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Analytical Dosimetric Study of Postoperative Brachytherapy and Electron Beam Irradiation in the Treatment of Complex Keloids

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1. Abstract

1.1. Purpose: Keloid is a common benign skin tumor in the outpatient department. Pathogenesis is unknown, and single-method treatment, such as surgery alone, has a high recurrence rate. Surgery followed by adjuvant radiotherapy is currently one of the most effective treatments for keloid. After long-term clinical practice, brachytherapy and electron beam radiotherapy have become the gold standard methods of radiation delivery. This study aimed to compare the dosimetric impact and possible risks between these two techniques and to determine the preferred technique for treatment of complex keloids.

1.2. Methods: We retrospectively identified twenty consecutive keloid patients who underwent postoperative high-dose rate (HDR) brachytherapy (BT) with Ir192 or electron beam irradiation (e- RT) between 2020 and 2022. HDR Patients treated with HDR BT received 12 Gy in2 fractions, while e- RT patients received 18 Gy in3 fractions. Both modalities were prescribed to 5 mm beneath the scar. HDR BT treatment was completed within 36 hours of surgery, while e- RT treatment was completed within 72 hours of surgery. The clinical target volume (CTV) for each case was subtracted 3mm from the skin surface to create an evaluation clinical target volume (CTVeval). Three normal tissue evaluation structures (NTs) were defined as NT5mm, NT10mm, NT15mm. These ring structures were generated by adding 5, 10 and 15 mm margins to the CTVeval, respectively, and excluding the CTVeval itself. Quality was assessed for each plan by performing a dosimetric evaluation of each CTVeval and NT. Dosimetric parameters evaluated for the CTVeval included mean dose (Dmean), minimum dose delivered to 90% of the volume (D90) and percentage of the CTV volume receiving 95%, 100%, and 200% of the prescription dose (V95, V100, and V200). The maximum dose received by 0.01cc of the CTVeval (V0.01cc) was also calculated. For the NTs, Dmean,

1.3. Results: HDR BT demonstrated significantly better prescription dose coverage of the CTVeval (Dmean ($p=0.028$), D90 ($p<0.001$), V100($p=0.015$) and V95($p<0.01$)) compared to e- RT. However, HDR BT produced a more heterogeneous dose distribution within the CTVeval, with significantly higher D0.01 cc on average ((392.7% ± 20.9% (HDR BT) vs. 127.7% ± 26.5% (e- RT)) compared to e- RT. The Finally, HDR BT demonstrated improved dose fall-off outside the CTV. Dmean values of the NTs using HDR BT were reduced 103%, 135% and 148% for NT5mm, NT10mm and NT15mm, respectively. the Dmean of NTs using e- RT was reduced 14%, 32% and 50% in NT5mm, NT10mm and NT15mm, respectively.

1.4. Conclusions: Compared to e- RT, single-catheter HDR BT improves target coverage in complex keloid treatment, and offers superior normal tissue sparing.

2. Introduction

Keloids are dermal lesions generated by increased production of collagen due to abnormal and prolonged wound healing. As compared to hypertrophic scars, keloids tend to grow into the healthy surrounding skin. Although the histopathological presentation of keloids is well defined, the pathophysiology is less known [1].

This creates challenges for the treatment and management of keloids. The major concern for patients as well as the treating physician is the chance of recurrence. The incidence of recurrence is extremely high if only conservative measures, such as intralesional steroids, are used. If surgery alone is considered, the recurrence rate is 45%–100% [2]. However, adding radiotherapy postoperatively reduces the recurrence rate to <40% [3]. Radiation--induced damage to the healthy surrounding tissue and secondary malignancy are the primary risk factors for perioperative adjuvant radiation therapy. The adjuvant radiation therapy can be delivered using a number of different treatment modalities, including external beam radiation therapy with superficial X-rays or electrons, High-Dose-Rate (HDR) or low-dose-rate (LDR) brachytherapy [4]. Previous studies have examined the benefits and challenges of these varying modalities, and their ability to reduce damage to healthy skin and the chance of recurrence [5,6]. In addition, different radiation dose and fractionation schedules were also examined, including HDR brachytherapy with Ir192 at 8 Gy/1 fraction (F), 9 Gy/3F or 20 Gy/4F; or external beam electron therapy at 18 Gy/2F or 30 Gy/15F. The endpoints of these study were analysis of the control rate and toxicity [5,6]. However, to the best of our knowledge, no consensus has been reached on the total dosage, fractionation or optimal timing of the delivery of radiotherapy. A comparison of the dosimetric properties of radiation treatment plans generated using various treatment modalities has also not been fully examined. The purpose of this study was the retrospective evaluation of radiation plan quality differences between HDR brachytherapy (HDR BT) and electron external beam radiation therapy (e- RT) when treating complex keloids. This study is the first clinical dosimetry report utilizing volume-based dosimetric analysis to compare these modalities.

