

ABS Consensus Statement

The American Brachytherapy society consensus statement for skin brachytherapy

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ABSTRACT

PURPOSE: Keratinocyte carcinoma (KC, previously nonmelanoma skin cancer) represents the most common cancer worldwide. While surgical treatment is commonly utilized, various radiation therapy techniques are available including external beam and brachytherapy. As such, the American Brachytherapy Society has created an updated consensus statement regarding the use of brachytherapy in the treatment of KCs.

METHODS: Physicians and physicists with expertise in skin cancer and brachytherapy created a consensus statement for appropriate patient selection, data, dosimetry, and utilization of skin brachytherapy and techniques based on a literature search and clinical experience.

RESULTS: Guidelines for patient selection, evaluation, and dose/fractionation schedules to optimize outcomes for patients with KC undergoing brachytherapy are presented. Studies of electronic brachytherapy are emerging, although limited long-term data or comparative data are available. Radionuclide-based brachytherapy represents an appropriate option for patients with small KCs with multiple techniques available.

CONCLUSIONS: Skin brachytherapy represents a standard of care option for appropriately selected patients with KC. Radionuclide-based brachytherapy represents a well-established technique; however, the current recommendation is that electronic brachytherapy be used for KC on prospective clinical trial or registry because of a paucity of mature data. © 2020 American Brachytherapy Society. Published by Elsevier Inc. All rights reserved.

Key Words:

Radiation therapy; Skin cancer; Brachytherapy; Electronic brachytherapy; Keratinocyte carcinoma; Basal cell carcinoma; Cutaneous squamous cell carcinoma

Introduction

Keratinocyte carcinoma (KC, previously nonmelanoma skin cancer) consists of basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC) and represents the most common form of cancer, affecting more than three million people annually in the United States alone (1). In addition, the number of cases diagnosed annually continues to grow (2). Despite low rates of mortality relative to other cancers, KC represents a significant source of morbidity and also represents a huge economic burden (3). Patients

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diagnosed with KC have a multitude of treatment options including surgical and nonsurgical approaches such as electrodesiccation and curettage, excision, Mohs micrographic surgery, systemic and topical drug therapy, as well as radiation therapy, with the common goal of achieving durable disease control while preserving function and cosmesis.

With respect to radiation therapy, multiple techniques are available including external beam (teletherapy) using particles (electrons) or photons (superficial, orthovoltage, or megavoltage) as well as brachytherapy (BT) (radionuclide or electronic). Recently, electronic brachytherapy (EB) has emerged as a treatment technique for multiple cancers including KC (4). Over the past decade, there has been a rapid increase in the use of EB for the treatment of KC with concerns raised about the lack of adequate safety and efficacy data, long-term outcomes, and appropriate comparisons with traditional treatment techniques (5,6). This was framed across the backdrop of rapidly increasing use of billing codes for EB and led to recommendations by national organizations to modify treatment codes associated with EB (5,6). Previously, the American Brachytherapy Society (ABS) has presented guidelines regarding skin BT (7). In light of the growing use of EB, and limited guidelines available, we present an updated consensus statement regarding skin BT focusing on EB separately from radionuclide-based BT while providing guidelines for patient evaluation, treatment selection, dosimetry, dose/fractionation, and technique.

Methods

The ABS Board of Directors appointed a group of physicians and physicists with expertise in skin cancer to provide a consensus statement on skin BT. The goals of the project were to provide a summary review of the technique and dose/fractionation as well as clinical recommendations regarding workup, indications, target delineation, dosimetry, and quality assurance. A review of the literature was performed, with a focus on clinical trials, prospective studies, meta-analyses, multi-institutional series, as well as single institution reports published after the previous consensus guideline addressing clinical outcomes and toxicities with BT or EB. Guidelines/clinical recommendations were drafted and consensus among the authors was obtained, with points of disagreement noted in text. Before publication, the consensus statement was approved by the ABS Board of Directors.

Results

Patient evaluation

Patient evaluation incorporates (1) patient history, (2) clinical examination, and (3) histopathology examination.

Patient history

This should include evaluation of symptoms, which may suggest a greater extent of disease than appreciated on physical examination. For example, neurologic symptoms such as pain, paresthesia, pruritis, or formication may suggest the presence of perineural spread, which warrants further evaluation and an alternative to BT. In addition, symptoms of regional lymphatic spread should be assessed. The presence of other medical conditions should be ascertained, such as the presence of significant comorbidities that obviate the need for treatment of low-risk KC, the presence of immunosuppression (which is associated with worse outcomes) (8), the presence of other skin cancers and how they were treated (including prior radiotherapy), as well as for the presence of conditions which could heighten radiosensitivity (active collagen vascular disease, ataxia-telangiectasia mutants, xeroderma pigmentosa, basal cell nevus syndrome).

