face. The implantation procedure requires general or local anaesthesia. Often the flexible implant tubes are inserted using rigid introducers, 8–12 mm apart, and secured by fixation buttons or sutured to the skin (Fig. 2). Some authors use rigid metallic needles. Definition of the catheter positions follows the rules of the Paris system that in HDR and PDR becomes Stepping Source Dosimetry System (SSDS) [48]. Plastic tubes are the first choice in not plain areas, since they allow a better, more flexible coverage of the target; however, the implant with the metallic needles offer a better and more stable implant geometry. For lesions with a thickness of 10 mm or less, a single-plane implant might be adequate with catheters embedded at half distance within the target. The catheters should be 3–4 mm beneath the skin surface to avoid telangiectasia, skin necrosis, or delayed healing along the source positions. If more than one plane of catheters are needed, separation of at least 5–7 mm should be considered between planes. Sometimes, for dose optimization on the external surface of the target, an additional plane of catheters outside the body can be necessary, adding a tissue equivalent bolus between the catheters in the air and the skin.

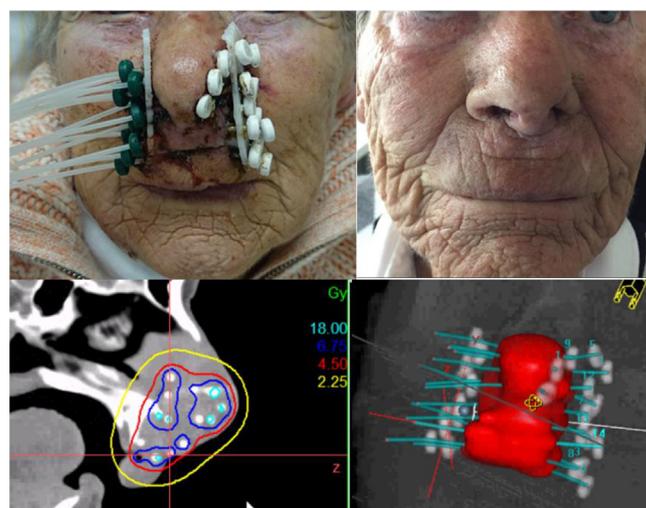


Fig. 2. Extensive interstitial implant to treat an SCC in the columella.

Individual blocks or distance keepers can minimize the surrounding normal tissue dose.

- Interstitial brachytherapy is indicated in cases with tumour thickness of 5mm or more, and in irregular surfaces.
- Interspace between catheters 8–12mm. Several planes outside the skin can be used with external fixation adding bolus material in the empty spaces.
- Catheters must be at least 3mm under the skin surface to avoid late toxicity.
- A CT scan with marks is necessary to define the CTV plus margins.

BT applications in skin – special considerations

Nose and ear

Due to very irregular shape of nose and ear, BT in such locations is often delivered with flexible plastic tubes, custom mould or interstitial technique. With interstitial LDR implants, 60 Gy was defined as the optimal dose [49] with a local control over 96% [50,51], good aesthetic result over 90% and 2% of complications with no Grade 3 complications. The results of interstitial HDR BT as primary treatments for nasal vestibule carcinomas were compared with surgery [52], without differences in locoregional control and survival; but the functional, aesthetic outcome and the degree of satisfaction of the patients were significantly better following HDR BT, with often superior organ preservation and cosmesis. Computed tomography-based surface mould BT for superficial lesions on irregular surfaces such as nose [19] and ear [53], is a highly conformal method with good homogeneity, with normal tissue sparing ability in high doses superior to EBRT [54].

Eyelid

The gold standard of NMSC of eyelid is surgery with good tumour control and preservation of the functional structures. However, if functional structure preservation is not possible, interstitial BT plays an important role. Often, BT is performed as an implant using LDR or HDR and results in high local control rates. The most common late toxicities are conjunctivitis and kerato-conjunctivitis sicca, epilation, eyelid malocclusion, pruritus, burn pain, and pigmentation changes. With LDR, doses of 60 Gy for BCC and 70 Gy for SCC achieved a local control rate over 96% with 18% local side effects (significantly more frequent in recurrent lesions) [55,56]. HDR BT for eyelid targets was reported in small number of patients with local control rates over 94% [57–59]. In 2015, a systematic review analysed six publications and concluded that BT is well tolerated, the local control is high (median: 95.2%), the toxicity is acceptable and the functional-cosmetic outcome is good [60]. Special care needs to be considered when upper outer eyelid is treated due to location of lacrimal glands and late complications with dry eye. Usually eyelid treatment requires internal shielding of the eye. The minimum bolus thickness that is needed to neutralize backscatter, above and below the shielding was 0.5 mm and 1 mm respectively [61]. (see [separate file for table](#)).

