Biological dose summation of external beam radiotherapy for the whole breast and image-guided high-dose-rate interstitial brachytherapy boost in early-stage breast cancer

Georgina Fröhlich, Ph.D.[a,b], Norbert Mészáros, M.D.[a,c], Viktor Smanykó, M.D.[a], Csaba Polgár, D.Sc.[a,c] , Tibor Major, D.Sc.[a,c]

a. National Institute of Oncology, Centre of Radiotherapy, Ráth György Street 7-9, H-1122 Budapest, Hungary

b. Eötvös Loránd University, Faculty of Science, Pázmány Péter mall 1/A, H-1117 Budapest, Hungary

c. Semmelweis University, Faculty of Medicine, Department of Oncology, Ráth György Street 7-9, H-1122 Budapest, Hungary

Corresponding author: Georgina Fröhlich, National Institute of Oncology, Centre of Radiotherapy, Ráth György Street 7-9, H-1122 Budapest, Hungary Tel: +36-1-224-8600, Fax: +36-1-224-8620, E-mail: frohlich.georgina@gmail.com

Biological dose summation of breast tele- and brachytherapy

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Abstract

Objective: To develop an alternative method for summing biologically effective doses of external beam radiotherapy (EBRT) with interstitial HDR brachytherapy (BT) boost in breast cancer. The total doses using EBRT boost will be compared with BT boost using our method.

Methods: Twenty-four EBRT plus interstitial HDR BT plans were selected and additional plans using EBRT boost were created. The prescribed dose was 2.67/40.05 Gy to the whole breast and 4.75/14.25 Gy BT or 2.67/10.7 Gy EBRT to the boost PTV. EBRT and BT CT was registered twice: fitting the target volumes and then using the lung, and the most exposed volume of critical organs in BT were identified on EBRT CT images. The minimal dose of these from EBRT was summed with their BT dose, and these EQD2 doses were compared using BT vs. EBRT boost. This method was compared with uniform dose conception (UDC).

Results: D90 of the boost PTV was significantly higher with BT than with EBRT boost: 67.1 Gy vs. 56.7 Gy, p=0.0001. There was no significant difference in the dose of the non-target and contralateral breast using BT and EBRT boost. The D_1 to skin, lung and $D_{0.1}$ to heart were 58.6 Gy vs. 66.7 Gy (p=0.0025), 32.6 Gy vs. 50.6 Gy (p=0.0002) and 52.2 Gy vs. 58.1 Gy (p=0.0009), while $D_{0.1}$ to ribs was 44.3 Gy vs. 37.7 Gy (p=0.0062), respectively. UDC overestimates D_1(lung) by 54% (p=0.0001), D_1(ribs) by 28% (p=0.0003).

Conclusions: Based on our biological dose summation method, total dose of the PTV in the breast is higher using BT boost, than with EBRT. BT boost yields lower skin, lung and heart doses, but higher dose to ribs. UDC overestimates lung and ribs dose.

Keywords: breast cancer; dose summation; integrated biological doses; boost; interstitial brachytherapy

Introduction

The standard of care in the curative treatment of early-stage breast cancer is breast-conserving surgery and postoperative external beam radiotherapy (EBRT) to the whole breast [1-3]. Since 67-100% of ipsilateral breast recurrences originate from the vicinity of the primary tumour site, dose escalation to the tumour bed has an essential role in the postoperative treatment [4]. Several randomized trials have confirmed that a local boost after the whole breast irradiation significantly decreased the local recurrence rate [4-7]. The most frequently used radiotherapy combination is whole breast EBRT with two tangential photon beams and image-guided interstitial brachytherapy (BT) or EBRT boost to the tumour bed [4-17]. This complex combined treatment requires reliable reporting of the dose received by the whole breast, the boost planning target volume (PTV) and the critical structures.

Modern high-dose-rate (HDR) interstitial BT boost approach results similar or more favourable local control rate than conventional EBRT boost, what is more, BT boost has been linked with lower incidence of late side effects [18-19]. Furthermore, the dose of the most exposed part of the organs at risk (OARs) correlates with normal tissue toxicity [20].

To report the dose-volume parameters properly, overall volumetric doses from external beam- and brachytherapy have to be integrated. As simple physical dose summation does not take into consideration the different biological effects, the equivalent dose given in 2 Gy fractions (EQD2) has to be calculated [21,22]. The dose distribution of the EBRT is assumed to be completely uniform, so the whole breast and the nearest OARs, included in the fields, receive the entire prescribed dose. Then, this equivalent uniform dose is calculated for dose summation with BT doses (Uniform Dose Conception, UDC) [23]. On the other hand, this assumption can be correct only for those organs, which are in the used tangential fields. It is well known that the most exposed part of the OARs in the integrated plans is located in the same region that receives the largest dose from boost BT. Nevertheless, this 1 or 0.1 cm^3 volume is not always in the same location as the most exposed volume of EBRT [24]. So, simple DVH addition sums the dose of two different volumes.