Clinical examination

The ability to delineate the borders of the tumor is critical. If the boundaries or location of the tumor are unclear, consultation with a dermatologist is recommended, and additional biopsies may be required. The tumor should be measured accurately and photographic documentation of the tumor before and after treatment is strongly suggested. Careful palpation of the tumor and movement relative to deeper tissues is recommended to assess for extent of tumor. Examination of the regional lymphatics and nerves are recommended for cancers with the propensity for perineural or lymphatic spread. The geometry of the tumor and the skin surface being targeted should be noted for appropriate applicator selection and placement.

Histopathologic examination

The tumor to be treated should be biopsied to confirm diagnosis, which defines natural history and extent of subclinical spread. This in turn aids in the target delineation process as it provides information regarding the type and subtype of KC (9,10).

Staging and workup

KC that is considered for BT is typically a small tumor with limited ability to spread to regional lymphatics, nerves, or distant sites. As such, staging workup is typically clinical and cross-sectional imaging is not advised unless high-risk features or more extensive disease is present; multiple options are available for identifying patients with a high risk of local recurrence or metastases including the National Cancer Comprehensive Network criteria (immunosuppression, prior RT/chronic inflammatory process, rapidly growing tumor, neurologic symptoms, recurrent disease, poorly defined borders, Area H [“mask areas of face”, genitalia, hands, and feet] regardless of size, Area M [cheeks, forehead, scalp, neck, and pretibial])

site ≥ 1 cm, Area L [trunk and extremities] site ≥ 2 cm, poorly differentiated, > 6 mm depth [may not be identified on clinical examination alone] or invasion beyond subcutaneous fat, perineural/lymphatic, vascular involvement) or alternatively other clinical criteria can be used (e.g. recurrent cancers, tumors >2 cm, > 6 mm depth of invasion, PNI, LVSI) (11–14). With respect to the primary tumor, imaging is not mandatory for cases considered for BT but can be considered on a case-by-case basis (e.g. more extensive cases where flaps or interstitial BT are utilized) (7). Of note, the eighth edition of the American Joint Committee on Cancer (AJCC) staging only stages head and neck cutaneous squamous cell carcinoma. The Union for International Cancer Control system provides parameters to stage keratinocyte carcinomas not covered by the AJCC (15). Although not mandatory, it is recommended that primary skin cancers are clinically staged (16).

General patient selection

Although surgery is often the primary treatment for KC, radiation therapy (including BT) can be considered in appropriate cases including those patients who are not surgical candidates or where surgery may not be preferred because of morbidity, functional loss, or cosmetic outcomes. Consistent with recent ASTRO guidelines, the recommendation is based on clinical consensus for definitive radiation in patients with KC who cannot or are unwilling to undergo surgery (17). BT may be particularly advantageous for patients with medical comorbidities, those who wish to avoid surgery, and in locations where excision will impact functional or cosmetic outcomes. The role of adjuvant BT remains controversial. Among the authors, there was lack of uniform consensus about the appropriate use of adjuvant BT.

BT is usually contraindicated in patients with bone invasion, clinical perineural spread, deep extension beyond subcutaneous fat, or orbital involvement; however, interstitial BT can be used for medial canthus tumors and interstitial/flap BT has been used in cases with extensive disease. Intraoperative BT may also be valuable in select cases of advanced disease. All radiation therapy techniques are relatively contraindicated in patients with genetic conditions such as ataxia-telangiectasia, DNA repair conditions, poorly controlled connective tissue disease, and basal cell nevus disorder (18); xeroderma pigmentosa is not a contraindication to radiation therapy although concern exists regarding the potential to develop many KCs (17).

Electronic brachytherapy

Technique

EB has previously been discussed in the ABS Electronic Brachytherapy guidelines (4). In summary, EB is defined by the American Association of Physicists in Medicine (AAPM) task group (TG) 152 protocol as “a method of

radiation therapy using electrically generated x-rays to deliver a radiation dose at a distance of up to a few centimeters by intracavitary, intraluminal, or interstitial application, or by applications with the source in contact with the body surface or very close to the body surface (19).” Most EB units are high-dose-rate (HDR) and work in the 50–70 kVp range. Low kilovoltage x-ray sources require minimal shielding, allowing increased mobility and ease of use in clinics without dedicated shielded rooms (4,19,20); In addition, EB may provide more collimation as compared with HDR radionuclide brachytherapy (RB) (18–23). EB is not regulated by the Nuclear Regulatory Commission although local regulations may apply. However, concerns regarding EB include dose calculations in tissue, lack of consensus with respect to EB dosimetry and potential increase in relative biological effectiveness with low-energy photons exist; currently, work is underway to answer these questions and standardize dose calculations, but a clear consensus is not present at this time (22,24–27). An additional concern is that with the use of low-energy photons, there is limited ability to prescribe beyond a few millimeters because of rapidly increasing surface dose with increased prescription depth (4). EB can be prescribed to the surface of the applicator/device (although often prescribed at depth), limiting surface dose, but leading to lower doses at depth. Rivard *et al.* studied the dosimetric parameters of one EB source and quantified the dose reductions at depth for this low-energy device showing the fast dose gradient associated with such low-energy sources compared with traditional Ir-192-based HDR (26). When prescribing at depth with EB, surface doses rise rapidly as well. In addition, with low-energy x-rays, a loss of backscatter occurs when treating a lesion over bony structures, reducing the surface dose by up to 7% (28). Finally, EB has not been utilized in large randomized or prospective studies and as such there are limited evidence-based protocols for EB techniques including imaging, dosimetry, and quality assurance (4); however, the American College of Radiology and the ABS have previously published a guideline to assist with treatment planning and delivery with EB (20).