3. Materials and Methods

3.1. Patient Selection and Treatment Workflow

Twenty patients with complex keloids treated with HDR BT or e-RT (10 each modality) were retrospectively selected for analysis. Patients were treated consecutively between 2020 and 2022. Patients selected exhibited the following characteristics: 15-60 years, Eastern Cooperative Oncology Group performance status of 0 to 2, pathologically confirmed keloids, and treated with surgical excision and radiotherapy. Eight patients were African American, which was consistent with literature indicating keloids are 15 times more likely to occur in darker-skinned individuals [7]. The location distribution of keloid scars was: 4 jaw-line, 3 ear, 5 posterior neck, 5 abdomens and 3 chest wall. The average length of the scars was 9.8 cm (range: 4.7 –17.4 cm).

3.2. Surgical Excision

Surgical excision was performed under general or local anesthesia in a standard operating room (OR). The typical keloid scar before surgical excision was as shown in Figure 1(a). In all cases, excision was preceded by subcutaneous injection of xylocaine 1% with adrenaline. A margin of at least 1mm was excised in addition to the primary lesion. For HDR BT patients only, flexible interstitial catheters (Best™ Medical International, Springfield, VA) were inserted subcutaneously at approximately 5 mm depth along the keloid scars and sutured in place following surgical excision and reconstruction. Catheters were secured with buttons on both ends at the skin entry points to restrict the catheter movement. One catheter was used for each scar. Wound closures were performed in two planes with interrupted Vicryl (polyglactin; Ethicon, Inc., Somerville, New Jersey) stitches on the subcutaneous plane and then a continuous running or interrupted Prolene (isotactic polypropylene; Ethicon) suture on the cutaneous plane as shown in Figure 1(b). Wounds were covered with gauze pads.

3.3. Radiation Therapy

Following surgical excision, for patients receiving HDR BT, all interstitial catheters were cut to the proper lengths so that the total channel length of the catheters and the source guide tubes added to a fixed length of 130 cm. Dummy wires were inserted in each catheter to assist with channel reconstruction, and to define the treatment area. For patients receiving e-RT, CT marker wires (Beekley Medical, Bristol, CT) were placed around the scar, typically 1-2cm from scar, to mark its extent and define the desired treatment area (Figure 1(c)). All patients were scanned using a 20-slice computerized tomography (CT) scanner (Somatom Sensation; Siemens, Germany) with a matrix size of 512 × 512, a pixel size of 0.51 mm in the x–y plane, and a slice thickness of 1.5 mm, at an X-ray tube voltage of 120 kV and a tube current of 300 mAs. Image data was transferred to the appropriate Treatment Planning System (TPS).

HDR BT plans were created using dedicated brachytherapy planning software, Oncentra® (version 4.5, Elekta, Veenendaal, The Netherlands). For each patient, the HDR BT target (CTV) was defined as 5mm below the skin surface following each catheter. Prescription dose was set to 6 Gy x 2 fractions (12 Gy total). Plans were inverse-planned initially using volume-based optimization to deliver the prescription dose to 5-10 mm depth. The range of the depths was due to variation in catheter depth. Although catheters were sutured at approximately 5 mm depth along the incision, exact depth along the length of each catheter varied, with a maximum noted depth of 10mm. Following inverse optimization, manual modification of the plan was utilized to ensure adequate skin coverage by the prescription dose. Patients were treated with an Iridium-192 (Ir192) remote after-loading system (Flexitron HDR™, Elekta, Veennendaal, The Netherlands). The first HDR BT session was systematically performed within 6 hours following surgery. For the second fraction treatment, the position of the interstitial needles was visually verified before treatment delivery. Total prescription dose was delivered within 36 hours following the completion of keloid excision surgery.