In previous investigations, authors did not consider the real biological dose of the PTV and the OARs in combined EBRT with BT or EBRT boost treatments. Terheyden et al. [25] used the above mentioned UDC method to estimate the doses from EBRT and applied relative physical BT doses only. Shahbazian et al. [26] compared interstitial BT versus EBRT using photon and electron beams for tumour bed boost in deeply seated tumours. Nevertheless, they calculated only the relative dose of the boost treatments, and they did not consider the total

dose of the combined therapy. There is no other study in the literature available, which deals with the biological summation of the dose in combined radiotherapy in early-stage breast cancer.

In the effort to calculate the total biological dose of combined EBRT and BT boost, applying the linear-quadratic formula for a dose-volume parameter is not correct, because the EQD2 dose of a voxel is based on the α/β value and the physical dose in the given voxel. In this way, the quadratic behaviour of the biological dose can not be taken into consideration. The biological dose has to be calculated voxel-by-voxel in the same organ, but currently this feature is not available in any of the treatment planning systems.

In the future, the deformable image registration (DIR) could be an appropriate method to integrate EBRT and BT doses both for the boost PTV and for the OARs, but at present, it results in significant errors, especially where the dose summation is sensitive due to the high dose gradient of BT. Beside the different breast and lung anatomy, the main problems are the plastic catheters in situ, which are not present on EBRT image data sets.

We have developed an alternative dose summation method in combined radiotherapy of cervical and prostate cancer [27,28]. The aim of the present study is to develop an alternative method for summing the biologically effective doses of whole breast EBRT with interstitial HDR BT boost in breast cancer, and compare the results with the UDC method. Additionally, the EQD2 total doses of EBRT for the whole breast plus HDR BT or EBRT boost will also be compared using our dose summation method.

Materials and methods

External beam radiotherapy

Twenty-four EBRT for the whole breast plus interstitial HDR BT boost plans **of the recently treated patients** with early-stage breast cancer were included for this study. The EBRT was performed in supine position, the patients were immobilized with an arm support system. The 40.05 Gy dose was delivered with two tangential 6 MV photon beams with 2.67 Gy daily fractions **in a TrueBeam linear accelerator (Varian Medical Systems, Palo Alto, USA)**. The dose was prescribed to 95% of the dose in the isocentre. Isocentre was located on the central axis CT slice in a midpoint between lung-chest wall interface and skin surface. **Field-in-field technique was used to avoid dose heterogeneities in the breast.** Eclipse v13.7 (Varian Medical Systems, Palo Alto, USA) treatment planning system was used. Based on our local IGRT protocol, CBCT verification was made before the first three fractions, then

the systematic error was calculated and corrected before the 4th fraction followed by weekly verification. For patients, whom BT is not accomplishable, **EBRT boost is performed using a uniform CTV→PTV expansion margin of 0.5 cm.** Therefore, during treatment planning, an additional EBRT boost plan was created **using two field-in-field conformal beams, where 10.7 Gy was prescribed to the PTV in 2.67 Gy daily fractions**, according to the recent recommendations [29].

Brachytherapy

EBRT to whole breast was complemented with CT-guided interstitial multicatheter HDR BT boost 2 to 3 weeks after completing EBRT. Patients were treated with an ^{192}Ir source with 370 GBq initial activity using afterloading technique. The implantations were performed under local anaesthesia. Preimplant CT simulation was performed with template on the breast to define the PTV according to the surgical clips in the tumour bed and plan the needle placement. The PTV (equal to the CTV) was defined as the excision cavity with a margin of 1 to 2 cm according to the surgical tumour-free margin in all main six directions. (The contouring protocol was the same as for EBRT boost.) Following preimplant simulation, 9 to 22 plastic needles (median: 16) were inserted into the previously targeted area in a triangular setting using template guidance. After then, a postimplant CT scanning was made for planning purpose **using the same Thorax-Mamma Hounsfield Unit set as in EBRT CT scan** with 3 mm slice thickness. The active lengths in the catheters were selected in such a way that the extreme source dwell positions in each catheter were on or close to the surface of the PTV. HIPO (Hybrid Inverse Planning Optimization) method (Oncentra Brachy v4.5.3, Elekta Brachytherapy, Veendendaal, The Netherlands) was used to achieve the optimal dose distribution where the target volume coverage by the reference dose is at least 90%, while keeping the dose non-uniformity ratio (DNR) less than 0.35. **The dosimetric assumptions were the following in HIPO preset: 100% minimal (weight: 75) and 150% maximal dose (weight: 25) to the CTV, 50% maximal dose (weight: 40) to the skin, 50% maximal dose (weight: 30) to the ribs and 120% maximal dose (weight: 5) to the normal tissue.** The prescribed dose was 14.25 Gy to the PTV in 3 fractions **(MicroSelectron v3 afterloader, Elekta Brachytherapy, Veendendaal, The Netherlands)**. The detailed description of our treatment method can be found in previous publications [30-34]. The total treatment time of EBRT and BT was 4 weeks (25-28 days). In clinical routine, the UDC method was used to determine the dose constraints for boost PTV and OARs in BT implant and calculate their total doses.