Currently, three commercially available EB units exist: Esteya (Elekta AB-Nucletron, Stockholm, Sweden), Axxent (Xoft, Inc., subsidiary of iCAD Inc., San Jose, CA), and Intrabeam (Carl Zeiss Surgical GmbH, Oberkochen, Germany) (4,29) (Table 1). The Elekta Esteya system is designed specifically for skin treatments and produces a 69.5 kV x-ray (1.6 mA current, decreased to 1.0 mA for fractions < 4 Gy and 0.5 mA for fractions < 2 Gy—setting selected based on dose and depth and to a marginal extent the cone used) with five applicators (10, 15, 20, 25, and 30 mm) and an aluminum flattening filter to provide a uniform dose distribution (dose profiles similar to the Valencia applicator) with a fixed end cap and a source to surface distance of 60 mm (22,23). The Xoft Axxent S700 system produces 50 kVp (approximately 0.3 mA beam current) Bremsstrahlung x-rays (mean energy 26.7 kV photons) with four circular cones

Table 1
Summary of electronic brachytherapy applicators

	Xoft (Axxent)	Esteya (Nucletron)	Intrabeam (flat)	Intrabeam (surface)
Voltage	50 kV	69.5 kV	50 kV	50 kV
Applicator sizes (mm)	10,20,35,50	10, 15, 20, 25, 30	10,20,30,40,50, 60	10,20,30,40
Dose rate (Gy/min)	0.73–1.72 (at surface)	3.76–4.07 (at surface)	0.4–3.15	1.1–5.65
Surface dose with 3 mm prescription	151.5%	124%	200–800% ^a (5 mm prescribed depth)	100% ^b (0.0 mm prescribed depth)
Source to surface (mm)	20.6–30.3 (applicator dependent)	60	9.5–25.5	9.5–21.5

^a For flat applicator users are instructed by manufacturer to prescribe to 5 mm depth. The maximum dose is at the edge of the applicator (ring at the periphery of the target). The smaller the applicator size the larger will be the maximum dose.

^b For surface applicator, users are instructed to prescribe to surface (0.0 mm). The maximum dose is at the center of the target.

(10, 20, 35, and 50 mm) with a built-in flattening filter to provide uniform dose at a depth of 2 mm (+/– 10%) and cutout shields (tungsten, 1.0 mm thickness) available to shape the field as well as a disposable end cap; the source to surface distance is 2 cm (23). The Carl Zeiss Intrabeam system offers two techniques to treat KC. Six flat applicators (10, 20, 30, 40, 50, and 60 mm) can be utilized with various thickness filters available to provide uniform dose distribution and different source to surface distances possible. In addition, four surface applicators (10, 20, 30, and 40 mm) can be used, providing higher dose rates due to thinner filters; an end cap is required as well (23). End caps are utilized to reduce electron contamination, provide firm and complete contact, and prevent tissue from entering the cone. For all techniques, it is essential to minimize air gaps (without compressing skin) to limit the risk of underdosing the target (approximately, 10% per mm) (23).

Dose/fractionation

At this time, there is limited prospective evaluation and comparison of different dose/fractionation schemes with EB in the management of KC (Table 2); as such definitive recommendations on dose/fractionation are not made. Of note, several studies have suggested a difference in radiosensitivity between BCC and SCC; however, many practitioners do not vary their dosing strategy by disease subtype (30). For patients with a BCC, dose/fractionation regimens should approximate a target EQD2-10 of 56 Gy or higher (30). For patients with cSCC, studies have demonstrated the need for higher doses and dose/fractionation regimens should approximate a target EQD2-10 of 65 Gy or higher (30). As an adjuvant treatment, an EQD2-10 of around 60 Gy is appropriate (17).

Commonly utilized fractionation choices include 42 Gy/6 fractions (7 Gy/fraction) delivered every other day or twice weekly, 42 Gy/7 fractions (6 Gy/fraction) delivered every other day or twice weekly, or 40 Gy/8 fractions (5 Gy/fraction) delivered every other day or twice weekly (7,17,21,23,31). Alternatively, more sensitive or larger areas can be treated at a lower dose per fraction with a larger number of fractions over a more protracted period (7,21–23,31).

