Eur J Nucl Med Mol Imaging
DOI 10.1007/s00259-012-2197-6

ORIGINAL ARTICLE

# 3D dosimetry in patients with early breast cancer undergoing Intraoperative Avidination for Radionuclide Therapy (IART®) combined with external beam radiation therapy

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Received: 20 March 2012 / Accepted: 13 July 2012


**Abstract**
*Purpose* Intraoperative Avidination for Radionuclide Therapy (IART®) is a novel targeted radionuclide therapy recently used in patients with early breast cancer. It is a radionuclide approach with $^{90}$Y-biotin combined with external beam radiotherapy (EBRT) to release a boost of radiation in the tumour bed. Two previous clinical trials using dosimetry based on the calculation of mean absorbed dose values with the hypothesis of uniform activity distribution (MIRD 16 method) assessed the feasibility and safety of IART®. In the present retrospective study, a voxel dosimetry analysis was performed to investigate heterogeneity in distribution of the absorbed dose. The aim of this work was to compare dosimetric and radiobiological evaluations derived from average absorbed dose vs. voxel absorbed dose approaches.
*Methods* We evaluated 14 patients who were injected with avidin into the tumour bed after conservative surgery and 1 day later received an intravenous injection of 3.7 GBq of $^{90}$Y-biotin (together with 185 MBq $^{111}$In-biotin for imaging). Sequential images were used to estimate the absorbed dose in the target region according to the standard dosimetry method (SDM) and the voxel dosimetry method (VDM). The biologically effective dose (BED) distribution was also evaluated. Dose/volume and BED volume histograms were generated to derive equivalent uniform BED (EUBED) and equivalent uniform dose (EUD) values.
*Results* No "cold spots" were highlighted by voxel dosimetry. The median absorbed-dose in the target region was 20 Gy (range 15–27 Gy) by SDM, and the median EUD was 20.4 Gy (range 16.5–29.4 Gy) by the VDM; SDM and VDM estimates differed by about 6 %. The EUD/mean voxel absorbed dose ratio was >0.9 in all patients, indicative of acceptable uniformity in the target. The median BED and EUBED values were 21.8 Gy (range 15.9–29.3 Gy) and 22.8 Gy (range 17.3–31.8 Gy), respectively.
*Conclusion* VDM highlighted the absence of significant heterogeneity in absorbed dose in the target. The EUD/mean absorbed dose ratio indicated a biological efficacy comparable to that of uniform distribution of absorbed dose. The VDM is recommended for improving accuracy, taking into account actual activity distribution in the target region. The radiobiological model applied allowed us to compare the effects of IART® with those of EBRT and to match the two irradiation modalities.

**Electronic supplementary material** The online version of this article (doi:10.1007/s00259-012-2197-6) contains supplementary material, which is available to authorized users.

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Published online: 14 August 2012

**Keywords** Three-dimensional dosimetry · IART® · Voxel dosimetry · Radiobiological model · Accelerated breast irradiation

## Introduction

A new procedure called IART® (Intraoperative Avidination for Radionuclide Therapy) was recently developed at the European Institute of Oncology and used in patients with early breast cancer undergoing conservative surgery [1, 2]. The purpose of the therapy was to irradiate the residual mammary gland immediately after surgery in order to give an "anticipated boost" corresponding to a biologically effective dose (BED) of at least 21 Gy. Four weeks after IART®, patients were scheduled for a shortened course of external beam radiation therapy (EBRT) [3]. IART® is a radionuclide targeted therapy based on the high affinity between avidin and biotin consisting of two steps. In the first step, after tumour removal during surgery, the surgeon injects 100 mg of avidin directly into the tumour bed. In the second step, 16–24 h later, $^{90}$Y-DOTA-biotin is intravenously injected and accumulates in the index quadrant with a high and stable uptake (the fraction of administered activity in the source region is about 10 % [4]).