Dose summation

First, the treatment planning CT for EBRT was registered with the postimplant CT set of BT in the EBRT treatment planning system in every case. During the manual registration, the EBRT CT set was shifted and rotated to match the CTVs of BT and EBRT plans (Figure 1a). Then, another registration was made matching the lungs and ribs of BT and EBRT plans (Figure 1b), when the first registration was not appropriate for these OARs too.

Then, the localisation of the most exposed part of the OARs in the sum of EBRT and BT plans was found. **Based on the evaluation of the dose distributions of whole breast EBRT and BT boost treatments (Figure 2a),** the most exposed part of the skin, ipsilateral lung and ribs is in the region where the dose maximum is in BT. So, the BT dose of the most exposed 1 (D_1) and 0.1 cm^3 ($D_{0.1}$) from BT were visualized in the EBRT CTs, and the intersection of this isodose volumes and the given organ was created (Figure 2b). The minimal dose of this intersection was calculated in EBRT plans and summed with the dose of this volumes from BT using the linear-quadratic radiobiological model. In the case of the contralateral breast and heart, the most exposed part is in the region where the dose maximum is in EBRT, as the dose contribution from the EBRT part is higher than the dose from BT boost. For these organs, the most exposed 1 and 0.1 cm^3 from EBRT were used with the same way. The α/β of breast tumour was assumed 4 Gy [29], while for OARs 3 Gy was used. The minimum dose delivered to 90% of the boost PTV (D90) was calculated in the EBRT and BT plans and these doses were summed using also the linear-quadratic model.

Wilcoxon-matched pairs test (Statistica 12.5, StatSoft, Tulsa, OK, USA) was used to compare biological total doses of the combination of whole breast EBRT and BT or EBRT boost in the treatment of early-stage breast tumour. The comparison of our biological dose summation (BDS) and the conventional UDC method was also performed with this statistical test.

Results

EBRT with BT boost

The mean volume of the boost CTV was 47.9 cm^3 (14.3-85.1 cm^3) in BT. The ratio of the boost CTV and the whole breast volume was 0.09 (0.03-0.21). Nine patients had tumour in her left breast and 11 patients in the right one. We found that EQD2 D90 of the boost PTV was 67.1 Gy (64.9-73.7 Gy) using EBRT for whole breast and BT boost. The EQD2 mean dose of the non-target breast was 45.5 Gy (45.4-45.6 Gy) on average. The D_1 and $D_{0.1}$ of

contralateral breast were 0.72 Gy (0.4-1.0 Gy) and 0.99 Gy (0.6-1.5 Gy). The D_1 and $D_{0.1}$ of skin were 58.6 Gy (47.2-79.9 Gy) and 65.8 Gy (49.2-85.6 Gy). The D_1 and $D_{0.1}$ of lung were 32.6 Gy (15.7-46.2 Gy) and 35.3 Gy (17.2-48.5 Gy). The D_1 and $D_{0.1}$ of heart were 50.6 Gy (37.6-61.7 Gy) and 52.2 Gy (38.4-64.0 Gy). The D_1 and $D_{0.1}$ of ribs were 40.2 Gy (34.1-48.1 Gy) and 44.3 Gy (40.0-53.0 Gy).

EBRT with EBRT boost

In EBRT boost, the volume of the PTV is larger than in BT, it was 85.3 cm^3 on average (range: 35.8-132.5 cm^3), however, the volume of the CTV was practically the same, 48.2 cm^3 (15.2-85.9 cm^3) and 47.9 cm^3 (14.3-85.1 cm^3) in EBRT and BT boost plans (p=0.1419). In comparison of BT and EBRT boost techniques, D90 of the boost PTV was significantly higher with BT than with EBRT: 67.1 Gy vs. 56.7 Gy, p=0.0001. There was no significant difference in the dose of the non-target and contralateral breast using BT and EBRT boost. The D_1 to skin was 58.6 Gy (47.2-79.9 Gy) and 66.7 Gy (65.5-67.5 Gy), p=0.0025, the D_1 to lung was 32.6 Gy (15.7-46.2 Gy) and 50.6 Gy (37.6-64.0), p=0.0002, $D_{0.1}$ to heart was 52.2 Gy (38.4-64.0 Gy) and 58.1 Gy (51.7-69.1 Gy), p=0.0009, while $D_{0.1}$ to ribs was 44.3 Gy (40.0-53.0 Gy) and 37.7 Gy (26.6-60.5 Gy), p=0.0062, respectively (Figure 3). The detailed results can be found in Table 1.

UDC-method

Comparing our dose summation method to the conventional UDC in the case of combined EBRT with BT boost, we found that the UDC overestimates D_1 of lung by 54% (p=0.0001), D_1 of ribs by 28% (p=0.0003). The detailed results can be found in Table 2.