Outcomes

The literature to date regarding EB has demonstrated low rates of recurrence and toxicity with short followup (31–39). A study from Ballester-Sanchez *et al.* compared dose/fractionation with EB with one group of 20 patients receiving 36.6 Gy in 6 fractions and the second group of 20 patients 42 Gy in 6 fractions. Higher complete response rates at 1 year were seen with the higher dose regimen

Table 2
Reported dose/fractionation regimens by treatment technique

Technique ^a	
Electronic brachytherapy	42 Gy/6 fractions
	42 Gy/7 fractions
	40 Gy/8 fractions
	Sensitive areas (e.g. face, lower extremity particularly anterior shin):
	40–50 Gy/8–10 fractions
	45–55 Gy/15–20 fractions
Radionuclide-based applicators	60–74 Gy/30–37 fractions
	42 Gy/6 fractions
	42 Gy/7 fractions
	40 Gy/8 fractions
	Sensitive areas:
	40–50 Gy/8–10 fractions
Molds/flaps	44–54 Gy/15–18 fractions
	40–50 Gy/10–12 fractions
	42 Gy/6 fractions
	42 Gy/7 fractions
	Sensitive Areas:
	60–70 Gy/30–35 fractions
	55 Gy/20 fractions
	40 Gy/10 fractions
	Postoperative:
	35–40 Gy/10 fractions
40 Gy–45 Gy/8–9 fractions	
Interstitial brachytherapy	42.5 Gy/17 fractions
	60 Gy/20 fractions
	30 Gy/10 fractions
	36–55 Gy/8–10 fractions
	Postoperative:
	30–50 Gy/9–10 fractions

BCC = basal cell carcinoma; cSCC = cutaneous squamous cell carcinoma.

^a For BCC, consider regimens with EQD2-10 of approximately 56 Gy, for cSCC, consider regimens with EQD2-10 of approximately 65 Gy.

Table 3
Target delineation by treatment technique and histology (by diameter)

Technique	
Electronic brachytherapy/radionuclide-based applicators	GTV = clinically and radiographically apparent tumor CTV: ^a BCC: Low-risk (nodular, superficial, pigmented, micronodular)/well defined: 5 mm Higher-risk (morpheaform, sclerosis, infiltrative, desmoplastic)/poorly defined: 5–10 mm cSCC: 7–20 mm (larger margins for larger tumors, moderate/poor differentiation, acantholytic, adenosquamous, desmoplastic). PTV: 2–5 mm to diameter, 1 mm for depth Depth: limit to 3–4 mm Postoperative: CTV ^a : 5–10 mm on scar PTV: 2–5 mm
Molds/flaps	Similar to surface applicators, depth up to 5 mm
Interstitial brachytherapy	GTV = clinically and radiographically apparent tumor CTV ^a = GTV +10 mm CTV = PTV Can prescribe deeper than 5 mm

GTV = gross tumor volume, CTV = clinical target volume, PTV = planning target volume, BCC = basal cell carcinoma, cSCC = cutaneous squamous cell carcinoma.

^a Larger volumes may be required as clinically indicated.

(95% vs 90%) with no differences in acute toxicity or cosmetic outcomes (35). Recent studies have attempted to compare outcomes with EB to traditional treatment techniques in the management of KC. A matched pair cohort study evaluated EB as compared with Mohs surgery (n = 188 EB, n = 181 Mohs); with greater than 3-year followup, no difference in recurrence rates were noted. However, there are limitations to this study; it should be noted that this was a lower-risk cohort with a median age of 81 years with the EB cohort having 25% of cases <1 cm, and nearly half *in situ* cancers (as compared with roughly 1/3 in the Mohs cohort). In addition, the impact of age on outcomes was not evaluated in this study (39).

In summary, while emerging data have reported early outcomes of EB, limited data are available comparing EB with traditional radiation therapy techniques (electrons, superficial/orthovoltage, HDR BT) or surgery (4). In addition, studies with EB lack mature followup further limiting the ability to present long-term comparative outcomes to patients (40). Although data from older techniques such as superficial/orthovoltage x-rays have been used to extrapolate to EB, prospective studies with EB with mature followup are needed.

Target delineation and dosimetric guidelines

Before treatment planning, it is important that patients undergo clinical assessment including consideration for immobilization devices as needed to ensure accurate positioning and to limit patient motion. When considering clinical target volumes, it is important to consider necessary surgical margins to achieve complete excision by histology for low-risk SCC and BCC; previous data have demonstrated for patients with SCC, 4 mm surgical margins are

ideal for excision with larger margins (e.g. 6 mm) for larger tumors, high-grade tumors, high-risk locations, and tumors with deeper extension (9). Similarly, for patients with BCC, surgical margins of 4 mm are recommended for tumors less than 2 cm (10,41).