For patients who received e-RT, plans were created using the Eclipse® (version 15.6, Varian medical Systems, Palo Alto, CA) radiation treatment planning system. Gantry, collimator, and couch angles, as well as source-skin-distance were chosen carefully to ensure the incident beam was entering enface to the skin surface and to avoid collision between the patient and the electron cone. The e-RT CTV was defined using the CT marker wire (Figure 1(c)), and included the area from the skin surface to a depth of 0.5mm. The electron block aperture was set to include a 5-7mm block margin beyond the CTV to ensure appropriate coverage. All plans used 6 or 9MeV electron beams and 0.5 -1 cm water-equivalent bolus to ensure coverage of the CTV. CT marker wires were assigned water density. All plans were normalized to the 90% isodose line following institutional protocol. Prescription dose was 6 Gy x 3 fractions (18 Gy total). Dose was calculated using the electron Monte Carlo algorithm. The first e-RT fraction was systematically delivered within 24 hours following surgery. Fractions were delivered daily, and the entire treatment course was completed within72 hours following keloid excision surgery.

Figure 1: Complex keloid before and after surgical excision with planned high dose rate brachytherapy (HDR BT) or electron radiation therapy (e-RT) treatment. (a) Example of complex keloid on the front of neck and chest prior to surgical excision. (b) Complex keloid post-surgical excision with subcutaneous catheter in place for planned HDR BT. treatment (c) Complex keloid post-surgical excision with radiopaque wire placed to define treatment area for planned e-RT treatment.

3.4. Plan Evaluation and Comparison

Retrospectively, an evaluation CTV (CTVeval) was created for each patient by pulling the away from the skin surface by 3-mm to ensure consistent statistics, and eliminate dose algorithm uncertainties at the patient surface. In order to evaluate dose, fall off, normal tissue evaluation structures were generated for each patient by creating 5, 10, and 15mm (NT5mm, NT10mm and NT15mm) were shown in Figure 2. ring expansions from the CTV. In all cases, these structures excluded the CTV itself. The 2D isodose lines (IDL) and 3D dose volume using HDR BT and e-RT were calculated and shown in Figure 3. The prescription dose (100%IDL) was shown as red. Dose volume histogram information was collected for each CTVeval and NT structure for each patient. Multiple dose parameters were extracted. For CTVeval these parameters included mean dose (Dmean), the percentage of the prescription dose received by 90% of the volume (D90), maximum dose received by at least 0.01 cc of the volume (D0.01cc), and the percentage of the volume receiving 95%, 100%, and 200% of the prescription dose (V95, V100, and V200). For each NT structure, the mean dose difference (ΔDmean(%)) compared to the corresponding CTVeval was calculated. The difference in dose received by 90% of the volume(ΔD90(%)), the difference in volume receiving 95 % of prescription (ΔV95 (%)), and the difference in volume receiving 100 % of prescription (ΔV100 (%)) compared to the corresponding CTVeval were also calculated. Finally, treatment time was also noted for each treatment plan.

CTVeval and NT dosimetric parameters and were compared for HDR BT and e-RT. Treatment time was also compared for each modality. The standard t-test was used with parametric data and the two-sided p-value was recorded. A p-value of < 0.05 was considered to indicate statistically significant difference.