Extremities

NMSC located at extremities represents a clinical challenge in radiotherapy. In areas of poor vascularisation and subjected to constant trauma, such as extremities, radiotherapy may cause prolonged healing, poorly treatable ulcerations and even necrosis, requiring subsequent surgical intervention (anterior tibial loca-

tions) or impaired hand function due to risk of radiation damage to tendons, joints and bones. BT can be applied safely over bones or cartilage where traditional EBRT may be less safe [4]. There are only handful of publications in the literature on the use of BT in NMSC located over extremities. Usually extremities' locations are included with other sites, and outcomes are analysed together. Leipzig applicators for HDR BT have been used on extremities [27], to a total dose of 36 Gy in 3 Gy per fraction given daily over 2 weeks, prescribed to 3–4 mm, and local control in 98% of cases. Grade 2 acute skin toxicity 34% with good or excellent cosmesis in 88%, and late skin hypopigmentation changes in 5%. Customized moulds, on the hand, arm or lower limbs for HDR superficial BT can be made, with total dose ranging from 12 to 50 Gy given in 1–15 fractions [14], on the dorsum of the hand and fingers with 40–45 Gy on the skin surface in eight fractions given on 5 consecutive days [60]. The cosmetic result and preserved hand function are good for most patients [62]. Large moulds to cover more than a half the circumference of the forearm (60 Gy in 2 Gy per fraction) [63] or the hand (50 Gy in 10 fractions, 3 fractions per week) [64], result in satisfactory cosmetic outcome. Marjolin's ulcer, an aggressive ulcerating form of SCC presenting in an area of previously traumatized, chronically inflamed or scarred skin (40% can occur on the lower limbs) has been treated with 45–47.5 Gy in 10 or 11 fractions [65], with poor healing or superficial necrosis. Considerable care is necessary when considering dose fractionation regimes for lower limb locations, and increased fractionation is advised.

Frail and elder patients

BT has proven to be effective in the elderly in many application sites. Reported side effects and local control of cancer after BT remain the same regardless of patients' age [66]. Delishaj et al. retrospectively analysed an elderly group of patients (median age 84 years) with NMSC treated with HDR BT and Valencia™ applicator in 8–10 daily fractions with high compliance for older patients [34]. Another fractionation schedule of 42 Gy in 6–7 fractions delivered twice a week (median age 78 years) also proved excellent results and facilitated good compliance [33]. Recent ABS report provided a detailed summary of 19 published protocols for skin cancer BT [9], median age of patient's falls into "elderly" category, and local controls were in the range of 90–100%. A study with Esteya™ applicator showed an effective, simple, safe and comfortable treatment for nodular and superficial BCC in patients with a mean age of 79 years [67]. Similar encouraging results in patients treated with electronic BT [42]. In general, it is acceptable that more hypofractionated treatments can be used in older and frail patients, even in large size areas, at the cost of reduced cosmetic result.

Keloids

BT to prevent keloid formation is effective, especially useful in complex and irregular surfaces. The excision should be as close to the lesion as possible to avoid further damage to surrounding tissues. Catheter(s) needs to be placed at least 4 mm deep from the skin surface and below the approximation sutures. Fixation buttons are used to secure catheter(s) in place. Careful consideration needs to be given to closure the scar over the catheter. If the wound is 4 cm long and/or 3 cm wide, subdermal sutures every 1–2 cm are required to approach the margins and to avoid tension in the skin. Intradermal continuous suture with 4–0 silk is preferable with adhesive reinforced skin closures. CTV definition includes 4 mm around the surgical wound and around the catheter, beyond each of the ends of the scar. The prescribed dose is at 4–5 mm from the center of the source, using dose points optimization. It is very important to start treatment as soon as possible after

surgery, if possible 90 min after surgery, and always before 24 h, to avoid the regrowth of the keloid. Different fractionations have been used and there is not a standard recommended schedule [68–77]. A systematic review of published papers [78] showed that the mean total radiation dose for studies investigating external radiation and HDR brachytherapy was the same (external, 13.5 ± 3.3 Gy; HDR, 13.7 ± 2.6 Gy) and higher when using LDR brachytherapy (19.3 ± 1.2 Gy). HDR brachytherapy was associated with the lowest mean recurrence rate (HDR: $10.5 \pm 15\%$; LDR: $21.3 \pm 2.1\%$; external: $22.2 \pm 16\%$) (Table 1)

- Keloids are effectively managed with HDR BT placing a single catheter during the surgery.
- The catheter must be at least 4mm under the skin.
- Dose prescription 4–5mm from the source.
- Start as soon as possible, the first session should be on the same day as surgery.
- Doses of 5–6Gy×3 fractions or 5Gy×4 fractions are recommended.