With respect to target delineation, the gross tumor volume (GTV) should be clearly delineated (Table 3, diameter based). For patients with SCC, the GTV should be expanded 0.7–2.0 cm for tumors to define the clinical target volume (CTV); larger margins can be considered for larger tumors, moderate/poor differentiation, as well as those patients with acantholytic, adenosquamous, or desmoplastic features (7,11,23). For patients with low-risk (nodular, superficial, pigmented, micronodular) BCC and clearly defined borders, a margin of 0.5 cm can be utilized while high-risk (morpheaform, sclerosing, infiltrative, desmoplastic) or poorly defined BCC should have larger margins of 0.5–1.0 cm to define the CTV; of note, while these represent recommendations, clinical evaluation may warrant larger CTV expansions based on clinical factors (e.g. larger tumors) (12,23). Depth of the tumor should be ascertained by a combination of physical examination and imaging when available; a CTV expansion of 0.1 cm in depth for imaging uncertainty can be considered. In addition, a margin of 0.2–0.5 cm should be added to create a planning target volume (PTV) to provide setup margin, accounting for daily set-up variation. PTV is added with these applicators in light of possible set-up error/motion, not frequently seen with many other forms of BT. Smaller margins can be considered in cosmetically sensitive areas or in cases where these expansions may result in unacceptable normal tissue toxicity risk. When delivering treatment postoperatively, a 0.5–1.0 cm expansion on the scar should be performed to

define the CTV (larger expansions may be utilized based on clinical situation) with a 0.2–0.5 cm PTV expansion.

The generation of EB treatment time calculations is based on published depth dose data and profiles provided, with CT simulation rarely performed in these cases. With Xofig treatment, assurance of the source to skin distance is important and should be verified. Esteya treatments have a fixed source to surface distance. Previously, dosimetric guidelines have been published; in summary, dosimetry should ensure when clinically appropriate that the prescription (i.e. 100% isodose line) encapsulates the target (PTV) while limiting surface dose, ideally less than 150% (7). One concern with EB as compared with RB is that the maximum prescription dose is most commonly less than 5 mm to avoid high surface doses (7); most commonly, a depth of 3 mm is chosen which results in a surface dose of 124–152% when using a 2 cm applicator, for example. Owing to surface dose limitations with EB, imaging can be utilized to assess tumor depth, ensuring appropriately selected patients receive EB (23,42–44). At this time, it is not recommended to treat tumors with a depth greater than 3–4 mm with EB due to surface dose concerns (23).

Quality assurance

With respect to treatment quality assurance, EB treatment time calculations should be generated by a qualified medical physicist or trained BT dosimetrist with approval by the radiation oncologist (authorized user) before treatment delivery. In addition, all treatment plans and calculations should be independently checked before treatment. Treatment prescription should be complete and signed before treatment initiation and include treatment site, total dose, dose per fractionation, treatment schedule, treatment depth, modality/energy (EB), applicator type/size, previous treatment, critical organs/dose constraints. With respect to reporting, documentation should include EB technique, applicator type and size, shielding, tumor type and treatment site, documentation of GTV/CTV/PTV, prescription including depth, dose per fraction and schedule, output factor with applicators, air kerma strength (including kV and dose rate), skin surface dose, and dose to organs at risk. Photograph of the tumor and applicator setup should be taken for reproducibility at time of initial planning. Special care should be taken to correctly identify the lesion to be treated when multiple lesions are present, and when treating body sites with little identifying features (e.g. back or extremities). Positioning of the applicator should be verified before each fraction by the authorized user with marks placed at the outer limit of the applicator at simulation for verification with the applicator in place for treatment. Treatments should be performed with the authorized user and qualified medical physicist in attendance.

At this time, recommendations are available for quality assurance including the previously published ACR/ABS guideline which highlights the need for a qualified medical physicist to perform quality assurance measures including determination of applicator specific dose rate (7,45,46).

Centers performing skin EB should have a program in place to ensure safety and consistency of treatment with guidelines previously published (19,45). A qualified medical physicist should perform quality assurance including controller-specific functionality, safety interlock tests (initially and with repair), timer accuracy, beam stability, and reproducibility, and assurance of dosimetric data (19,47). With respect to individual applicators, different quality assurance protocols are recommended (45). Documentation of initial as well as periodic quality assurance testing should be done. Daily checks of the applicator integrity and device/facility interlock should also be performed.

Patient selection and clinical recommendations

Patient selection for EB with KC includes superficial tumors less than 2 cm in diameter (as most patients treated to date had tumors less than 2 cm) and less than 0.4 cm in depth on regular surfaces in patients unwilling or unable to undergo surgical procedures or in cosmetically sensitive areas of the body (23). Contraindications include those noted in the general patient selection section as well as larger, infiltrative, or deeper tumors and tumors that cannot be appropriately targeted with EB.

Clinical recommendation. Consistent with the ABS EB guideline, EB is recommended to be used for KC on a prospective clinical trial or registry at this time because of lack of mature data and comparative data with traditional radiotherapy techniques, as well as concerns regarding the ability to extrapolate data from traditional BT to EB (4). It is recommended that prospective studies with mature followup be performed to provide a better understanding of the outcomes as well as acute and chronic toxicity profiles with EB.