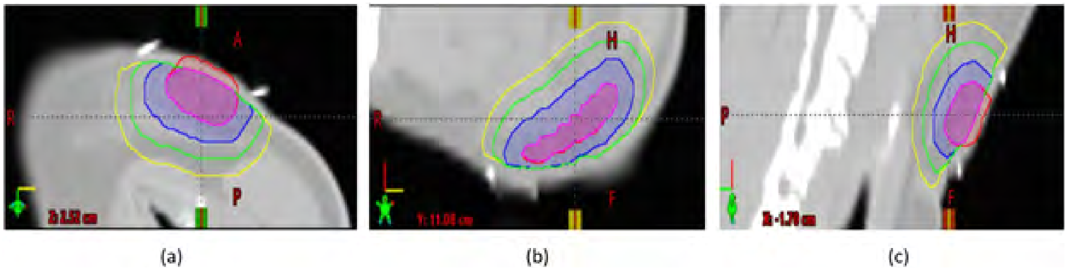

Figure 2: Representative target (clinical target volume (CTV) and normal tissue structures with 5, 10 and 15mm margins (NT5mm, NT10mm and NT15mm), respectively. (CTV: red; CTVeval: pink; NT5mm: blue; NT10mm: green; NT15mm: yellow)

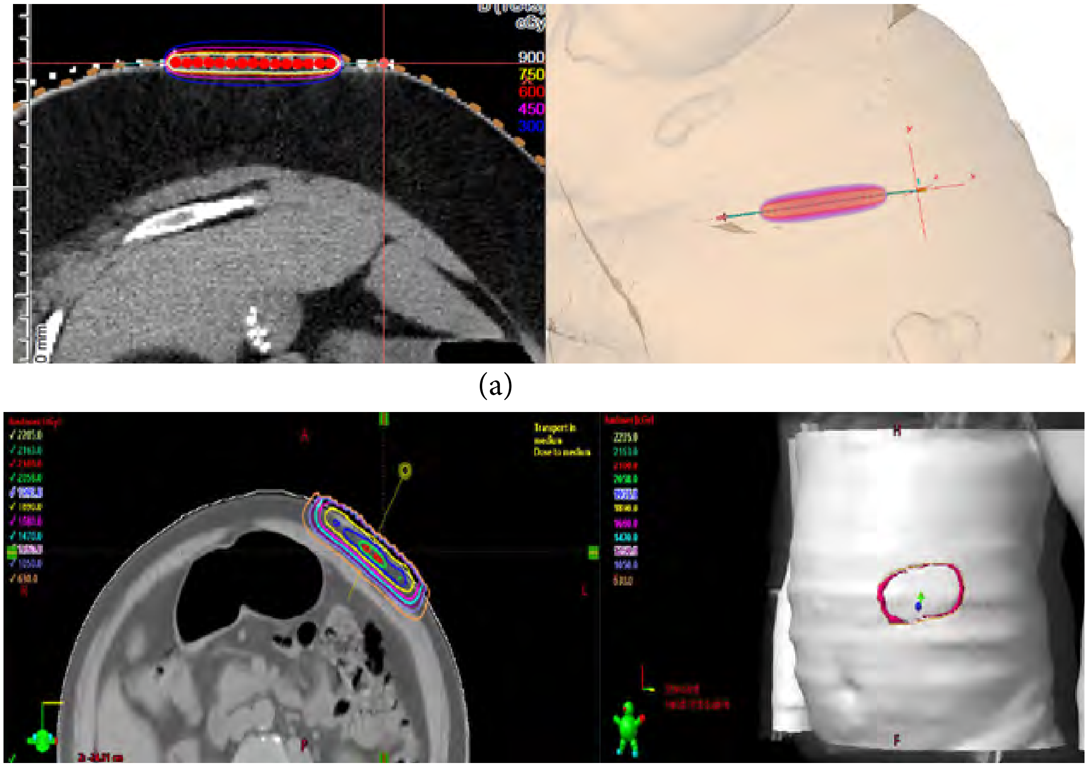

Figure 3: Representative CT images of keloid radiation therapy with 2D isodose lines (IDL) or 3D dose volume using (a) High dose rate brachytherapy (HDR BT) (b) electron radiation therapy (e-RT). The prescription IDL for both modalities is shown in red.