Discussion

Dose escalation has a fundamental role in the postoperative radiotherapy of early-stage breast cancer [4]. Presently, one of the best alternatives for boost is BT, however, a controversy still exists regarding the optimal technique. Traditionally, EBRT with electron or photon beams have been used to deliver the boost dose to the tumour bed [3]. Later, HDR BT has been also accepted as a safe alternative boost modality [4-17].

Poortmans et al. [18] have pointed out the favourable local control rate with BT boost compared to EBRT boost. They also showed the lower incidence of side effects with BT boost [18], what we confirmed in a previous study [19]. We also demonstrated the correlation between dose-volume parameters and side effects [20]. The volume of the PTV, the ratio of

the PTV and the whole breast, the volume irradiated at least the prescribed dose, the number of catheters and TRAK increase the risk of late side effects. The volume irradiated at least the 150% of the prescribed dose causes more Grade I pain in the breast, while maximal dose of the skin increased the risk of Grade I hyperpigmentation. The EQD2 prescribed dose to the boost PTV with our fractionation scheme is 65.3 Gy using BT and 56.4 Gy with EBRT boost. Despite the fact, that BT irradiated the boost volume almost with 10 Gy more dose, than EBRT boost technique, at the same time dose to the OARs is reduced with BT. In our study, using EBRT with HDR BT boost doses to all OARs can be kept under the tolerance levels. The EQD2 D90 of the PTV was 67.1 Gy, while the mean dose of the non-target breast was 45.5 Gy. The D_1 and $D_{0.1}$ of contralateral breast was negligible, 0.72 and 0.99 Gy. The D_1 dose of the skin was 58.6 Gy, 87% of the total dose of the PTV. The D_1 dose to the lung was 32.6 Gy on average, approximately the half of the prescribed dose, while the D_1 of the ribs was 40.2 Gy in our study, in spite of that the PTV is very close to the ribs in the case of deeply seated tumours. D_1 to heart was 50.6 Gy on average in the case of left sided tumours.

Notwithstanding, in EBRT boost larger target volume is used than in BT, the total dose to the PTV is 18% less in our patient cohort, D90 was 67.1 Gy using BT and 56.7 Gy with EBRT boost. There were no significant differences in the dose of non-target and contralateral breast between the two boost techniques. D_1 dose to the skin and lung were smaller with 14% (8.1 Gy) and 55% (18 Gy) using BT, than with EBRT boost. $D_{0.1}$ to heart was slightly higher with EBRT, than with BT boost (58.1 Gy vs. 52.2 Gy), but both doses are clinically acceptable. Only the dose to the ribs was higher with BT boost, D_1 was higher with 15% (5.2 Gy) than using EBRT boost. It has to be stated, that no ribs toxicity was detected in our study population. Terheyden et al. [25] concluded the same tendency in case of the OARs. They confirmed, that there is no difference between BT and EBRT boost for left-sided cancers regarding the dose to the heart, although they used physical maximal point doses in their study. Shahbazian et al. [26] also showed the reduced dose to OARs using BT instead of EBRT boost with photon or electron beams. However, they used only relative dose-volume parameters. The lower dose to the critical organs using BT boost can account for the less toxicity in the case of BT compared to EBRT boost.

In previous publications authors used the recommended UDC method to estimate the total dose of the prostate and OARs in combined therapy and calculated the relative dose-volume parameters only [25,26]. However, they did not consider the real biological doses. Since the most exposed part of the skin, lung and ribs is in the region where the dose maximum is in BT, and the most exposed part of the contralateral breast and heart is in the

region where the dose maximum is in EBRT, this most exposed 1 and 0.1 cm^3 can be used for the calculation of the total biological dose. In this small volume, we can disregard the quadratic dependence. Thus, our dose summation method is simple, timesaving and more personalised than the UDC method. The only more precise method would be a pixel-by-pixel calculation of the biological dose in the same organ after a deformable registration of BT and EBRT image series, but no treatment planning systems provides this possibility at the moment.

The effect of the dose summation technique on dose-volume parameters in combined EBRT and BT was also investigated in our study. The EQD2 D90 of the boost PTV was 0.7% higher in our BDS than the conventional UDC method, but this 0.5 Gy difference is clinically negligible. The mean dose to the non-target breast and the D_1 to skin was practically equivalent in our BDS and the UDC method. Nevertheless, UDC overestimates the total D_1 dose to lung by 54% (17.5 Gy) and D_1 dose to ribs by 2.5% (11.2 Gy) compared to BDS method. The cause may be the development of EBRT techniques, such as using field-in-field technique instead of wedges and image-guidance during dose delivery, resulting in decreased dose of critical structures. Accordingly, the potential advantage of the BDS method is that it considers the most exposed part of the OARs and thus sparing these parts from higher doses in EBRT before boost irradiation. On the whole, the dose to the OARs can be reduced using our alternative dose summation method, therefore the treatment related toxicity can be decreased.

It has to be mentioned that this dose summation method can cause uncertainties too. The possible sources of error could be the subjectivity of the manual registration process, difference between the EBRT and the BT boost CTV and possible movement of the surgical clips in the tumour bed due to tissue necrosis.

