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Skin CanceR Brachytherapy vs External beam radiation therapy (SCRiBE) meta-analysis

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Abstract

Background and Purpose—To compare cosmesis and local recurrence (LR) of definitive external beam radiation therapy (EBRT) vs brachytherapy (BT) for indolent basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) of the skin.

Materials and Methods—Studies including patients with T1-2N0 SCCs/BCCs treated with definitive EBRT/BT and ≥10 months follow-up were analyzed. The primary endpoint was post-treatment cosmesis, categorized as "good," "fair," or "poor." The secondary endpoint was LR. Mixed effects regression models were used to estimate weighted linear relationships between biologically equivalent doses with $\alpha/\beta=3$ (BED_3) and cosmetic outcomes.

Results—A total of 9,965 patients received EBRT and 553 received BT across 24 studies. Mean age was 73 years, median follow-up was 36 months, and median dose was 45 Gy/10 fractions at 4.4 Gy/fraction. At BED_3 of 100 Gy, "good" cosmesis was more frequently observed in patients receiving BT, 95% (95% CI: 88-100%) vs 79% (95% CI: 60-82%), $p<0.05$. Similar results were found for "good" cosmesis at BED_3 >100 Gy. No difference in "poor" cosmesis was noted at any BED_3. LR was <7% for both at one year.

Conclusion—BT has favorable cosmesis over EBRT for skin SCCs/BCCs at common fractionation regimens. Prospective studies comparing EBRT vs BT are warranted.

Keywords

external beam radiation therapy; brachytherapy; skin cancer; basal cell carcinoma; squamous cell carcinoma; meta-analysis

INTRODUCTION

Non-melanoma skin cancer is the most commonly diagnosed malignancy in the US [1], and its incidence increases with age [2]. Among these cancers, basal cell carcinoma (BCC) makes up 75-80% of diagnoses and squamous cell carcinoma (SCC) makes up the majority of the remaining cases [3,4]. Most localized (i.e. T1-2 N0) BCCs and SCCs are destroyed

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locally (excised, desiccated, frozen); however, several factors may preclude surgical extirpation, including patient comorbidities, anticoagulant use, and tumor location near a critical organ (e.g. orbit). Thus, radiation therapy (RT) is an efficacious alternative for localized tumors [5,6].

There are two categories of radiotherapy used for skin BCCs/SCCs: (1) external beam radiotherapy (EBRT) and (2) brachytherapy (BT), which is typically delivered using either radionuclide like Ir-192 (termed radionuclide BT in this work), or a miniature x-ray source (termed electronic brachytherapy, eBT, in this work). Subtypes of EBRT and BT are juxtaposed in Table 1. Generally, eBT is categorized as a type of BT due to its name and because it resembles surface applicator-based BT [7]. However, unlike radionuclide-based BT, eBT involves treatment with miniaturized x-ray sources in the 50-100 kV range, without a radionuclide [8]. Thus, eBT shares more similarities with superficial kV x-rays used in EBRT.

In 2010, eBT was introduced to for the treatment of skin SCCs and BCCs, and there has been a 20-fold increase in its use from 2011 to 2013, most likely due to its higher reimbursement [9]. However, Current Procedural Terminology codes for eBT were modified in 2016 and have made the criteria for reimbursement more stringent and also less profitable so it remains to be seen if eBT will continue to gain a foothold in skin BCC and SCC treatment [10]. As of 2017, the National Comprehensive Cancer Network (NCCN) and the American Society of Radiation Oncology (ASTRO) discourage the use of eBT given the lack of evidence regarding its efficacy or toxicity [5,11].

Although the proponents of skin BT (particularly those using eBT) report excellent cosmesis and local recurrence rates at short median follow-up times [12], a formal comparison of BT vs EBRT has not been performed. A 2017 meta-analysis reported favorable cosmesis with various fractionation regimens [13], 50Gy/15 fractions, 36.75Gy/7 fractions, or 35Gy/5 fractions; however, EBRT and BT were not juxtaposed. The purposes of the current study are to compare the cosmetic outcomes (i.e. normal tissue complication probability) and local recurrence (i.e. tumor control probability) of EBRT and BT. The results will provide patients, physicians, and payors evidence regarding the safety and effectiveness of the modalities and facilitate the treatment decision making process.