4. Results

Dosimetric parameters for CTVeval are summarized in Table 1. On average, the volume receiving at least 95% of prescription dose (V95) is similar for HDR BT (100 ± 0.1%) and e- RT (95.9 ± 2.4%) (p=0.014). The dose covering 90% of the CTVeval (D90) was 4% different between HDR BT (106.0 ± 0.5 (%)) and e- RT (102.6 ± 3.9 (%)) (p=0.028) when averaged across all cases for each modality. However, the HDR BT delivered significantly higher Dmean (174.8 ± 3.8 (%) (HDR BT) vs.. 112.9 ± 16.7(%) (e- RT), p<0.001) and maximum dose (D0.01cc) (392.7 ± 20.9 (%) (HDR BT) vs.. 127.7 ± 26.5 (%) (e- RT), p<0.001). Dose fall-off for NT structures compared to CTVeval is outlined in Figure 4(a-d). The percent volume receiving 100% of the prescription (V100 (%)) decreased significantly 84%-97% using HDR BT, with NT15mm showing the largest reduction compared to CTVeval. Reductions for e- RT for this parameter were significantly less across all NTs (62%-83%), indicating additional spillage of the prescription isodose. Additionally, the Dmean of the NTs using HDR BT was reduced by 103%, 135% and 148% in NT5mm, NT10mm and NT15mm, respectively compared to CTVeval. For e- RT this reduction was 14%, 32% and 50% for NT5mm, NT10mm and NT15mm, respectively. Reduction in dose received by 90% of each NT compared to CTVeval (ΔD90(%)) and reduction in volume percentage of each NT receiving 95% of prescription (ΔV95 (%)) compared to CTVeval showed similar improvement for HDR BT compared to e- RT. The treatment time for the HDR BT plans was on average 6.5 minutes per patient (range: 5.5 –8.5 minutes) assuming a nominal activity of 10 Ci. Because of electron cone setup, bolus verification, and gantry head speed, the average and maximum total treatment time using e- RT was 15.3 minutes and 25.6 minutes, respectively.

Table 1: Modality-specific plan quality metrics for evaluation clinical target volume (CTVeval).

	Target Coverage				Dose Heterogeneity		Treatment Time (min)
	D_{90} (%)	D_{mean}(%)	$V_{100\%}$ (%)	$V_{95\%}$ (%)	$V_{200\%}$ (cc)	$D_{0.01cc}$ (%)	
HDR brachytherapy (HDR BT)	106.0 ± 0.5	174.8 ± 3.8	100 ± 0.1	100 ± 0.0	1.3 ± 0.5	392.7 ± 20.9	6.5±1.9
Electron radiotherapy (e^- RT)	102.6 ± 3.9	112.9 ± 16.7	95.9 ± 2.4	98.1 ± 2.0	0.1 ± 0.3	127.7 ± 26.5	15.3±10.3
p-value	0.028	<0.001	0.014	<0.001	<0.001	<0.001	<0.001

Abbreviations: cc = cubic centimeter; $V_{90\%,}$ $V_{100\%,}$ $V_{200\%}$ = volume of CTV_{eval} receiving 90%, 100 % and 200% of prescription dose, respectively; D_{mean}= mean dose; D_{90} = dose received by 90% of the CTV_{eval}. $D_{0.01cc}$ = maximum dose received by 0.01 of the CTV_{eval}