Radionuclide brachytherapy

Techniques

RB predominantly consists of iridium-192-based treatments with an energy of 380 kV; RB techniques include radionuclide-based applicators (Leipzig and Valencia), flaps and custom molds, and interstitial BT. Guidelines for treatment are based on the AAPM TGs 40, 43, and 56 (25,48,49). Radionuclide-based applicators are made of a small high-z material, shielded devices with a single dwell position at the vertex, with fixed geometry and short source to skin distances. The Leipzig applicator is a shielded applicator (10, 20, 30 mm) with a plastic cap (to minimize electron contamination) and can be placed such that the source is parallel or perpendicular to the skin surface with standardized dosimetry available (50–52). Caps must be used and care should be taken to ensure the correct source to skin distance. The Valencia applicator (20, 30 mm) was developed more recently with the goal of improved dose flatness through the use of a flattening filter (though this does increase treatment time) and is also used with a cap (53,54). Caps must be used with these applicators to avoid significant overdose

at the skin surface due to electron contamination (55). Applicator setup must be evaluated at each fraction with selection of the appropriate size applicator to ensure that adequate margin around the tumor is present. Owing to high-dose gradients, small changes can lead to large dosimetric consequences. Full contact of the applicator with the skin surface is required (moderate pressure of the applicator to the surface is recommended to reduce air gaps) and monitored throughout treatment (often with in room television).

Beyond radionuclide-based applicators, alternative techniques to deliver RB exist including custom surface molds, which are customized to a patient's skin surface allowing them to be utilized on not flat surfaces (irregular, greater curvature) as an alternative to electrons (50,56–59); molds can be made of different materials (wax, rubber, silicone, thermoplastic material, 3D printed) and within them, catheters are laid in parallel, equidistant (<10 mm apart) with dwell positions a minimum of 2 mm, and ideally 5 mm from the skin surface (7,23,50). Guidelines for surface BT are provided by the AAPM TG 253 (60). Development of molds must minimize dose to organs at risk that may occur based on transit from the afterloader to the area of treatment (50). Alternatively, superficial techniques include mats with catheters and newer custom surface molds including use of the Harrison Anderson Mick applicator (Mick RadioNuclear Instruments, EZ Bebig), catheter flap (Varian Medical Systems), and Freiburg flaps (Nucletron). Catheters are placed 10 mm apart, 5 mm from skin surface attached to silicon spheres, which provide premade consistent devices (61–63). Larger, more irregular tumors can be treated using multiple molds/pieces or flaps for conformality with growing use of customized 3D-printed applicators. Finally, for tumors deeper than 5 mm, interstitial BT should be considered (64–67). Catheters can be placed in single or multiple planes based on the total thickness of the tumors. A single plane half way through is used for thickness of 1 cm or less. Catheters are placed approximately 10 mm apart and if more than one plane is used, approximately 10-mm spacing between planes should be used. Superficial catheters should ideally be placed 5 mm from the skin surface to limit superficial dose, which may result in toxicities (optimization performed to minimize hot spots at the skin surface) (7). The number of catheters and length of the implant is predicated on the size and shape of the tumor. When RB is used in cases such as eyelid tumor, it is recommended that internal shielding (i.e. eye shield) be utilized; with such cases, bolus or backscatter caps can be utilized to avoid backscatter; similarly, internal shielding can be used in other sites such as the ears, nose, and mouth (68).

Dose/fractionation

Multiple dose and fractionation regimens are available with recommendations based on technique used as well as location; as noted previously, limited prospective data are available comparing dose/fractionation schemes with

a survey of skin BT users finding significant heterogeneity in dose and fractionation with varying EQD2 range as well (69). A list of dose and fractionation schemes is presented in Table 2; definitive recommendations are not made because of a lack of comparison between regimens. Similar to EB, for patients with a BCC, regimens used should approximate an EQD2-10 of 56 Gy or higher (30). For patients with cSCC, higher doses are required with regimens recommended to have an EQD2-10 of 65 Gy or higher (30). As an adjuvant treatment after surgery, consider regimens with EQD2-10 of around 60 Gy (17). Based on location and organs at risk, a more protracted fractionation can be considered when anticipated morbidity with hypofractionated regimens may be high (50,70–72).

Radionuclide-based applicators. Similar to EB, common dose/fractionation regimens include 42 Gy/6 fractions (7 Gy/fraction) delivered every other day or twice weekly, 42 Gy/7 fractions (6 Gy/fraction) delivered every other day or twice weekly, or 40 Gy/8 fractions delivered every other day or twice weekly (7,50).

Molds/flaps. For treatment with flaps, dose/fractionation regimens include 40–50 Gy/10–12 fractions (5 Gy/fraction) delivered every other day or twice weekly or a shorter course of 42 Gy/6–7 fractions (6–7 Gy/fraction) delivered every other day or twice weekly. More protracted courses of 2–4 Gy daily can be considered with 30–35 fractions (2 Gy/fraction), 20 fractions (2.75 Gy/fraction), and 10 fractions (4 Gy/fraction) considered. Postoperatively, dose/fractionation regimens include 35–40 Gy/10 fractions (3.5–4 Gy/fraction) or 40–45 Gy/8–9 fractions (5 Gy/fraction) delivered twice weekly, 42.5 Gy/17 fractions (2.5 Gy/fraction) or 60 Gy/30 fractions (2 Gy/fraction) delivered daily, or 30 Gy/10 fractions delivered twice daily (Table 2) (7,50).