Clinical and dosimetric results of phase I and II studies have already been reported [1–3], and show that IART® releases a boost of 21±4 Gy BED to the index quadrant in patients receiving 100 mg avidin and 3.7 GBq of $^{90}$Y-biotin with excellent tolerability and compliance. The previously reported results [2, 3] provided absorbed-dose estimates averaged at the level of the selected breast regions using a standard 3D imaging approach [5]. Although robust for a first investigation and more accurate than the data obtained from planar imaging, the limitations of this method are clear: median self doses are available, and only for activity uniformly distributed in areas of spherical shape, neglecting the real geometry, activity distribution, and crossfire contribution from surrounding tissues.

The next challenge was to obtain more detailed information for the implementation of personalized treatment planning, focusing on the distribution of the radiopharmaceutical in the breast tissues. SPECT images allowed heterogeneity in activity distribution within the targeted breast region to be taken into account and 3D absorbed-dose calculations to be performed at the voxel level by using the voxel dosimetry method (VDM) [6]. We thus applied the VDM to he patients treated with IART® in the phase II study and compared the results with those obtained from the previous approach (standard dosimetry method, SDM) with which the simplification of targeted areas of spherical shape is accepted [2, 3]. We also analysed the impact of possible heterogeneity on therapy outcome using the linear quadratic radiobiological model. The BED volume histograms (BVH), equivalent uniform BEDs (EUBED) and equivalent uniform doses (EUD) were derived as the basis for the integration with the external beam radiation modality.

## Materials and methods

### Patients

We studied 14 out of 35 patients enrolled in the phase II study [3]. Only patients who had received 100 mg of avidin (experimentally shown to be the optimal amount for injection) were selected for this analysis. IART® was performed according to a previously described method [3]. Avidin (100 mg; Sigma-Tau, Pomezia, Italy) was injected into the tumour bed during surgery, as described elsewhere [3]. About 18 h after avidin administration (range 14–24 h), 10 mg of biotinylated human serum albumin (HSA-biot; Sigma-Tau) was administered intravenously over 5 min to chase any excess circulating avidin before the administration of radiolabelled biotin [2]. Starting 10 min later, $^{90}$Y-DOTA-biotin (3.7 GBq, 4 GBq/mg) premixed with 185 MBq of $^{111}$In-DOTA-biotin (4 GBq/mg) was administered intravenously over 30 min. Both radiolabelled compounds were prepared as described elsewhere [2]. $^{111}$In was used as a biological surrogate to trace the biodistribution of the $^{90}$Y-labelled therapeutic agent. Four weeks after IART®, patients underwent EBRT in the residual breast, with a total absorbed dose of 40 Gy released in standard fractions of 2 Gy for 5 days per week over a shortened 4-week period [3].

### Dosimetry and radiobiological estimates

Biodistribution and pharmacokinetics were assessed as previously reported [3]. Briefly, sequential whole-body images (at 1.5±0.5 h, 5±2 h, 16±4 h, and 24±6 h after injection) plus SPECT (at 16±4 h after injection) were acquired (Infinia II; GE Healthcare, Waukesha, WI) [1, 3]. Planar images [5] were corrected for scatter (energy window subtraction method) and attenuation (transmission scan), while SPECT images were scatter-corrected and reconstructed by filtered back-projection. For more detailed information see the Supplementary data. Absorbed dose estimates for non-target organs have been reported elsewhere [1, 2], while in the present study dosimetry and radiobiological evaluations focused on the breast with a comparison between 3D SDM and VDM.

The activity distribution in the breast typically showed a selective concentration at the avidin injection site, with a marked decrease in nearby tissues. For each patient, planar images were used to characterize the biokinetics of the

whole breast uptake region, while the SPECT scan provided the 3D activity distribution. That is, planar whole-body images were used to derive biokinetics data based on the relative method [7, 8] to quantify the activity at any time in the total body and in the regions of interest. At the time of SPECT acquisition the majority of the injected activity would have been eliminated and the remaining activity would essentially be localized in the breast tissue (more than 8 % of the total activity in the breast, less than 7 % in other organs and the remainder of the body—mean values among patients). So the treatment can be considered as a locoregional one, with the uptake concentrated in a limited region of the breast, without involvement of the intrathoracic structures. This amount of activity, determined from the whole body, was associated with the counts within the corresponding area in the SPECT images and used to derive the activity distribution at one time-point.