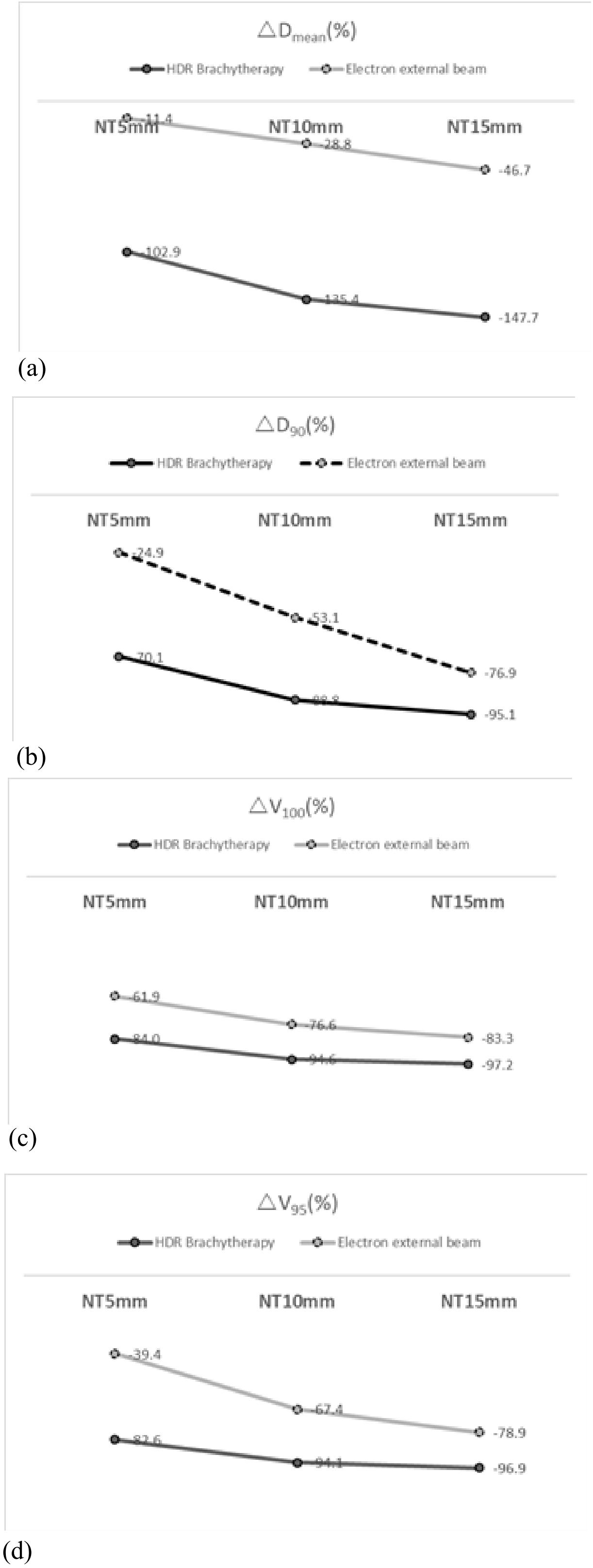

Figure 4: Average percent change in dose metrics for normal tissue structures (NTs) compared to corresponding CTVeval for high dose rate brachytherapy (HDR BT) and electron radiation therapy (e-RT). NT5mm, NT10mm and NT15mm represent 5, 10, and 15mm expansions from the CTVeval, respectively. (a) mean dose difference (ΔDmean(%)) (b) difference in dose received by 90% of the volume(ΔD90(%) (c) difference in volume receiving 100 % of prescription dose (ΔV100 (%)) (d) difference in volume receiving 95 % of prescription dose ΔV95 (%)

5. Discussions

A recent radiobiological analysis of more than 2500 patients from multiple centers found that a high biological effective dose was necessary for local control of keloids11. The analysis recommended a treatment concept with few fractions and high doses per fraction delivered in a short period of time as early as possible after resection. This can be achieved with interstitial HDR BT. Our results prove the feasibility and the efficacy of postoperative brachytherapy for the prevention of keloids. The results also suggest that this approach may play a role in the prevention of high-risk keloids or as salvage treatment of keloids that recur after failure of external beam radiation therapy.

It was observed that the target coverage in the HDR BT plans was superior to e-RT, with average Dmean increasing by 11.2 Gy (ie.,62% of prescription dose). For e-RT, under coverage of the CTVeval was often observed at the ends of the scars, especially on curved surfaces due to unavoidable obliquity of the treatment beam (i.e., chest wall and jawlines). In order to achieve similar coverage of the CTVeval compared to HDR BT, e-RT plans would need to be normalized to significantly lower isodose lines (55% on average), leading to increased dose to normal tissue, as well as skin dose to over 125% of the prescription dose. HDR BT target coverage is highly associated with the implant quality, i.e. the proximity of the catheters to the keloid scars. The HDR source (Ir-192) features a low energy of ~380 keV resulting in limited treatment depth from the source. It is difficult to achieve optimal target coverage when the catheter is >1cm from the keloid scar.