Interstitial brachytherapy. Dose/fractionation regimens include a range from 36 to 55 Gy/8–10 fractions (3–5.5 Gy/fraction) delivered twice daily for definitive treatment (7,50,72). Postoperatively, dose/fractionation regimens are 30–50 Gy/9–10 fractions (3–5 Gy/fraction) delivered twice daily (7,43).

Outcomes

Multiple series have been published evaluating BT in the treatment of KC, demonstrating local control rates of more than 95% at 5 years with limited toxicity and good cosmetic outcomes with varying techniques being utilized for more than 50 years (59,65–67,73–91). Beyond cumulative data, multiple series have been performed evaluating BT at specific clinical sites including the scalp, nasal skin, pinna, as well as the hands (57,64,66,67,78,80,81,92–100). Frakulli *et al.* performed a review of BT used for KC of the eyelid, demonstrating a median local control of 95% with low rates of toxicity and high rates of good cosmetic outcomes, which has been confirmed by additional series

(64,80,94,101). Overall, with respect to toxicity, a review from Delishaj *et al.* found low rates of grade 2+ acute and late toxicity with BT for KC (95). In addition, data are available across a wide range of patient age groups, demonstrating excellent outcomes (50,102).

Comparative data evaluating BT have been published. An older randomized single-center trial included 347 patients with BCC of the face who were randomized starting in 1982 to surgery or radiation therapy (55% interstitial BT, 33% contact therapy, and 12% conventional treatment). At 4 years, radiation was associated with an increased rate of local recurrence (7.5% vs 0.7%); when comparing radiation techniques (which were used at the discretion of the radiation oncologist, and not subject to randomization) the rate of recurrence was 8.8% with BT as compared with 6.6% with contact therapy and 5% with conventional radiation (103). Cosmetic outcomes were not compared between the radiotherapy modalities. However, Zaorsky *et al.* performed a meta-analysis evaluating BT as compared with EBRT. More than 10,000 patients (9,965 EBRT, 553 BT) with T1-2N0 BCC/cSCC were included with a minimum of 10 months of followup. With a median followup of 36 months, patients receiving BT had improved rates of “good” cosmesis with comparable local recurrence rates noted, although followup was short and the median age was 73 years old (104). A second meta-analysis from this group evaluated 9,729 cases of BCC/cSCC (9,255 EBRT, 474 BT) and found hypofractionated schedules led to good cosmetic outcomes, with less than 8% having poor cosmesis (70). Finally, a recent meta-analysis of more than 21,000 patients compared BT with surgery, Mohs, and EBRT. In patients with T1-2N0 skin cancer, BT and Mohs were associated with improved cosmetic outcomes as compared with EBRT or excision with similar local control at 1 year (105). It should be noted that patient and tumor characteristics were not balanced between arms; therefore, Mohs, excision, and EBRT remain more appropriate for aggressive, high-risk, and large tumors which are beyond what can be appropriately treated with BT.

Target delineation/dosimetric guidelines

Similar to EB, before target delineation and treatment planning, patients should undergo evaluation to determine positioning, with consideration for the need for immobilization devices. With respect to treatment planning, CT-based imaging is recommended for molds/flaps and interstitial BT to allow for catheter reconstruction (7). As noted in the EB section, target margins should consider surgical margins and risk of microscopic disease; margins are presented in Table 3 (9,10,41). With respect to target delineation, RB technique should be considered. For radionuclide applicators, please refer to the EB section on target delineation. For custom molds and flaps, it is recommended that the distance between catheters not exceed 10 mm, with at least 5 mm from the skin surface, with no bolus required. Catheters can be placed in an immobilization device.

Maximum prescription depth with molds and flaps is typically ≤ 5 mm (3–5 mm) (23). With interstitial implants, it is recommended that the distance between catheters be 8–12 mm and at least 5 mm from the skin surface (7,23); with use of iridium-192, bolus is not traditionally required but can consider placement between catheters. The CTV is a 1.0-cm expansion on the GTV. With interstitial implants, no expansion from CTV to PTV is required. Interstitial implants are required when prescribing to a depth greater than 5 mm.

For radionuclide-based applicators, hand calculations or standardized libraries are available to assist with generation of basic treatment plans, with standardized dose distributions provided by the manufacture (and confirmed by a medical physicist at the time of device commissioning); care should be taken to verify the source-to-indexer length before each treatment (7,106). With a single dwell position (Leipzig or Valencia applicators), the dose distribution cannot be optimized compared with other radionuclide-based applicators (flaps, molds) so treatment plans should ensure that the PTV is adequately covered by the prescription isodose line. Similar to EB, the maximum prescription depth with radionuclide-based applicators is 3–4 mm because of high surface dose with increased prescription depth (125–155% of prescription with 3 mm prescription depth); there is a lack of surface dose constraints for radionuclide-based applicators and as such these represent consensus recommendations from the group (7). As compared with 6 MeV electrons, RB provides a different dose distribution with higher surface doses (105–110% of prescription) than electrons and at 5 mm the dose falloff is much steeper with radionuclide-based applicators (10–12%/mm) providing 85% of prescription dose (normalized at 2 mm) as compared with 98% with electrons (50,59).

