Original paper

Highly conformal CT based surface mould brachytherapy for non-melanoma skin cancers of earlobe and nose

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Abstract

Purpose: Brachytherapy (BT), due to rapid dose fall off and minor set-up errors, should be superior to external beam radiotherapy (EBRT) for treatment of lesions in difficult locations like nose and earlobe. Evidences in this field are scarce. We describe computed tomography (CT) based surface mould BT for non-melanoma skin cancers (NMSC), and compare its conformity, dose coverage, and tissue sparing ability to EBRT.

Material and methods: We describe procedure of preparation of surface mould applicator and dosimetry parameters of BT plans, which were implemented in 10 individuals with NMSC of nose and earlobe. We evaluated dose coverage by minimal dose to 90% of planning target volume (PTV) (D_{90}), volumes of PTV receiving 90-150% of prescribed dose (PD) ($VPTV_{90-150}$), conformal index for 90 and 100% of PD ($COIN_{90}$, $COIN_{100}$), dose homogeneity index (DHI), dose nonuniformity ratio (DNR), exposure of organs. Prospectively, we created CT-based photons and electrons plans. We compared conformity ($COIN_{90}$, $COIN_{100}$), dose coverage of PTV (D_{90}, $VPTV_{90}$, $VPTV_{100}$), volumes of body receiving 10-90% of PD (V_{10}-V_{90}) of EBRT and BT plans.

Results: We obtained mean BT-DHI = 0.76, BT-DNR = 0.23, EBRT-DHI = 1.26. We observed no significant differences in $VPTV_{90}$ and D_{90} between BT and EBRT. Mean BT-$VPTV_{100}$ (89.4%) was higher than EBRT-$VPTV_{100}$ (71.2%). Both $COIN_{90}$ (BT-$COIN_{90}$ = 0.46 vs. EBRT-$COIN_{90}$ = 0.21) and $COIN_{100}$ (BT-$COIN_{100}$ = 0.52 vs. EBRT-$COIN_{100}$ = 0.26) were superior for BT plans. We observed more exposure of normal tissues for small doses in BT plans (V_{10}, V_{20}), for high doses in EBRT plans (V_{70}, V_{90}).

Conclusions: Computed tmography-based surface mould brachytherapy for superficial lesions on irregular surfaces is a highly conformal method with good homogeneity. Brachytherapy is superior to EBRT in those locations in terms of conformity and normal tissue sparing ability in high doses.

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Key words: brachytherapy, ear, mould, nose, skin cancer.

Purpose

Skin cancer is the most common cancer occurring in human. Its incidence is increasing in recent decades and is estimated at over 3 million in the USA [1]. In many countries, the number of this type of cancer is significantly underreported in medical records [1,2].

Brachytherapy (BT) history dates back to the beginning of the 20th century when radium tubes were used for treatment of superficial skin lesions [3]. Brachytherapy, at its' inception, was used in a wide range of indications like hemangioma and acne [3]. The initial enthusiasm gradually decreased due to concerns over late toxicity, especially cancerogenesis [3,4].

Nowadays, role of surgery is well established as a primary treatment of non-melanoma skin cancer (NMSC) [5,6]. Although, the sole so far randomized clinical trial showed a higher frequency of recurrences after radiotherapy (RT) as compared to surgery for facial basal cell carcinoma (BCC) (7.5% vs. 0.7%) [7], RT results in less relapses than any other treatment modality [5,8]. According to the NCCN guidelines, radiation therapy can be used as a primary treatment for patients disqualified from surgery, and patients in whom good cosmetic and functional result cannot be achieved [5].

Radiation exposure matters of low-dose-rate (LDR) BT and technology development of external beam radiation therapy (EBRT) limited usage of BT in many treat-

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ment sites [9]. With introduction of remote afterloading high-dose-rate (HDR) BT, this treatment modality has been rediscovered [3,9,10]. Superiority of BT over EBRT is a rapid dose fall-off outside the target volume and short duration of treatment [9,11,12,13,14].

Early methods of treatment with brachytherapy were based on atlases, tables, and experience of physicians. Currently, for many locations like prostate, cervix, or breast cancers, the treatment plans rely on 3D-planning, modern imaging [15]. Superficial skin cancers can be successfully treated with 2D-planing conical applicators [16]. In most challenging treatment locations like nose and earlobe where conical applicators are difficult to be used, 3D-planing BT has a lot to offer. Main disadvantages of EBRT in this treatment sites are set up errors and difficulties in planning on irregular, thin surfaces, and thus, a significant margin must be added [11]. In brachytherapy treatment, the source is fixed to a target [11].