This study is the starting point of the development of an algorithm for the summation of EBRT and BT biologically effective doses, which uses an artificial-intelligence-based DIR algorithm to match the critical anatomical structures in the two radiotherapy modalities. Further investigations are needed to assess whether our method predicts toxicity better than the recent UDC method.

Conclusions

Based on our biological dose summation method in EBRT for whole breast with interstitial HDR BT or EBRT boost treatment in early-stage breast cancer, total dose of the boost PTV is higher using BT boost, than EBRT. Following the recommended fractionation scheme, BT

boost yields lower skin, lung and heart doses, but higher dose to ribs. UDC overestimates lung and ribs dose compared to our method.

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Tables:

EQD2	EBRT + BT boost	EBRT + EBRT boost	**p-value
D90 (Gy)	67.1 (64.9-73.7)	56.7 (55.3-58.4)	**0.0001**
D_{mean}(non-target breast) (Gy)	45.5 (45.4-45.6)	47.0 (38.8-54.3)	0.1590
D_1(contralat breast) (Gy)	0.72 (0.4-1.0)	0.64 (0.1-1.0)	0.3787
$D_{0.1}$(contralat breast) (Gy)	0.99 (0.6-1.5)	1.1 (0.6-1.6)	0.3341
D_1(skin) (Gy)	58.6 (47.2-79.9)	66.7 (65.5-67.5)	**0.0025**
$D_{0.1}$(skin) (Gy)	65.8 (49.2-85.6)	67.4 (65.9-70.4)	0.5197
D_1(lung) (Gy)	32.6 (15.7-46.2)	50.6 (37.6-64.0)	**0.0002**
$D_{0.1}$(lung) (Gy)	35.3 (17.2-48.5)	52.2 (38.4-61.7)	**0.0002**
***D_1(heart) (Gy)**	50.6 (37.6-61.7)	53.2 (51.0-55.5)	0.0765
***$D_{0.1}$(heart) (Gy)**	52.2 (38.4-64.0)	58.1 (51.1-69.1)	**0.0009**
D_1(ribs) (Gy)	40.2 (34.1-48.1)	35.0 (20.0-57.3)	0.0642
$D_{0.1}$(ribs) (Gy)	44.3 (40.0-53.0)	37.7 (26.6-60.5)	**0.0062**

Table 1. The EQD2 total doses of external beam radiation therapy plus interstitial HDR BT boost (EBRT + BT boost) and external beam radiation therapy plus external beam radiation therapy boost (EBRT + EBRT boost). D90: the minimum dose delivered to 90% of the boost PTV (Gy), D_{mean}(non-target breast): the mean dose of non-target breast, D_1(x), $D_{0.1}$(x): the minimal dose of the most exposed 1 and 0.1 cm^3 of 'x' organ at risk, where x are contralateral breast (contralat breast), skin, lung, heart and ribs. *Left sided tumours. **Wilcoxon-matched pairs test.

EQD2	BDS	UDC	*p-value
D90 (Gy)	67.1 (64.9-73.7)	66.6 (65.3-72.2)	**0.0386**
D_{mean}(non-target breast) (Gy)	45.5 (45.4-45.6)	45.5 (45.5-45.6)	0.7353
D_1(skin) (Gy)	58.6 (47.2-79.9)	57.7 (47.2-73.5)	0.3061
$D_{0.1}$(skin) (Gy)	65.8 (49.2-85.6)	63.5 (46.2-88.4)	0.0534
D_1(lung) (Gy)	32.6 (15.7-46.2)	50.1 (47.0-57.3)	**0.0001**
$D_{0.1}$(lung) (Gy)	35.3 (17.2-48.5)	51.1 (47.2-60.3)	**0.0001**
D_1(ribs) (Gy)	40.2 (34.1-48.1)	51.4 (47.0-61.6)	**0.0001**
$D_{0.1}$(ribs) (Gy)	44.3 (40.0-53.0)	53.5 (47.5-65.7)	**0.0003**

Table 2. The EQD2 total doses of external beam radiation therapy plus interstitial HDR BT boost calculated by our biological dose summation (BDS) and the uniform dose conception (UDC) method. D90: the minimum dose delivered to 90% of the boost PTV (Gy), D_{mean}(non-target breast): the mean dose of non-target breast, D_1(x), $D_{0.1}$(x): the minimal dose of the most exposed 1 and 0.1 cm^3 of 'x' organ at risk, where x are skin, lung and ribs. *Wilcoxon-matched pairs test.