Brachytherapy dose calculation and planning

Most current treatment planning systems used for BT dose calculation are based on American Association of Physics in Medicine (AAPM) TG-43 dosimetric parameters where scatter defect is not considered [79]. Differences at the prescription depth, between TG-43 and Monte Carlo calculations, were negligible for Ir-192, therefore no bolus over the mould is required. The Freiburg™ flap is composed of small spheres or “pellets”, the scatter defect plus interpellet air gap effect is smaller than 5%. In surface HDR BT with mould/flaps, a lead shield covering the implants reduce dose to radiosensitive organs, then, the backscatter overdose can be avoided by just adding a few mm of bolus to the lead [61]. The Leipzig™ and Valencia™ applicators are equipped with an attachable plastic cap to be placed during fraction delivery to prevent secondary electrons from reaching the skin surface. Users must check always that the plastic cap is in place because if the cap is

not used, the skin dose is 2.5 and 10 times higher for the Valencia™ and Leipzig™ applicators respectively [80].

The ABS report includes some treatment planning and clinical practice recommendations and there is a specific section dedicated to recommendations in commissioning and QA [9]. The AAPM joined with the European Society for Therapeutic Radiation and Oncology (ESTRO) have in progress a Task Group (TG-253) to include recommendations for quality management. In an interstitial implant, the PTV equals the CTV. Expansion of at least 5 mm from GTV to CTV is required in cases of superficial applicators. For radionuclide-based BT and electronic BT applicators, an extra margin of approximately 1–2 mm (PTV) should be added to account for any misalignment. Excellent results are obtained comparing electronic BT and Mohs surgery [81]. A very useful method for applicators setup is the use of templates, as the template La Fe/ITIC™ for the superficial shielded applicators [32]. Once the GTV is drawn, with graduated rules, it is possible to select the applicator size according the required margin taking into account the useful beam. An air gap between the applicator and the skin surface can result in significant underdosage. Too much pressure on the applicator can cause tissue compression resulting in possible overdose or hypoxic change to the target tissue. Additional shielding might be necessary over the eyes, inside the lip, or in the nasal cavity with appropriate lead thickness and paraffin (or other bolus material). Currently, most users are relying on hand calculation or a library plan for the dose distribution for the Leipzig™ and Valencia™ applicators, a phantom generated plan for these applicators, that does not use CT data.

In interstitial BT and surface moulds, CT imaging is the recommended standard for reconstruction of catheters and the target area, using CT wire markers with minimal distortion to define the target at surface. The CT images should be contiguous and no more than 2-mm thick in the axial plane for good target and catheter reconstruction. High-resolution US systems with frequency transducers preferably higher than 18 MHz are recommended for cutaneous lesions as they provide better detail of the skin surface, but there is some uncertainty for tumours smaller than 3 mm. Dermoscopy can detect more accurately the lateral borders in BCCs than clinical examination alone [82].

Table 1
Results of Brachytherapy in keloids.

Author	Year	N. lesions	Dose rate	Dose × fractions	Prescription	Total dose	Start session	Follow up (months)	Local control
Escarment P et al. [68]	1993	570	LDR	–	5 mm	20 Gy	<24 h	82 months	79%
Arnault JP et al. [69]	2009	55	LDR	–	5 mm	18 Gy	Within 7 h	84 months	76.4%
De Cicco L et al. [70]	2014	46	LDR	–		16 Gy	<24 h		69.6%
		50	HDR	4Gy × 3		12 Gy			62%
Guix B et al. [71]	2001	147 periop 22 radical	HDR	5 Gy × 4 5 Gy × 6	4 mm	20 Gy 30 Gy	Within 1 h, 3times a day	84	96.6% 86.4%
Garg MK et al. [72]	2004	17 recurrences after RT	HDR	5 Gy × 3	10 mm	15 Gy	<24 h Twice a day	26	88%
Veen RE et al. [73]	2007	9 38 7	HDR	4 Gy + 3 Gy × 2 6 Gy + 4 Gy × 2 6 Gy × 3		10 Gy 14 Gy 18 Gy	Within 6 h		55% 97% 100%
Arneja JS et al. [74]	2008	25 ear	HDR	5 Gy × 3	3–6 mm	15 Gy	<24 h Twice a day	36	92%
VanLeeuwen MC et al. [75]	2014	67	HDR	6 Gy × 2		12 Gy	Within 4 h and 24 h	33	96.9%
Jiang P et al. [76]	2016	32	HDR	6 Gy × 3	5 mm	18 Gy	<24 h Twice a day	29	94%
Hafkamp CJ et al. [77]	2017	29	HDR	13 Gy × 1		13 Gy	<24 h	53	75.9%