METHODS AND MATERIALS

Evidence acquisition

The inclusion criteria for the literature search was defined using the Population, Intervention, Control, Outcome, Study Design (PICOS; Supplementary Table 1) approach [14]. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; Supplementary Figure 1) literature selection protocol was used for article selection. Further, the meta-analysis of Observational Studies in Epidemiology (MOOSE; Supplementary Table 2) were used [15]. Clinical trials, prospective studies, retrospective studies, and case reports published in English at any time up to January 31, 2017 were searched in PubMed and MEDLINE. Details are reported in Supplementary Text 1. Minimum follow-up time was set at 10 months to capture recurrences [16]. Levels of evidence were assigned to each included

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study based on Centre of Evidence Based Medicine (CEBM) criteria. This meta-analysis shares similar methods for evidence acquisition and statistical analysis with the previously published study on hypofractionated RT for T1-2 non-melanoma skin cancer [17]; however, inclusion criteria were expanded to capture studies with shorter follow-up and BT. Studies in eBT were excluded systematically due to limited long-term data; in the future, eBT may be included as its own category as more data become available.

Outcomes Measures

Cosmesis—The primary endpoint was cosmesis because local control is generally >90%; thus, most clinicians are more concerned about cosmesis than control, and the proponents of BT systems tout them as having improved cosmesis over EBRT [9]. We characterized cosmesis discretely in three categories: “good,” “fair,” and “poor.” Most studies reported the presence of moderate-severe toxicities, and these were coded as “poor” for the purposes of our analysis. Two studies reported “excellent” cosmesis, and this was coded as “good” [18,19]. The Radiation Therapy Oncology Group (RTOG) grading system (or an analogous system) was used in coding.

Follow-up time when cosmesis was evaluated was not routinely reported in studies. Cosmesis grades were marked for individual fractionation regimens of each study at the latest time of follow-up available. Cosmesis is expected to worsen over time, and this is important in interpreting the findings of studies with relatively short follow-up times. All data from studies were reviewed and discussed by three of the authors to maintain reporting accuracy.

Local recurrence (LR)—The secondary endpoint, LR, was defined per authors of individual studies. We chose to analyze LR because this is a major outcome of interest for patients being treated with RT, particularly when comparing technologies. Other outcomes (e.g. lymph node metastases, distant metastases) are uncommon in BCCs and superficial SCCs, unless patients are immunocompromised and/or recurrent. Thus, cancer specific mortality is also uncommon [20].

Statistical analysis

Calculation of the biologically equivalent dose (BED) is described in Supplementary Text 1 [21–25]. Weighted mixed effects regression models were used to estimate weighted linear relationships between BED_3s and the observed percentages of patients experiencing cosmetic outcomes, with 95% confidence intervals (CIs). In this analysis, BED_3 and cosmesis were plotted as continuous variables. To characterize cosmesis at fractionation regimens with different BED_3s that represented the gamut of the regimens used in the literature, we calculated the 95% confidence interval for cosmesis at each of three discrete values that represent this entire spectrum: BED_3 of 80 Gy, 100 Gy, and 120 Gy.

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RESULTS

Treatment characteristics, outcomes, and cosmesis of individual EBRT studies are listed in Table 2, and those of BT studies in Table 3. Table 4 lists cosmesis outcomes of BT vs EBRT at three dose levels that span the gamut of fractionations used.

Study characteristics

The meta-analysis included 10,518 patients (n) from 24 studies (N) [12,16,18,19,26–45]. The patients were treated from year 1985 to 2016. There were 9,965 patients treated with definitive EBRT [16,26–42] and 553 treated with BT [12,18,19,43–45]. Only one study was prospective [16]. The studies were from the United States [31,33,34], United Kingdom [30,32,43,44], France [26,42], Germany [36], Italy [12,28,29,35], Australia [18,27], Spain [19,39,45], Canada [37,38], the Netherlands [40], and Switzerland [41]. Overall, patient follow up times ranged from 12-77, median 36 months. For EBRT, median follow-up was 36 months (range: 18-77); for BT, median follow-up was 30 months (range: 10-66). The median patient age range was 73 years (range: 62-84). For EBRT, median age was 74 years (range: 62-81), and for BT, median age was 74 years (range: 67-84). The vast majority of studies included patients with T1-2 BCCs/SCCs, only 4 studies included tumors >T2 (60 patients total) [16,29,36,44]. No study focused on very elderly (>80 years) or immunocompromised patients.