Although BT intuitively should be a better option for small, demanding targets, evidences in comparing studies are missing. Brachytherapy is omitted in many leading guidelines like NCCN. Most studies relied on experience with 2D-planning. Data concerning 3D-planning are scarce. The purpose of the study is to compare computer tomography (CT)-based brachytherapy treatment plans with 3D conformal radiotherapy (3D-CRT) EBRT irradiation.

Material and methods

Patient characteristics

From March 2014 to May 2015, 10 patients with NMSC of nose and earlobe treated with HDR-BT with surface mould individual applicator were enrolled to analysis. All individuals aged 66 to 92 years old (median 75.5) had histopathologically confirmed NMSC, BCC, or squamous cell carcinoma (SCC). Out of 10 patients, two had macroscopic disease and 8 underwent non-radical surgery. None of the patients presented with positive lymph nodes or distant non-skin metastases at the time of treatment. The clinical examination was performed by two radiation oncologists.

Patient preparation

The first step involved preparation of individual mould applicator (Figures 1 and 2). Lead spherical shields were placed on eyeballs. Mixture of wax and paraffin formed 5 mm and 10 mm layers and were cut to shape covering of nose or earlobe. This mould material heated in water bath of 50ºC was placed and adopted to patient's face curvatures by gentle pressure. Borders of obtained impression were marked on patient skin to maintain intra fraction position accuracy. After material of individual applicator become rigid it was taken off the face. Then, parallel channels were hollowed out by heated tool in the outer part of the applicator. Depth, location, and spacing between channels were chosen to deliver dose to target volume. To ensure proper dose delivery on borders of target, number of catheters was selected to cover the whole target with margin. Distance from source position to skin surface was usually 5 mm. It was adopted in specific clinical situations. For example, distance was reduced in deep infiltration or lesion located close to OARs, extended in skin grafts to prevent overdosage. Three to seven brachytherapy catheters were installed into channels. Liquid mixture of wax and paraffin was used to fill up the empty space around catheters in channels. Before the placement of an applicator, ultrasound gel was applied on skin surface to avoid air gaps between skin and applicator. Whole procedure took less than 30 minutes.

Treatment planning

Computed tomography contrasting wire with metal core was attached to skin in order to mark treatment area during CT scanning. Target volume consisted of tumor or tumor bed in post-surgery condition with 5 mm margin. Markers for reconstruction of source dwell position were

Fig. 1. Earlobe and nose mould applicator


Fig. 2. Inside nasal vestibule mould applicator

inserted into catheters. Computed tomography scans in 8 patients and bone beam computer tomography (CBCT) scans in 2 patients were performed. Target volume was delineated according to skin markers visible on CT scans, histopathology results, and clinically assessed depth. Bones, eyeballs, lens, distal part of nose (cartilaginous nasal pyramid and tip area), and earlobe were delineated as organs at risk. After reconstruction of catheters and source dwell positions, TG-43 compliant BrachyVision™ (Varian Medical Systems, Palo Alto, USA) was used to create 3D-based treatment plan by physician trained in field of brachytherapy. All plans with dose volume histograms (DVH) were approved by radiation oncologist.

Treatment

Whole treatment took 10-12 working days, fractions were delivered once daily from Monday to Friday. Total 45 Gy, 40 Gy, or 36 Gy in 4.5 Gy, 4 Gy, or 3 Gy fractions daily were prescribed. Dose of 45 Gy in 10 fractions was used for macroscopic lesions, 40 Gy in 10 fractions was used after non-radical surgery, 36 Gy regimen was prescribed for adjuvant treatment on locations where risk of acute toxicity was high. Ultrasound gel was applied on skin to avoid minor air gaps between skin and individual applicator every day before treatment. Applicator was attached to treatment area and its position was checked on the basis of pre-marked lines on the skin. Daily clinical examination and applicator match was performed by physician. Treatment delivery was performed with GammaMed Ir192 HDR afterloader device (Varian Medical Systems, Palo Alto, USA), weighted mean energy of 0.38 MeV. Median of active catheters was 4 (range 3 to 7).