Recommended margins for prescription in NMSC (CTV):

- BCC 5mm margin for well defined lesions, 7–10mm margin for poorly defined, large, infiltrative, morphoeic and/or sclerotic types of BCC.
- SCC at least 10mm margin, if the lesion is <20mm it is necessary to add a margin of 10–15mm, for lesions >20mm the margin of 15–20mm is usually required (NCCN squamous cells cancer guidelines 2016 version 1).
- Merkel cell carcinoma: at least 20–30mm peripheral margin, deep margin at least 5–10mm below visible extension (by imaging).
- Post-operative cases: whole surgical site to be included. Peripheral and deep margins as per histopathology report from surgery.
- An extra margin is needed (PTV) to account for any misalignment for radionuclide and electronic based shielded applicators and for flaps.

Brachytherapy doses and fractionation

With LDR the prescribed dose was 60 Gy at the 85% reference isodose, covering the minimum target dose (peripheral dose), at dose rates between 45–70 cGy/h to be delivered in 4–6 days. Although doses up to 70 Gy were given in some large tumours, without unacceptable sequelae, the increase in cosmetic damage was greater than the gain in local control expected from a dose increase above 60 Gy. With PDR similar doses to LDR are recommended. With interstitial HDR BT, high dose per fraction is used, twice a day, separated at least 6 h between fractions. With PDR similar doses are recommended. In case of PDR/HDR because the SSDS system, the reference isodose is 90%. Depending on the volume to be treated and the organs at risk, the chosen dose per fraction is between 2.5 and 4 Gy, in order to finish the treatment in one–two weeks.

When using contact BT, the schedule is similar to electron beam, and 3–5 Gy per fraction 2–3 days per week in 4–5 weeks is effective [16]. In large areas such as scalp, 2–3 Gy per day fractionation is preferable [83–85]. In small epithelial tumours, 5–7 Gy per fraction 2–3 days per week can be recommended [4]. For old and fragile patients, higher doses per fraction, 9–10 Gy but only once a week have been used, even a single dose of 20 Gy. With skin surface applicators the chosen dose is 5 Gy × 8 fractions or 7 Gy × 6 fractions twice a week [41]. In cases of very thin skin or with underlying cartilage, such as the nose, lower doses per fraction probably allow better cosmetic long-term results [28]. No clear recommendations can be made due to the great variety of published schedules and the prescribed dose is based more on experience than on evidence [86,87]. The total dose depends on the chosen dose per fraction. Some extra fraction can be added with gross tumour, or can be reduced in postoperative indications. Commonly used regimens are presented in Table 2.

It has been proposed to express these doses in Biological Equivalent Dose (BED), but the total time of treatment is variable, therefore BED is not a useful tool to compare different duration schemes, but in interstitial treatments. Take into account that in surface treatments, the doses to the skin surface are always higher than the prescribed dose, and they can change depending on the bolus width and the depth of prescription. If the dose gradient is considered, the biological effect is still higher [88]. A study of these vari-

ables is mandatory to achieve a consensus on the ideal doses required in skin surface BT. Meanwhile the dose on the skin surface should be recorded to correlate the outcome with late side effects.

- Recommended BT schedules for surface moulds and flaps:
 - o 3Gy per fraction, 17–18 fractions, 3 times a week, total dose 51–54Gy.
 - o 4Gy per fraction, 10–12 fractions, 3 times a week, total dose 40–48Gy.
 - o 5Gy per fraction, 10–12 fractions, twice a week, total dose 50–60Gy.
 - o 5Gy per fraction, 8 fractions, twice a day, daily, total dose 40Gy.
 - o Higher doses per fraction, once a week.
- For Leipzig applicator
 - o 3Gy per fraction, 17–18 fractions, 3 times a week, total dose 51–54Gy.
 - o 5Gy per fraction, 8 fractions, twice a week, total dose 40 Gy.
 - o 10Gy per fraction, 3 fractions, once a week, total dose 30 Gy.
- For Valencia, Esteya and Xoft applicator
 - o 7Gy per fraction, 6 fractions, twice a week, total dose 42 Gy.
 - o 5Gy per fraction, 8–10 fractions twice a week, total dose 40–50Gy.