Figures:

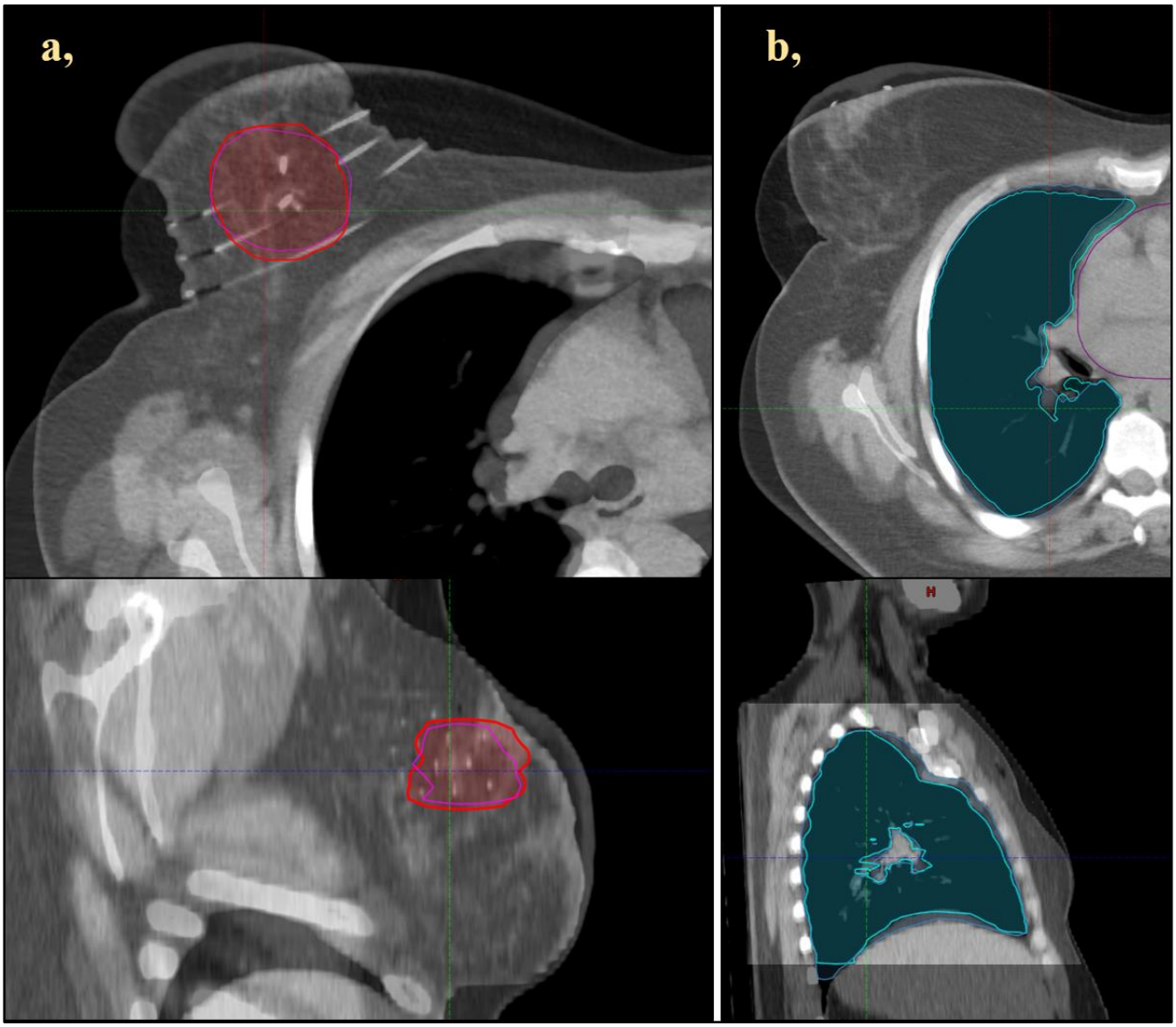

Figure 1. Registration of the EBRT and BT CT sets based on the CTVs (red and pink) (a,) and the lung contours (turquoise and blue) (b,) on an axial (top) and a sagittal (bottom) plane.