For molds, flaps, and interstitial implants, CT simulation is routinely performed. Treatment planning consists of activation of dwell points to provide coverage to the CTV/PTV, with catheters extending to the edge of target volumes to ensure adequate coverage of peripheral margins while limiting hot spots (minimize V_{150}). Optimization can be used with these cases to limit dose to critical structures with a skin maximum dose of 140% of prescription for molds and 125% for flaps; there is a lack of standardized constraints for these techniques and as such these represent consensus recommendations from the group. Plans should ensure that the 100% isodose line encompasses the PTV. With interstitial implants, care should be taken to minimize the V_{200} . When target volumes are in close proximity to bone, it should be recognized that target dose close to the interface may be lower than expected. Dose calculations should be based on TG-43 parameters (24,25). In general, the lack of backscatter for superficial treatments means that TG-43-based calculation may overestimate the dose delivered. Model-based dose calculation may be used to assess actual delivered dose. However, at this time, reported clinical outcomes and prescriptions are largely based on TG-43 water medium calculations (25).

RB treatment plans should be generated by a qualified medical physicist or trained BT dosimetrist with approval by the authorized user before treatment delivery. In addition, all treatment plans and calculations should be independently checked before treatment. For all superficial applicators, integrity should be checked, with output factor verified; positioning of applicator should be verified before each fraction by the authorized user with marks placed at the outer contour of the applicator at simulation for verification. Flatness/symmetry should be verified as should the location of the dwell point within the applicator. Care should be taken with respect to measuring and verifying catheter lengths and dwell positions for molds/flaps/interstitial cases. Treatment prescription should be complete and signed before treatment initiation; the items included are treatment site, total dose, dose per fractionation, treatment schedule, treatment depth, modality/energy, applicator type/size or number of catheters, previous treatment, and critical organs/dose constraints. With respect to reporting, documentation should include RB technique, applicator type and size when applicable, shielding, tumor type and treatment site, documentation of GTV/CTV/PTV, prescription including depth, dose per fraction and schedule, dwell points, source indexer length, output factor with applicators, air kerma strength, skin surface dose, and dose to organs at risk. Before treatment, confirmation that catheters are properly connected should occur. When initiating treatment, transit dose (dose received as source moves) from the afterloader, through the transfer tubes, to the applicator should be minimized by ensuring that transfer tubes are further away from any patient surface (elevated with use of pillow etc.) and placed over the shortest skin distance possible excluding organ at risk structures. During treatment, emergency precautions should always be available. Treatments should be performed with a board-certified radiation oncologist who is an authorized user as well as a qualified medical physicist.

Quality assurance

Quality assurance protocols are available for individual radionuclide-based applicators as well as for mold/flaps/interstitial implants; in summary, it is recommended that applicators be commissioned and have consistent checks performed to confirm that the applicator is functioning properly (physically intact, output, depth doses, flatness/symmetry, source to indexer distance, treatment times, treatment planning system) (7,51,52,54). Centers performing skin RB should have a program in place to ensure safety and consistency, guidelines previously published (7). A qualified medical physicist should perform quality assurance including controller-specific functionality, safety interlock tests (initially and with repair), timer accuracy, beam stability, and reproducibility, and assurance of dosimetry data. With respect to individual applicators, different quality assurance protocols are recommended (19,47,48). For molds/flaps, the qualified medical physicist should

perform end-to-end testing with a phantom. Documentation of initial (including commissioning of flaps/molds) as well as periodic quality assurance testing should occur. Daily checks of the applicator integrity and device/ interlock should occur.

Patient selection and clinical recommendations

Patient selection for RB is dependent on the technique chosen. For radionuclide-based applicators, treatment should be limited to superficial tumors less than 2 cm on regular surfaces. Molds/flaps can be considered for deeper tumors (up to 5 mm) and can be used on irregular surfaces or curved surfaces more easily. Tumors more extensive or deeper than 5 mm should be considered for interstitial BT or EBRT. Contraindications with RB include those noted in the patient selection section as well as larger tumors that cannot be adequately targeted.

Clinical recommendation. RB can be considered for patients with T1-2N0M0 KC (AJCC or UICC eighth edition) when able to meet dosimetric constraints. Technique should be based on tumor location, depth of invasion, and treatment volume required.

Conclusions

BT represents a standard of care treatment approach for appropriately selected patients with early-stage KC. RB is a well-studied approach, which offers several techniques to choose from, allowing clinicians to base their choice on the extent of disease and anatomic considerations. EB represents a newer treatment technique; at this time, data are promising but further study is needed before utilization outside of prospective registries or clinical trials.

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