EBRT planning

All acquired CT, CBCT images, and BT treatment plans were transferred through Aria™ Oncology System (Varian Medical Systems, Palo Alto, USA) to Eclipse™ Treatment Planning System. The primary BT bolus density was removed (changed to air equal density). For EBRT planning, bolus was virtually added (5 mm or 10 mm water density bolus). Brachytherapy high risk clinical target volume (HR-CTV) was defined as planning target volume (PTV), no additional margin was added. Plans using analytical anisotropic algorithm (AAA) or Monte Carlo algorithm were created by physicist trained in field of EBRT planning. For each individual, two to four EBRT plans were created (2 or 3 fields 6 MV 3D-CRT, and an electron plan when clinically and technically feasible). We attempted to create plans to cover whole PTV by isodoses from 95-107% of prescribed dose, as described in ICRU 50 report [17]. The one with best coverage of target volume with acceptable doses in OAR was chosen for comparison. We have chosen 2 laterally opposing field 6 MV photons plans for 7 patients, for 3 patient 6-12 MeV electron beams (two earlobe lesions and connection of nasal cartilage and upper lip) (Figure 3).

Plans comparison

We evaluated dose homogeneity index inside PTV (DHI), dose nonuniformity ratio (DNR), minimum doses to most exposed 0.1 cc and 2 cc ($D_{0.1cc}$, D_{2cc}) of organs at risk (OAR) for BT plans. For EBRT plans, we reported EBRT-DHI minimal dose to 5% and 95% of the PTV (D_5, D_{95}). Doses delivered at OAR were calculated by treatment planning system without taking into consideration lead protective shield to eyeballs. In order not to distort the results, we didn't contour eyeballs and lenses in patients treated for earlobe lesions. We included into analysis more exposed of even organs. Both plans BT and EBRT for each patient were compared by following parameters. Dose coverage of PTV was assessed by minimal dose to 90% of the PTV (D_{90}), volumes of PTV receiving 90%, 100%, 125%, and 150% of prescribed dose ($VPTV_{90}$, $VPTV_{100}$, $VPTV_{125}$, $VPTV_{150}$), defined as percentage of whole PTV volume. We calculated conformal index for 90 and 100% of prescribed dose ($COIN_{90}$ and $COIN_{100}$). We compared volumes of PTV receiving 10%, 20%, 30%, 50%, 70%, 90%, and 100% of prescribed dose (V_{10}, V_{20}, V_{30}, V_{50}, V_{70}, V_{90}, and V_{100}) for both plans.

All doses are expressed as a percentage of the total dose. The prefix BT or EBRT before name of parameter applies to the BT or EBRT plan. The following definitions for parameters were:

$COIN_{100} = (VPTV_{100\,[cc]}/VPTV_{[cc]}) \times (VPTV_{100\,[cc]}/V_{100\,[cc]})$,
$COIN_{90} = (VPTV_{90\,[cc]}/VPTV_{[cc]}) \times (VPTV_{90\,[cc]}/V_{90\,[cc]})$,
$DNR = V_{150\,[cc]}/V_{100\,[cc]}$,
BT-DHI inside PTV = $(VPTV_{100\,[cc]} - VPTV_{150\,[cc]})/VPTV_{100\,[cc]}$,
EBRT-DHI = D_5/D_{95}.