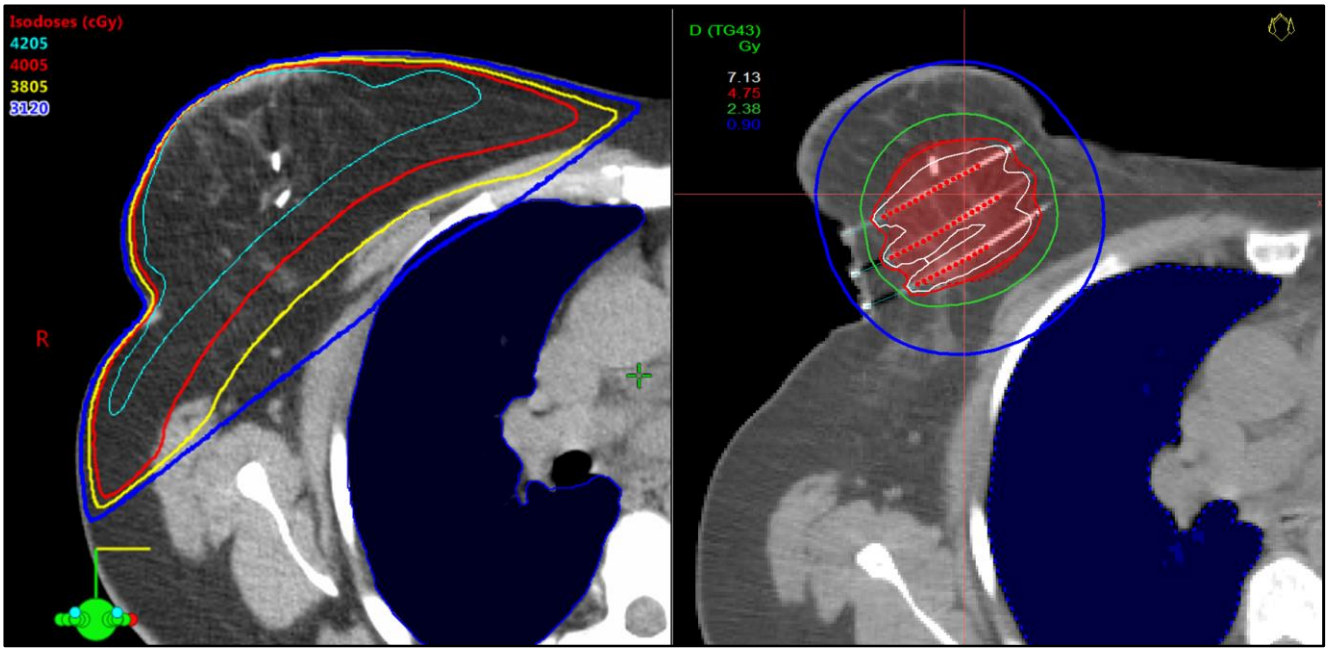

Figure 2a. Typical dose distribution of whole breast EBRT (left) and BT boost (right) in the axial slice where the most exposed 1 cm^3 part of the lung (blue) is (CTV: red).