Conclusions

- (a) Available data confirm that brachytherapy is an efficient and well tolerated treatment that offers excellent cosmesis and low toxicity for skin cancer patients. Variety of available skin BT schedules offers options of shorter overall length of the treatment, with better patient compliance, particularly in the elderly group, the vast majority of patients treated with skin BT.
- (b) Carefully tailored BT is a good alternative, if not the treatment of choice for those lesions that cannot be safely removed by surgery.
- (c) The majority of publications in the field of skin BT is single institution and involves a relatively small number of patients. Despite very promising results, randomized controlled trials, systemic reviews and meta-analysis are lacking in literature.
- (d) HDR and PDR can be used in interstitial implants twice daily, usually 2.5–4 Gy per fraction, or 0.8–1 Gy per pulse in PDR technique.
- (e) In skin tumours with a depth of <5 mm, non-invasive contact BT through flaps, moulds, superficial radionuclide or electronic based shielded applicators without anaesthesia are effective.
- (f) In small size tumours, Leipzig™, Valencia™ applicators or electronic devices yield excellent results with high doses per fraction (5–7 Gy) delivered once or twice a week.
- (g) In extensive flat lesions, flaps or customized moulds with embedded or taped plastic tubes at a distance from skin of at least 3–5 mm to avoid overdose on the skin, can be used at 3–5 Gy per fraction daily or every other day.

Table 2
Different effective doses and fractionation for superficial brachytherapy.

Author	Year	N. patients	N. Fractions	Dose per fraction	Total dose	Days per week	Fractions per day	Prescription	Applicator
Svoboda et al. [14]	1995	130	1	20 Gy	20 Gy	1	1	Surface	Mould
			3	9–10 Gy	27–30 Gy	1	1	Surface	Mould
			10	4 Gy	40 Gy	5	1	Surface	Mould
Guix et al. [17]	2000	136	33–36	1.8 Gy	59.4–64.8 Gy	5	1	5 mm	Mould
Skowronek et al. [18]	2005	179	5	10 Gy	50 Gy	1	1	5 mm	Mould/flap
			12	5 Gy	60 Gy	2	1	5 mm	Mould/flap
			11 or 12	4 Gy	44–48 Gy	3	1	3 mm	Mould/flap
Maroñas et al. [19]	2011	51	18	3 Gy	54 Gy	3	1	3 mm	Mould
			5	7 Gy	35 Gy	2	1	3 mm	Mould
			17	3 Gy	51 Gy	3	1	5 mm	Mould
Arenas et al. [28]	2015	13	8	5–5.5 Gy	40–44 Gy	5	2	2–3 mm	Mould
Allan et al. [53]	1998	28	8	4.7–5 Gy	37.6–40 Gy	4	2	5 mm	Mould
Rembielak	Unpublished data		8	4.7–5 Gy	37.6–40 Gy	4	2	5 mm	Mould
Arenas et al. [28]	2015	101	15–19	3 Gy	45–57 Gy	3	1	3–5 mm	Leipzig
Köhler-Brock et al. [26]	1999	520	8	5 Gy	40 Gy	2	1	6–8 mm	Leipzig
			3	10 Gy	30 Gy	1	1	6–8 mm	Leipzig
			8	5 Gy	40 Gy	2	1	Variable	Leipzig
Ghaly et al. [35]	2008	67	8	5 Gy	40 Gy	2	1	Variable	Leipzig
Gauden et al. [27]	2013	236	12	3 Gy	36 Gy	5	1	3–4 mm	Leipzig
Tormo et al. [33]	2014	78	6–7	6–7 Gy	42 Gy	2	1	3–4 mm	Valencia
Delishaj et al. [34]	2015	84	8	5 Gy	40 Gy	2 or 3	1	3–4 mm	Valencia

(h) No standard schedule can be recommended and total doses are based on experience. The dose on the skin surface should be recorded to correlate the outcome with late side effects.

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Conflict of interest

The authors declare that they have no competing interests.

None of the authors has any financial and personal relationships with other people or organisations that could inappropriately influence (bias) of this work.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.radonc.2018.01.013>.

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