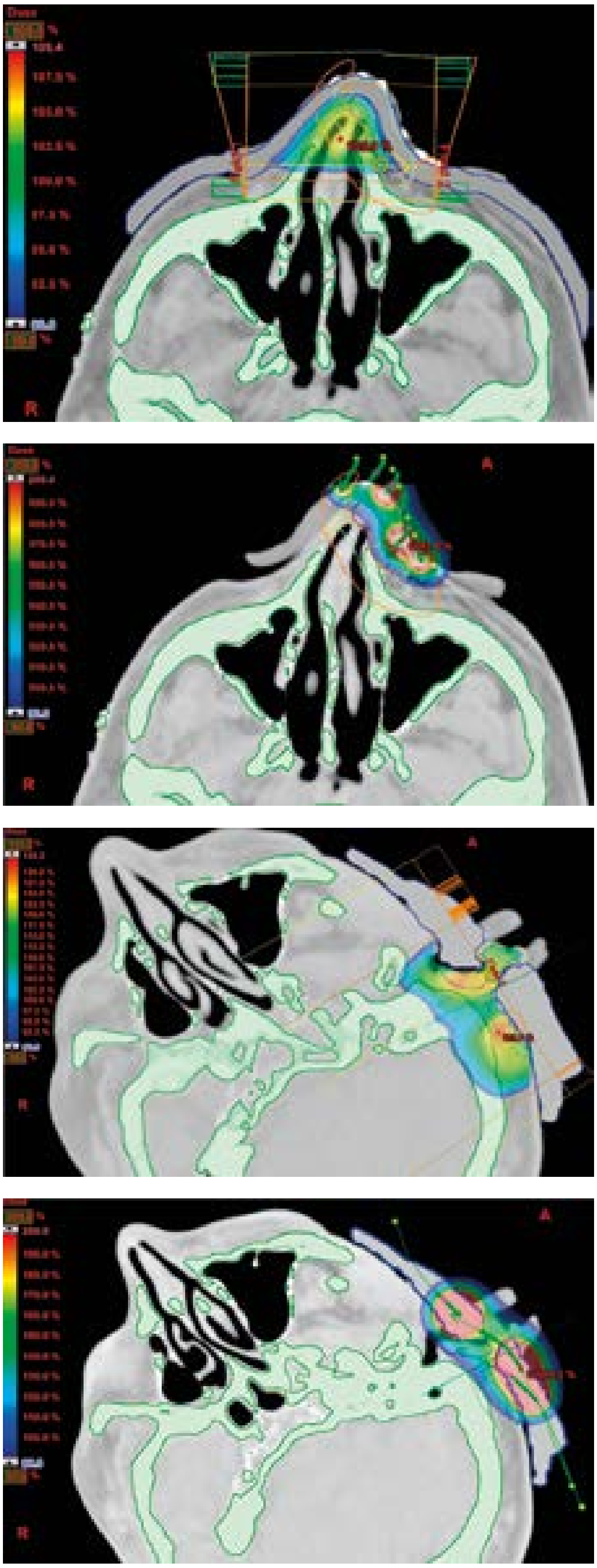

Fig. 3. Comparison of dose coverage of brachtherapy plans and external beam radiation therapy plans. Nose lesion (two upper images) 2-fields 6 MV photons plan vs. high-dose-rate brachytherapy (HDR-BT) plan. Earlobe lesion (two lower images) 12 MEV electron plan vs. HDRBT plan

None of significant OAR was covered by 90% or 100% of prescribed isodose, COIN definitions were adopted as above.

Data analysis

All data were statistically analyzed. Normality of data distribution was confirmed using Shapiro-Wilk test. Normal data distribution applied for $COIN_{90}$ and $COIN_{100}$, $VPTV_{100}$. For those data comparison, *t*-test for paired samples was used. V_{10}, V_{20}, V_{30}, V_{50}, V_{70}, V_{90}, D_{90}, $VPTV_{90}$ was compared on basis of Wilcoxon's test. Results were regarded as significant when $p < 0.05$. Statistica™ ver. 12 (StatSoft, Inc., Tulsa, USA) software was used for calculation.

Results

Analysis of brachtherapy and external beam radiation therapy plans

Equivalent dose in 2 Gy fractions (EQD2 $\alpha/\beta = 10$) for 36 Gy, 40 Gy, 45 Gy were as following 39 Gy, 46.7 Gy, 54.4 Gy. Average PTV volume was 2.59 cc, standard deviation (SD = 1.31). Average BT-D_{90} was 99.4% (SD = 6.5%). Mean BT-$VPTV_{90}$ value was 96.4% (SD = 4.6%). Mean BT-$VPTV_{100}$ was 89.4% (SD = 7.5%).

BT-DHI inside PTV was calculated as 0.76 (SD = 0.13). Mean BT-DNR was 0.23 (SD = 0.13). We obtained conformity index on average BT-$COIN_{90}$ 0.46 (SD = 0.12) and BT-$COIN_{100}$ 0.52 (SD = 0.15). Number of active catheters was correlated with BT-$COIN_{90}$ ($p < 0.05$, $r = 0.67$), and BT-$COIN_{100}$ ($p = 0.01$, $r = 0.76$). Average BT-$VPTV_{125}$ was 46.6% (SD = 14.7%), BT-$VPTV_{150}$ was 18.6% (SD = 11.6%). For deeper infiltrating tumors we tried not to exceed 200% of prescribed dose to most exposed 0.1 cc of skin surface inside PTV. We achieved this goal in all apart from one patient (V_{200} = 0.3 cc). In this individual, technique with insertion of the catheters coated by mould applicator into nasal vestibule was applied. Average $D_{0.1cc}$ and D_{2cc} for bones was 77.7% (SD = 14.2%) and 41.8% (SD = 12.1%), respectively. Mean $D_{0.1cc}$ and D_{2cc} for eyeballs was 17.4% (SD = 7.6%) and 12.1% (SD = 4.5%), respectively. Mean $D_{0.1cc}$ for lens was 12.5% (SD = 5.2%). For EBRT plans, average EBRT-D_5 and EBRT-D_{95} was 109.9% (SD = 8.2%) and 89.6% (SD = 11.7%), respectively. EBRT-DHI was calculated as 1.26 (SD = 0.26). In none of the plans ICRU criteria was fully met with average maximum dose to PTV 112% (SD = 9.3%).