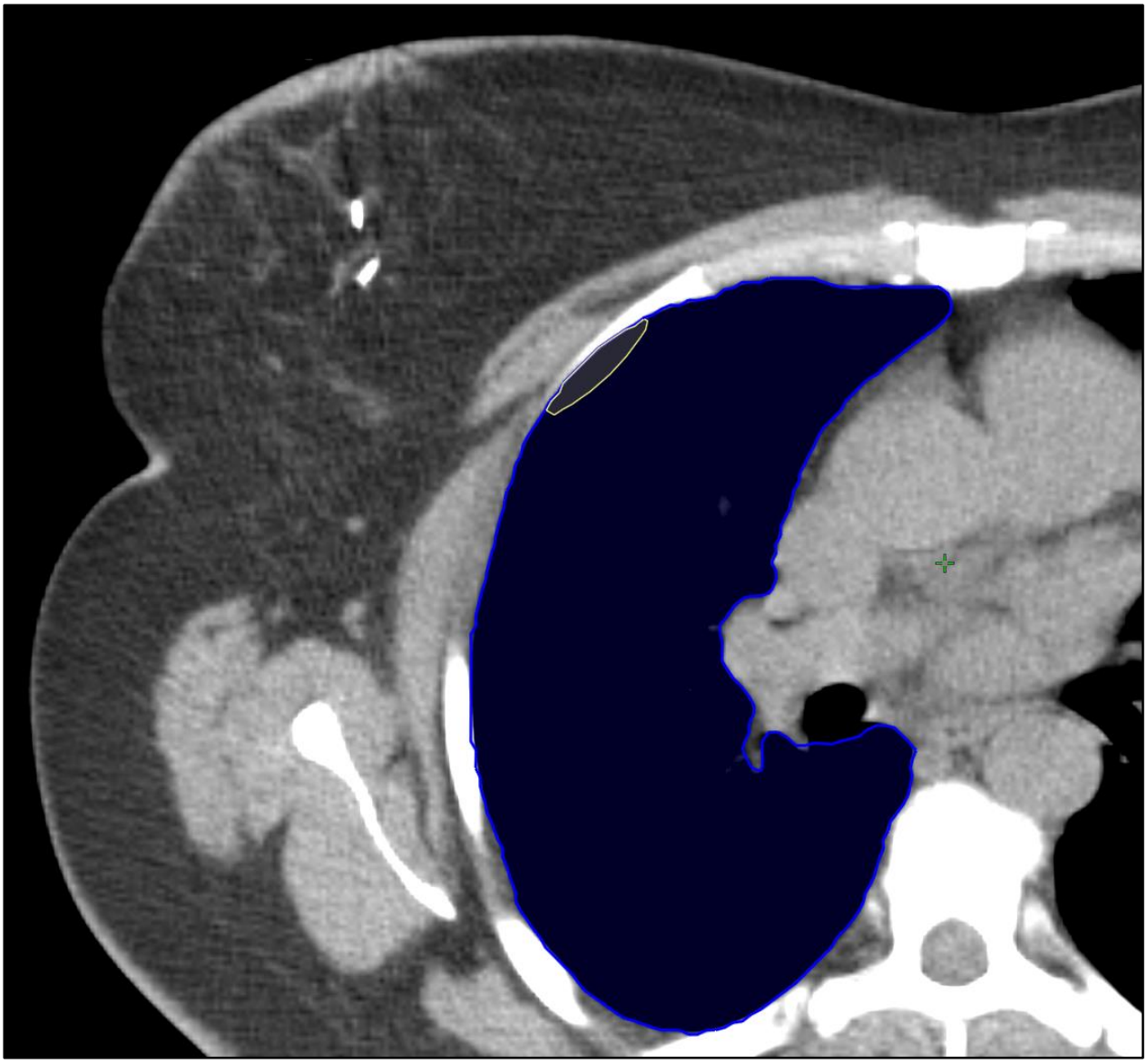

Figure 2b. The most exposed 1 cm^3 part (yellow) of the lung (blue) in an axial slice of the EBRT CT.

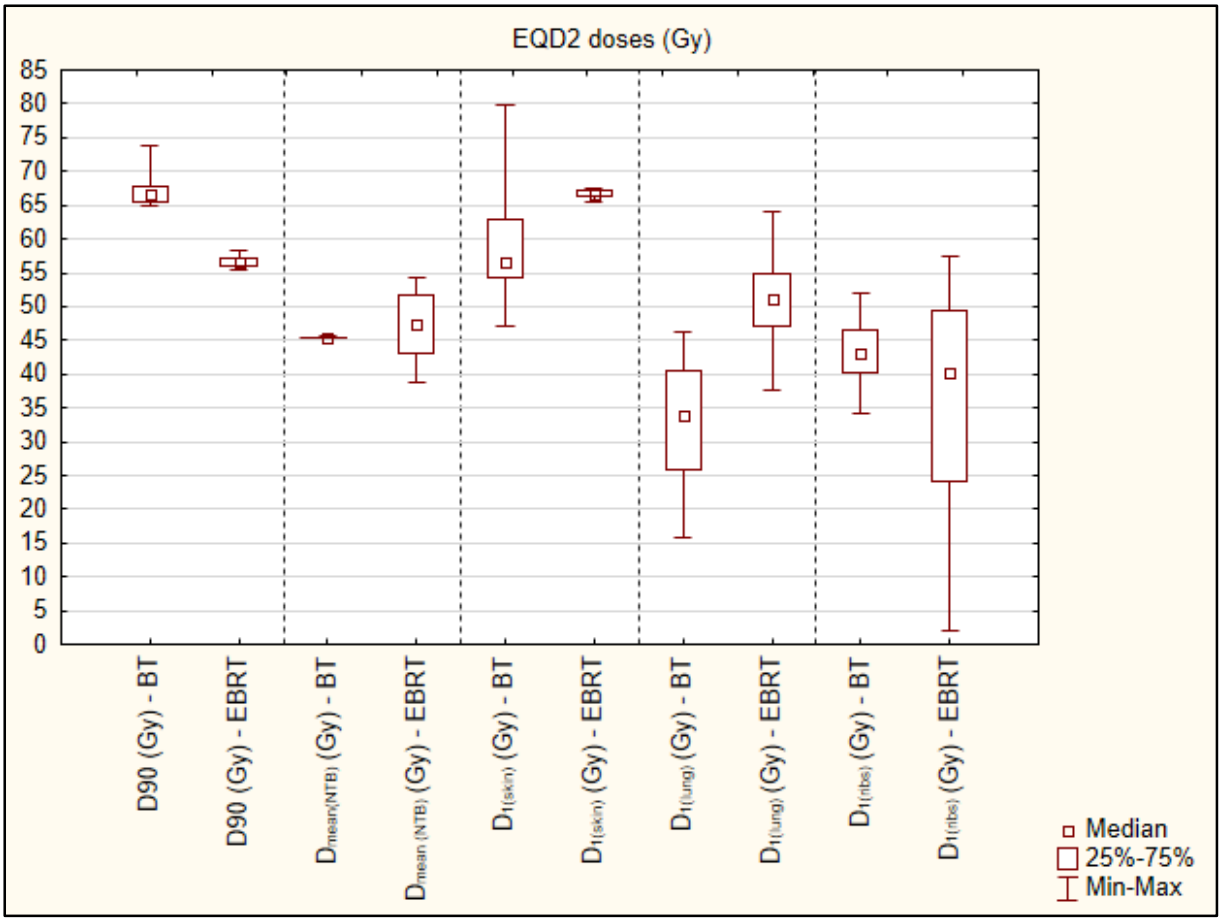

Figure 3. The EQD2 total doses of external beam radiation therapy plus interstitial HDR BT boost (BT) and external beam radiation therapy plus external beam radiation therapy boost (EBRT). D90: the minimum dose delivered to 90% of the boost PTV (Gy), D_{mean}(NTB): the mean dose of non-target breast, D_1(x), $D_{0.1}$(x): the minimal dose of the most exposed 1 and 0.1 cm^3 of 'x' organ at risk, where x are skin, lung and ribs.