Median dose among all studies was 45 Gy/10 fractions (interquartile range [IQR]: 36 Gy/5 fractions-55 Gy/17 fractions) at 4.4 Gy/fraction (IQR: 3 – 7 Gy); the most hypofractionated was 22.5 Gy/1 fraction using EBRT [30]. For EBRT, median dose was 45 Gy/12 fractions (interquartile range [IQR]: 36 Gy/6 fractions-55 Gy/19 fractions) and mean BED_3 was 112 Gy (range: 60-191 Gy). For BT, the median dose was 41 Gy/9 fractions (interquartile range [IQR]: 31.5 Gy/5 fractions-49 Gy/12 fractions) and mean BED_3 was 109 Gy (range: 60-153 Gy).

Cosmesis

There were 3,399 patients whose long-term cosmesis was evaluated, 2,945 of whom received EBRT and 454 of whom received BT. The majority of patients in both EBRT and BT groups had “good” cosmetic outcome for any fractionation regimen included in the meta-analysis: the median % of patients with “good” cosmesis was 95% (IQR: 75% - 100%). The median % of patients with “fair” cosmesis was 1% (IQR: 0% - 15%). Notably, there were 675 patients treated to 30.6 Gy in 10.2 Gy/fraction in a single study; of these, 50% developed “fair” cosmesis with this very hypofractionated technique [26]. The median % of patients with “poor” cosmesis was 2% (IQR: 0% - 7%).

Cosmetic results from BEDs representative of the dose fractionation spectrum are shown in Table 4 and Figure 1. “Good” and “fair” cosmesis were similar at BED_3 of 80 Gy for BT and EBRT, as evidenced by the overlapping 95% CI regions. At BED_3 of 100 Gy, there was a slight benefit for BT over EBRT in terms of “good” cosmesis over “fair” cosmesis: 79% (95% CI: 60-82%) vs 95% (95% CI: 88-100%), $p<0.05$. At BED_3 of 120 Gy, “good”

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cosmesis was more frequently observed in patients receiving BT, and this difference was more pronounced: 68% (95% CI: 60-74%) vs 99% (95% CI: 90-100%), p<0.05.

Overall, with increasing BED_3, there was a decreasing frequency of "good" cosmesis for EBRT and increasing frequency of "fair" cosmesis. Percent change in cosmesis vs 10 Gy change in BED (slope) of the linear regression for "good" cosmesis in EBRT was -2.5%, p=0.121. Percent change in cosmesis vs 10 Gy change in BED of the linear regression for "good" cosmesis in BT was 2.8%, p=0.002. Slope of the linear regression for "fair" cosmesis in EBRT was 3.2%, p=0.068. Slope of the linear regression for "fair" cosmesis in BT was -1.7%, p=0.010. "Poor" cosmesis was noted in <10% of patients for EBRT and BT for any BED_3 (p>0.05).

The most common late toxicities noted were hyperpigmentation and telangiectasias. There were no reports of ulceration or necrosis. There were no Grade 4-5 toxicities or any surgical intervention necessary to correct late toxicity. There was no evidence of increased toxicity for higher doses or more hypofractionated schedules (Figure 1, **lower panel**).

Outcomes

Overall, LR was <7% for both EBRT and BT at one year; there was too few events to evaluate BT at a longer time point. The 1-year and 5-year LR percentages of individual studies, as well as cosmesis and fractionation regimens, are listed in Tables 2 **and** 3. The 1-year LR rate was typically <10% for any fractionation regimen. The 5-year LR rate was <20% for any fractionation regimen, and only one study using BT reported these long-term outcomes. The median 1 year LR rate was 2% (IQR: 1-5%) and the 5-year LR rate was 14% (IQR: 7-14%) for all fractionation regimens. For EBRT, the median 1 year and 5 year LR rates were 3% (IQR: 1-6%) and 14% (IQR 6-15%), respectively. For BT, the median 1 year and 5 year LR rates were 0% (IQR: 0-0%) and 2% (IQR: 2-2%), respectively.