Comparison of external beam radiation therapy and brachtherapy plan

We observed no significant differences in $VPTV_{90}$ and D_{90} between BT and EBRT plans.

Mean BT-$VPTV_{100}$ (89.4%) was higher than EBRT-$VPTV_{100}$ (71.2%) ($p < 0.05$) (Table 1).

Both $COIN_{90}$ and $COIN_{100}$ were superior for BT plans. BT-$COIN_{90}$ 0.46 was significantly higher than EBRT-$COIN_{90}$ 0.21 ($p < 0.01$). BT-$COIN_{100}$ 0.52 was better than EBRT-$COIN_{100}$ 0.26 ($p < 0.01$). We compared volumes receiving 10%, 20%, 30%, 50%, 70%, and 90% of prescribed dose for BT and EBRT (Table 2). We demonstrated more

Table 1. Mean values of dosimetry parameters (described as percentage of total volume) for BT and EBRT plans

	BT plans	EBRT plans	*p*
D_{90}	99.4%	93.9%	0.139
V_{PTV90}	96.4%	95.8%	0.721
V_{PTV100}	89.4%	71.2%	0.013

BT – brachytherapy; EBRT – external beam radiation therapy; D_{90} – minimal dose to 90% of the PTV; V_{PTV90}, V_{PTV100} – volumes of PTV receiving 90% and 100% of prescribed dose

Table 2. Mean volumes for BT and EBRT plans

	BT plans	EBRT plans	*p*
V_{10}	183.4cc	65.7cc	0.005
V_{20}	69.4cc	49.6cc	0.017
V_{30}	37.2cc	42.1cc	0.959
V_{50}	16.7cc	31.3cc	0.074
V_{70}	9.1cc	23.6cc	0.005
V_{90}	5.5cc	16.0cc	0.005

BT – brachytherapy; EBRT – external beam radiation therapy; V_{10}, V_{20}, V_{30}, V_{50}, V_{70}, and V_{90} – volumes of PTV receiving 10%, 20%, 30%, 50%, 70%, and 90% of prescribed dose

exposure of normal tissues in low doses for BT plans; for high doses, BT plans were superior to EBRT plans. BT-V_{10} and BT-V_{20} volume was significantly higher than EBRT-V_{10} and BT-V_{20} ($p < 0.05$). V_{30} and V_{50} volumes were no significantly different but tendency in favor of BT plan exist for V_{50} ($p = 0.07$). Both BT-V_{70} ($p < 0.01$) and BT-V_{90} ($p < 0.01$) were lower than EBRT-V_{70} and EBRT-V_{90}. BT-V_{10} values are understated, because in a few individuals 10% isodose slightly exceed out of imaged area. The difference between the results would have been more pronounced.

Discussion

Plenty of BT modalities dedicated for skin lesions are used in daily clinical practice. Although Leipzig, Valencia, and electronic BT have been proven to be effective for NMSC, they are not feasible for irregular surfaces [12,16,18,19]. We treat patients with individual mould applicators, which were found to be both safe and suitable for superficial lesions in unfavorable locations [20,21].

Its advantages are even more highlighted with 3D-planning. Experience presented in literature in mould BT with 3D-planning is very limited. There are series of cases concerning usage of mould brachytherapy for oral cavity, lips, and other head and neck cancers [22,23,24]. Precision, accurate dose distribution, and normal tissue sparing were highlighted in those studies [22,23]. Intensity modulated radiation therapy (IMRT) was reported to be better option for total scalp irradiation for extensive tumors, but authors admit that BT may be clinically feasible for minor lesions [24]. We found no data about 3D mould brachytherapy for small superficial skin lesions on irregular surfaces. Exact position of catheters determined on basis of CT-images are crucial to calculate dwell position time, and cover of whole PTV on irregular surfaces without overdosage on skin surface.