Analysis of the dose fall-off outside the CTV showed that dose fall-off was significantly more rapid for HDR BT compared to e-RT, with NT5mm, NT10mm, and NT15mm, all showing a greater reduction in dose compared to the CTVeval for HDR BT for all parameters evaluated. This difference in dose fall off is likely due to differences in radiation characteristics for each modality. E-RT deposits radiation dose via accelerated electrons, which allows for the delivery of a high surface dose, combined with a rapid dose fall-off beyond the target depth, making it an ideal modality for superficial tumors. However, treatment with e-RT necessitates an additional treatment margin beyond the keloid scar for both creations of the CTV and field aperture. These additional margins, previously discussed, account for setup uncertainty, as well as constriction of the isodose distribution at depth. In addition, extended distance was essential in most of the cases due to clearance issues (jawline and neck region), which causes broadened penumbra of the field edge. Both of these aspects have the effect of increasing spillage dose beyond the CTV. HDR BT involves treatment with a radioactive isotope (Ir192). The Ir192 radionuclide emits a complex scheme of gamma rays, X-rays, beta, internal conversion electrons, and Auger electrons. The dose deposited by this spectrum decreases rapidly with distance from the source. Because the HDR BT catheter is surgically implanted, setup uncertainty is reduced compared to e-RT, negating the need for additional expansion of the CTV. However, catheter placement is crucial for acceptable dose coverage. On average, HDR BT demonstrates approximately 30% greater reduction than e- RT in D90 of NTs compared to the CTV (84.7% (HDR BT) vs. 51.7 (e- RT)) and an approximately 20% greater reduction in V100 as shown in Figure 4 (b) and (c). The advantages of brachytherapy over electrons are a rapid dose fall-off outside the target volume and short duration of treatment. Moreover, with respect to difficult areas such as in and around the nose or earlobe, major disadvantages of electron e- RT are the set-up errors and difficulty in planning in small, irregular fields and so a significant margin (2cm) must be included.

Evaluation of average treatment time showed a benefit for HDR BT, with an approximately 55% reduction in treatment time on average compared to e- RT. In addition to extended treatment time, e-RT also often requires extensive clinical simulation time, including the creation of electron templates, cutouts, and in some cases, on-skin collimation for better dose conformality. This simulation time can take 0.5 – 1hr, often with the patient in a treatment position, potentially increasing patient discomfort, and disturbing the clinical workflow. e- The addition of bolus (5-10mm) during simulation and treatment, common for e-RT treatment, adds additional complexity to the treatment delivery due to verification of bolus placement and thickness. In comparison, placement and suturing of HDR BT catheters takes approximately 10 minutes of operating room time. Sizing and verification of catheters for simulation takes an additional 10 minutes. Catheters also require removal, requiring approximately 2 minutes at completion of treatment. Overall, HDR BT offers significant time savings for both patient and provider.

HDR BT offers a variety of theoretical and practical advantages for treatment of complex keloid compared to e-RT. These advantages include improved target coverage, reduced dose to normal tissue, and reduction in treatment and simulation time. HDR BT is a cost-effective treatment technique that can be offered in most radiation therapy centers. A 2-fraction treatment schedule reduces the treatment period and is therefore convenient for patients. In addition, the treatment can be performed as an outpatient procedure.

6. Conclusions

In conclusion, we demonstrate the feasibility of defining volume-based dosimetric parameters for keloids treated with catheter-based HDR BT and e-RT. Dosimetric comparison reveals that significantly higher average D90 and Dmean to the keloid scars was achieved in the HDR BT plans than in the e-RT plans. Meanwhile, better conformity enables HDR to irradiate significantly less normal tissue volume and faster dose fall than e-RT. Clinical workflow is more streamlined and efficient dose delivery with HDR BT procedures. Future studies should aim to assess the feasibility of prospective volume-based target delineation for the adjuvant treatment of keloids with brachytherapy to determine whether there are clinically meaningful dosimetric correlates. However, data comparing HDR BT and e-RT are limited and this study aims to provide the insight into complex keloid treatment.

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