DISCUSSION

EBRT and BT (historically delivered with Ir-192) are treatment options for BCCs and SCCs of the skin. eBT has had a dramatic increase in use since 2010, and the NCCN guidelines state that there is insufficient evidence for its use [5]. Despite the stance of the NCCN, no studies comparing the EBRT vs BT (with Ir-192 or eBT) have been published. We performed the first meta-analysis to compare cosmesis and tumor control of EBRT and BT. We found that the rate of "good" cosmesis is improved with BT over EBRT when using common fractionation regimens of 64 Gy/32 fractions, 55 Gy/20 fractions, 50 Gy/15 fractions, which are also endorsed by the NCCN [5]. Among fractionation regimens with higher dose, cosmesis appears to also be superior with BT.

EBRT has been available as a treatment option for indolent skin cancers not amenable to extirpation for longer than BT; thus, data supporting its use for BCC and SCC are more robust. As such, only 6% of patients from studies that met the inclusion criteria were treated with Ir-192 BT [12,18,19,43–45]. Despite this discrepancy, fractionation regimens and median follow-up times were similar between EBRT and BT studies. Three of six BT studies included in our meta-analysis reported median follow-up times of ≤12 months

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[12,19,44]. Other eBT studies in the studies that did not meet inclusion criteria for this analysis similarly had shorter follow-up times of 10 and 12 months [46,47].

Cancer recurrence rates were similar between EBRT and Ir-192 BT, although most of the included Ir-192 BT studies lacked 5-year LR. Recurrence for skin tumors is best captured when follow-up extends to 4 years [16]. Several studies using EBRT also report a 6-fold increase in LR at 5 years [16,27]. We encourage investigators of eBT to similarly report long-term outcomes of this new technology.

Overall, both EBRT and BT demonstrate similar “good” and “fair” cosmesis at low BED_3 of approximately 80 Gy. At higher BED_3 of 100 Gy, which encompasses most common definitive fractionation regimens, there is a significantly higher proportion of patients with “good” cosmesis with BT compared to EBRT, 95% (95% CI 88-100%) vs 79% (95% CI: 60-82%), as per Figure 1 and Table 4. Even a higher BED_3 of 120 Gy results in significant increase in “fair” cosmesis in patients treated with EBRT over BT.

This difference in “good” and “fair” cosmesis at common fractionation regimens may be attributable to a number of factors. First, there is patient selection that benefits BT. Given the higher reimbursement for BT [9,11], there may be a financial conflict of interest for studies mentioning name brands of the devices used. Further, it is expected that larger sized tumors would be preferentially treated with EBRT, specifically, electron therapy with bolus. Electron therapy would therefore require larger fields (e.g. 4x4 cm) to account for the beam penumbra and setup uncertainty. The idea of the small field is only relevant to an extremely small tumor, and is not applicable to larger tumors. Unfortunately, we are unable to differentiate T1 vs T2 tumors in this analysis. Further, the issues with penumbra and bolus do not apply to orthovoltage therapy and are a reason that it is favored as an EBRT modality to treat skin cancers. We are not able to differentiate electrons from orthovoltage therapy in the current analysis. BT does not have a large penumbra like electron therapy and would be expected to have less setup uncertainty. These differences likely contribute to some of the cosmesis benefits noted of BT over EBRT.

This work has other limitations. First, we based toxicity evaluations on clinician evaluations of patients, using a simple scoring system. Patient evaluation of their own cosmesis was taken into account in only one study [16]. In general, most acute reactions (e.g. erythema, edema, itch) resolve within 3 months; late reactions (e.g. fibrosis, ulceration, necrosis) start to develop after 3 months, with a rising incidence over time. Thus, cosmesis depends on the median follow-up time of each study. Intra- and inter-observer differences may be present. In some studies, assistants were able to help grade toxicity [16,40]. We also did not blindly evaluate photographs of the skin after treatment.

We did not evaluate ethnic subpopulations or patient-reported outcomes, which have been shown to be important in prostate and breast cancer [48–50]. We do not have comorbidity data of these patients; those with peripheral arterial disease and diabetes would be expected to have worse toxicity [51]. We strongly encourage future investigators to provide detailed reports of toxicities among their patients, and for basic scientists to identify biomarkers of RT toxicity [52].