Dynamic EBRT modalities like IMRT and volumetric arc therapy (VMAT) show advantage in many clinical situations but should be used with caution for irradiation of small target volumes [25]. The concept of IMRT and VMAT is to deliver dose from sum of multiple dynamic fields, which size is smaller than used for 3D conformal radiotherapy for the same target. In our group of patients, the average volume of PTV was 2.59 cc. We did not perform IMRT and VMAT plans due to concerns of major uncertainties of dose delivery with conventional multileaf collimator on small irregular surfaces.

In our group of patients, we obtained excellent coverage of PTV (BT-D_{90} = 99.4%, BT-$VPTV_{90}$ = 96.4%) with acceptable overdosage inside PTV (BT-$VPTV_{125}$ = 46.6%, BT-$VPTV_{150}$ = 18.6). Even without taking into consideration lead shield on eyeballs, doses to D_{2cc} and $D_{0.1cc}$ of OAR were acceptable. Number of catheters was correlated with COIN. We revealed superiority of BT over EBRT in $VPTV_{100}$, which was due to difficulties in planning external beam on irregular thin surfaces as cartilages of nose and earlobe. $VPTV_{100}$ values suffer from uncertainties on skin air gaps interfaces. Deficiencies in dose coverage was observed in spite of perfectly adjacent bolus added by the planning system. This may underscore the superiority of BT. We applied ultrasound gel between skin and mould. It seems to be cost effective and easy to perform method for avoiding minor air gaps between applicator and skin [26]. Haunsfield Unit density is comparable to water [26]. A gel, due to its half liquid form, is only feasible to fill minor gaps to ensure intra fraction reproducible. It cannot be used to overcome bad quality applicators.

We have found BT to be more conformal than EBRT for both $COIN_{90}$ and $COIN_{100}$. Better normal tissue sparing ability of BT was observed for medium to high doses (> V_{50}). Usage of outer lead cover placed on the mould could limit radiation to undesired directions outside of planning target. Small doses may have little relevance for the elderly population, which we included into analysis.

Comparison of homogeneity between presented modalities, due to different dose delivery methods, must be performed on multiple levels. Brachytherapy, with regards its short distance from source to target, is less homogenous modality. DHI formulas describing EBRT and BT are different. We believe that DHI parameters do not show the ultimate value. It is important how inhomogeneity is distributed inside PTV. As described in our paper, we treated patients with lesions with superficial pattern of spread [27]. Isodoses above prescribed dose for BT were located in areas of highest risk of local failure, mainly in macroscopic tumor.

Analysis of small doses suffer from inaccuracies of TG-43 formalism, thus the results for those doses described above (V_{10}, V_{20}, V_{30}, OAR doses) must be handled with caution. We did not perform comparison of doses delivered to OAR. We used shields only during treatment, not while planning CT, and it was not taken into consideration to access doses to OAR. Lead shields placed during imaging cause artefact, preventing proper evaluation of CT. Styrofoam models with geometry of lead shields with override density on planning system could be the solution. In addition, geometry of fields/source position makes those shields more feasible for BT modality. In EBRT, when laterally opposing fields are located on lateral sides of patient, a shield is not positioned on way from virtual source point to OAR (lens). Comparison of BT and EBRT plans was made on basis of widely used algorithms. Both EBRT and BT planning techniques have some limitations for small superficial lesions. We used most common TG-43 formalism for BT planning, which have inaccuracies estimated as 3% for ^{192}Ir skin surface mould applicator [28]. Dosimetry of small photons field is also more complex than standard-size fields [29]. Set-up errors for immobilization in thermoplastic mask are significant, and that implicates the need for margins for EBRT. We did not add margins to make plans more comparable. This underscores the conformity of BT.

As described above, limitations of this study are favoring EBRT, which we showed to be less conformal and normal tissues sparing modality for medium to high doses.

Conclusions

Computed tomography-based surface mould brachytherapy for superficial lesions on irregular surfaces is highly conformal method, which enables perfect dose coverage of PTV with good homogeneity. Brachytherapy is superior to 3D-CRT EBRT in those locations, in terms of conformity and normal tissue sparing ability in medium to high doses. Dose inhomogeneity typical for BT may be desirable, taking into account the way of infiltration of skin cancers. Although, it seems to be common knowledge, literature evidences are missing. This study provides some insight into this subject.

Disclosure

Authors report no conflict of interest.

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