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Additionally, despite the cosmesis benefits of BT at higher BED_3, few BT studies on non-melanoma skin cancer were found that met inclusion criteria (Table 1 **and** Table 3). The published experience with BT is lacking, and thus we performed the current meta-analysis. There are currently no guidelines on the required expertise to deliver BT; data from prostate cancer radionuclide BT suggest that practitioners need >20 cases to become proficient [53]. The existing radionuclide BT literature may be limited due to the special equipment necessary, which is not widely available. The use of eBT has increased 20-fold from 2011 to 2013, likely secondary to self-referral and increased reimbursement [9,11]. Cost of setup of eBT is also lower than traditional radionuclide BT due to the minimal shielding needed and eliminating the handling costs of radioactive sources [8].

Further, the BED equation may not adequately characterize extremely hypofractionated regimens (e.g. >8 Gy/fraction), cellular death due to different modes surrounding mitotic catastrophe (e.g. necroptosis) [54] or molecular pathways behind recurrence (e.g. vasculogenesis) [55]. The BED equation also does not take into account target volume, treatment field sizes, presence of hot spots, or prescription method (e.g. organ, margin around tumor, isodose line) [56]. We have a limited follow-up time of < 5 years because most elderly skin cancer patients are unable to come for extended follow-up. Many of the BT studies reported near 100% “good” cosmesis outcomes and 0% LR although mean follow-up times 10-12 months.

CONCLUSION

In this landmark meta-analysis, we found that BT has more favorable cosmesis over EBRT for skin BCCs and SCCs at common fractionation regimens of 64 Gy/32 fractions, 55 Gy/20 fractions, and 50 Gy/15 fractions. BT demonstrates an extraordinarily high rate of clinician reported good cosmesis after treatment. Whether this is secondary to the superiority of the technique, patient selection, or another unidentified factor is unknown. Prospective studies comparing the techniques are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

BCC	basal cell carcinoma
BED	biologically equivalent dose
CI	confidence interval
CPT	current procedural terminology

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EBRT	external beam radiation therapy
HDR-BT	high dose rate brachytherapy
IQR	interquartile range
PICOS	Population, Intervention, Control, Outcome, Study Design
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RT	radiation therapy
RTOG	Radiation Therapy Oncology Group
SCC	squamous cell carcinoma

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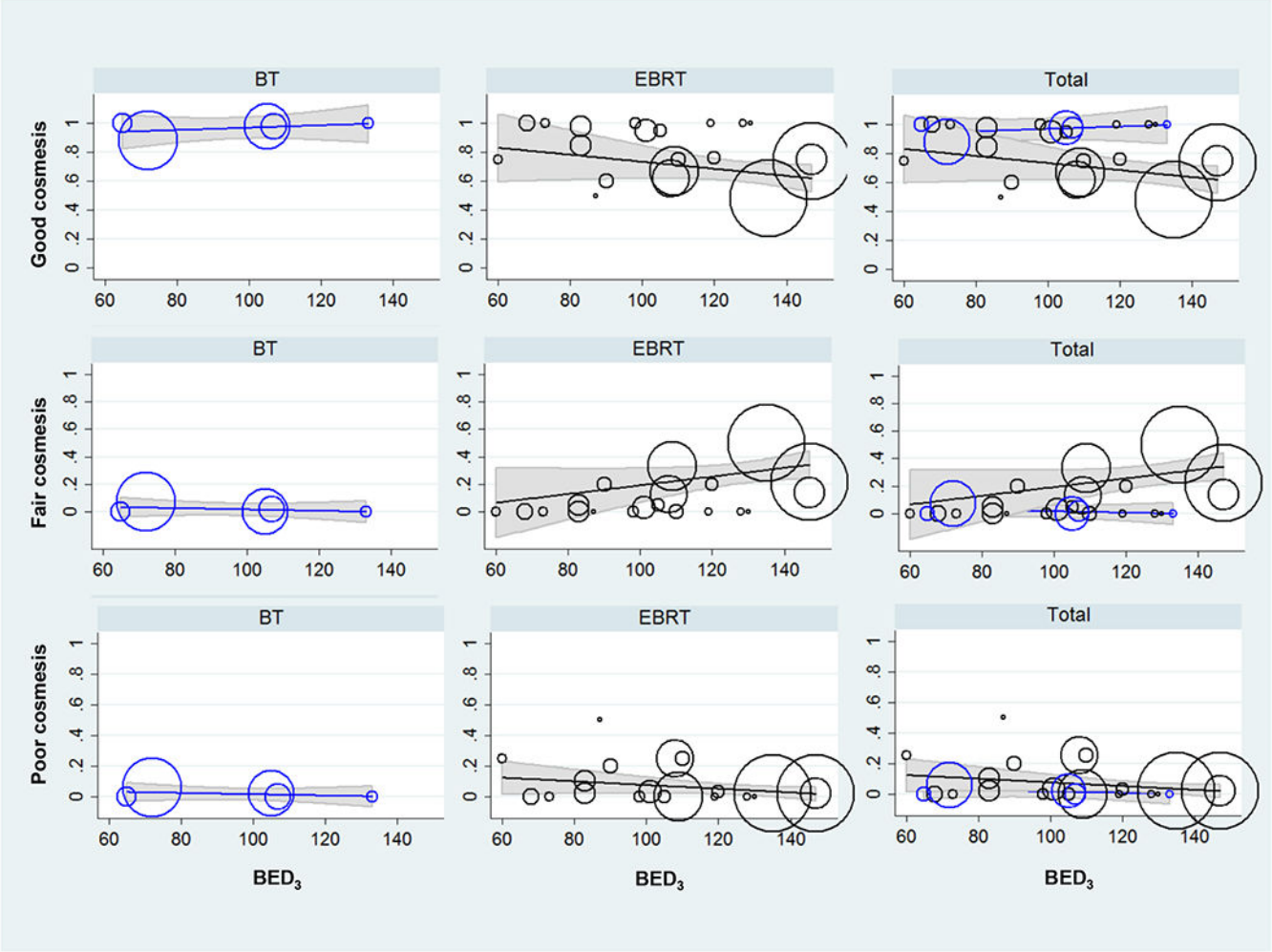

Figure 1. SCC and BCC post-radiation cosmesis as a function of BED for BT and EBRT

The rates of "good" (upper panel), "fair" (middle panel), and "poor" (lower panel) cosmesis are plotted vs. biologically equivalent doses with $\alpha/\beta=3$ (BED_3). The % good/fair/poor cosmesis vs BED_3 is plotted for brachytherapy (BT, left column), external beam radiation therapy (EBRT, center column), and both techniques co-plotted (right column). The cosmetic outcomes for BT and EBRT were similar up to BED_3 of ~100 Gy (as evidenced by overlapping 95% confidence intervals), which is equivalent to about 64 Gy/32 fractions, 55 Gy/20 fractions, 50 Gy/15 fractions. Neither technique was associated with poor cosmetic outcomes, independent of the dose or fractionation. At higher BED_3s, e.g. 35 Gy/5 fractions, or BED_3 of 120 Gy, BT was associated with higher likelihood of good cosmesis vs. fair cosmesis.

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Table 1.

Comparison of treatment modalities in the management of skin cancer.

	Diagnostic x-rays	Superficial x-rays	Orthovoltage x-rays	MV x-rays (i.e. 6 MeV)	MV gamma ray	MeV electrons	Electronic BT (eBT)	BT with Ir-192	Other BT radionuclide (e.g. I-125, Pd-103, Cs-137)
Modality	N/A	EBRT	EBRT	EBRT	EBRT	EBRT	BT (per billing codes)	BT	BT
Used to treat skin cancer?	No	Yes	Yes	Yes	Yes, historically	Yes	Yes	Yes	No
Included in current analysis?	No	Yes	Yes	Yes	Yes	Yes	No	Yes	No
Contemporary availability of technology	Available	Rare	Rare	Widely available. Robust data.	Depends	Widely available. Robust data.	Relatively new, as of ~2010	Depends	Depends
Body of evidence for skin cancer (relative)	N/A	Robust historical data	Robust historical data	Robust historical, contemporary data	Minimal	Robust historical, contemporary data	Nearly non-existent, to meet inclusion criteria	Some historical and contemporary data	N/A
Particle	Photon	Photon	Photon	Photon	Gamma, Co-60 decay via beta-	Electron	Photon	Ir-192 decay mostly via beta-	Depends
Radionuclide replacement, radioactive waste	No	No	No	No	Yes, half-life = 5.3 y	No	No	Yes, half-life = 74 d	Yes
Energy	~20-150 kV	~40-200 kV	~150-500 kV	6 MV (max)	1.25 MeV (average), similar to 4 MV x-ray	6-15 MeV	10-90 kV	0.38 MeV, Max 1.09 MeV	Depends
Shielded room necessary	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Depends
Cone, cutout, block needed?	N/A	Cone	Cone	Blocks / collimator	Cone	Cutout	No	No, but mold or catheter needed	N/A
Bolus needed?	N/A	No	No	Yes	Yes	Yes	No	No	N/A
d_{max}	N/A	Skin surface	Skin surface	~1.5 cm	0.5 cm	$\bar{E}_0$ / 5	Skin surface	Catheter surface	N/A
90% isodose line	N/A	5 mm	2 cm	~ 6 cm	1.5 cm	$\bar{E}_0$ / 3.4-4, 1 cm inward from block edge	< 1cm	< 1cm	Depends

Abbreviations: BT: brachytherapy; $\bar{E}_0$: initial energy of beam; EBRT: external beam radiation therapy; N/A: not applicable.

Note: Electronic brachytherapy (eBT) is regarded as a type of BT but actually involves x-ray treatment. BT uses a surface applicator, similar to that of superficial kV EBRT. Data for eBT are lacking; thus, it was excluded from this analysis.

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Table 2.

EBRT outcomes and toxicity

Study	CEBM Level of Evidence	n	Technique, energy	Total dose (Gy)	Gy/ fraction	Mean FU (mo)	LR 1y (%)	LR 5y (%)	OS	Cosmesis rating (%)		
										Good	Fair	Poor
Abbatucci, 1988	2b	675	Muller RT 100, 1000R/min	31	10.2	24	1	5.3	NR	47.5	50.1	2.4
Avril, 1997	1b	20	85-250 kV	60-65	2-4	41	1.2	7.5	72.6	76	20	3
Caccialanza, 2005	2b	110	55-120 kV	45-70	5	28.8	NR	10.4	98.2	74.8	13.5	1.8
Caccialanza, 2009	2b	671	55-120 kV	30-75	5	38	2.5	5.7	NR	74.5	22.4	2.4
				60+23	2+5	38						
Lovett, 1990	2b	325	kV, MV, and MeV	40-60	1-4	24	NR	14	NR	88.3	3.0	6.8
Mazeron, 1989	2b	71	MV, Mev, Co-60	30.6-70	2-10.2	>24	19[a]	NR	NR	52	37	11
		639	~100kV				4.8[a]	NR	NR	61	22	17
Van Hezewijk, 2010	2b	159	4-12 MeV	54	3	42.8	1.5	2.5	NR	62	13	25
		275		44	4	42.8	2	3.9	NR	67	33	0
Ashby, 2001	2b	360	5-7 MeV, MV	24	6	12	0.7	4.3	98.9	NR	NR	NR
Chan, 2007	2b	464	45-100kV	22.5	22.5	18	1	8	NR	NR	NR	NR
		499		20	20	18	3	10	NR	NR	NR	NR
Cognetta, 2012	2b	1715	80 kV	35	7	31.5	1.1	5	NR	NR	NR	NR
Hernandez, 2007	2b	710	14-50 kV	45-56	4	12	1.9	5.9	NR	NR	NR	NR
				36	9							
Hall, 1986	2c	19	130 kV	35	7	12	0	NR	NR	NR	NR	NR
		30		38	3.8	24	6.7					
Grossi Marconi, 2016	2b	521	80-200 kV	50	3	44	NR	0.8	NR	NR	NR	NR
				55	3							
		500		60	2	44	NR	2.7	NR	NR	NR	NR
Pampena, 2015	2b	275	50-300 kV	37	5	30.4	1.1	5.5	69.5	NR	NR	NR
		161		45	3	34.3	1.2	3.7	83.9	NR	NR	NR
Schulte, 2005	2b	1019	10-100 kV	45	5	77	NR	4.5	74.4	NR	NR	NR
		245		60	5		NR	6.9	57.1	NR	NR	NR
Silva, 2000	2b	47	100-250 kV, MV MeV, Co-60	18-20	18-20	40	6.2	21.8	63.8	NR	NR	NR
		123		35	7							
		68		43-45	4-5							
		41		50-65	2-3							
Tsao, 2002	2b	34	75-250 kV, 9-20 MeV	35	7	35	5	15	58	NR	NR	NR
		20		45	5							
		10		50	3							
		11		20	20							

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Study	CEBM Level of Evidence	n	Technique, energy	Total dose (Gy)	Gy/ fraction	Mean FU (mo)	LR 1y (%)	LR 5y (%)	OS	Cosmesis rating (%)		
										Good	Fair	Poor
Zagrodnik, 2003	2b	148	20-50 kV	40-48	8	48	6.4	15.8	NR	NR	NR	NR
				40-52	4							
				52-60	2							

Abbreviations: BED: biologically equivalent dose; CSS: cancer-specific survival; EBRT: external beam radiation therapy; FU: follow-up; Gy: Gray; n: number of patients per group; NR: not reported; LR: local recurrence; OS: overall survival

Note: Gy and BED rounded to whole numbers. LR rounded to nearest tenth. Combined cells apply to all doses as they were the only results given in their respective studies. Bold line separates studies with cosmesis, above, from studies without cosmesis, below. For technique/energy, kv implies orthovoltage photons, MV implies megavoltage photons, MeV implies electrons, Co-60 implies Cobalt units.

[a] LR at 2 years

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Table 3.

HDR-BT outcomes and toxicity

Study	CEBM Level of Evidence	n	Source	Total dose (Gy)	Gy/ fraction	Mean FU (mo)	LR 1y (%)	LR 5y (%)	OS	Cosmesis rating (%)		
										Good	Fair	Poor
Delishaj, 2015	2c	48	Ir-192 + applicator	40	5	12	0	NR	NR	98	2.1	0
		9		50	5		0	NR	NR	100	0	0
Gauden, 2013	2b	236	Ir-192 + applicator	36	3	66	2[a]	NR	NR	88	6.5	5.5
Guix, 2000	2b	136	Ir-192 + mold	60-65	1.8	12	NR	2.21	NR	98	0	2
				75-80	1.8							
Somanchi, 2008	2c	25	Ir-192 + mold	42.5	5.3	60	0	0	NR	100	0	0
Svoboda, 1995	2b	54	Ir-192 + mold	32	4.5	10	0	NR	NR	NR	NR	NR
Tormo, 2014	2c	45	Ir-192 + applicator	42	7	47	NR	2[b]	NR	NR	NR	NR

Abbreviations: BED: biologically equivalent dose; BT: brachytherapy; CSS: cancer-specific survival; FU: follow-up; Gy: Gray; n: number of patients per group; NR: not reported; LR: local recurrence; OS: overall survival

Note: Gy and BED rounded to whole numbers. LR rounded to nearest tenth. Combined cells apply to all doses as they were the only results given in their respective studies. Bold line separates studies with cosmesis, above, from studies without cosmesis, below.

[a] LR at 2 years

[b] LR at 4 years

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Table 4.

Cosmesis outcomes of BT vs. EBRT

	BED_3=80	BED_3=100	BED_3=120	Slope ∔
Good cosmesis				
BT	94% (82-100%)	95% (88-100%) *	99% (90-100%) *	2.8% p=0.002
EBRT	79% (60-95%)	79% (60-82%) *	68% (60-74%) *	−2.5% p=0.121
Fair cosmesis				
BT	4% (0-10%)	3% (0-9%)	2% (0-9%) *	−1.7% p=0.010
EBRT	12% (0-31%)	18% (8-31%)	22% (18-28%) *	3.2% p=0.068
Poor cosmesis				
BT	5% (0-9%)	5% (0-7%)	4% (0-8%)	−1.3% p=0.005
EBRT	10% (1-18%)	8% (2-12%)	5% (1-7%)	−1.2% p=0.130

Note:

* denotes p-value < 0.05 for BT vs. EBRT for particular cosmetic outcome, 95% CI in parentheses,

∔ denotes percent change vs 10 unit change in BED

Note that this analysis is performed on all patients in the dataset. The selected dose levels (80 Gy, 100 Gy, 120 Gy) represent the gamut of the doses, as shown in Figure 1; further, there are no “good”/”fair”/”poor” cosmesis all.