In previous studies, the whole uptake (WU) region was divided into three areas on both SPECT and planar images: (1) high uptake (HU) area (defined as iso-ROI-50 %, which includes all the voxels having more than 50 % of the maximum count), (2) mean uptake (MU) area (defined as the region between iso-ROI-50 % and iso-ROI-30 %), (3) low uptake (LU) area (defined as the region between iso-ROI-30 % and iso-ROI-10 %). The WU region determined on the whole-body images at 16±4 h was copied to the other planar images. Time–activity curves for the WU region were built and fitted by a monoexponential function. The effective half-life and the time-integrated activity coefficient, $\tilde{a}$ [4], were obtained and indicated by $\tilde{a}_{\mathrm{WU}}$. The value of $\tilde{a}$ for the WU area on SPECT images was set equal to the one obtained from planar images. To consider the activity distribution from SPECT images within the WU region, the region was further analysed for the three distinct areas (HU, MU, LU) based on simple proportions of the counts obtained in SPECT images, that is:

$$\widetilde{a}_{HU} = \widetilde{a}_{WU} \cdot \frac{counts_{HU}}{counts_{WU}} \tag{1a}$$

$$\widetilde{a}_{MU} = \widetilde{a}_{WU} \cdot \frac{counts_{MU}}{counts_{WU}} \tag{1b}$$

$$\widetilde{a}_{LU} = \widetilde{a}_{WU} \cdot \frac{counts_{LU}}{counts_{WU}} \tag{1c}$$

This was considered acceptable after observing that in planar images, the shape/extension of each breast region did not change with time. The volumes of all uptake areas were determined from SPECT images.

*Standard method*

The volumes of the three uptake areas were approximated as sources of spherical shape with uniformly distributed activity. The self absorbed dose per unit activity in each area was calculated, inserting the $\tilde{a}$ values in the sphere module of the OLINDA/EXM software [9]. Applying the linear quadratic model, the BED was evaluated for each of the three areas (UP, MU, LU), according to [10]:

$$BED = D\left(1 + \frac{D \cdot \lambda}{(\mu + \lambda) \cdot \alpha/\beta}\right) \tag{2}$$

where

- $D$ is the absorbed dose in the breast area due to injection of $^{90}$Y-DOTA-biotin.
- $\mu$ is the sublethal damage recovery constant (0.5 $h^{-1}$) [11].
- $\lambda$ is the effective dose rate constant in the whole breast region (patient-specific; $h^{-1}$).
- $\alpha/\beta$ is a radiosensitivity parameter relating the intrinsic radiosensitivity ($\alpha$) to the potential sparing capacity ($\beta$) for a specified tissue or effect. The $\alpha/\beta$ parameter was set at 10 Gy for tumours [11].

*Voxel method*

The voxel method was applied to the breast region with the hypothesis of homogeneous density. We assumed that the biokinetics of each voxel followed that of the whole breast region. The value of $\tilde{a}$ in any single voxel was derived from the $\tilde{a}_{\mathrm{WU}}$ value by proportion:

$$\widetilde{a}_{voxel} = \widetilde{a}_{WU} \cdot \frac{counts_{voxel}}{counts_{WU}} \tag{3}$$

For calculation of the voxel absorbed dose, a program [12] developed in the MATLAB® (MathWorks) environment was used. Reconstructed SPECT images were the input data for the program to analyse the activity distribution map and to derive the activity volume histograms for the HU, MU and LU areas. As a second step, the program calculated the absorbed dose distribution map according to MIRD 17 [6], with the absorbed dose at the voxel level evaluated according to:

$$D_{\mathrm{voxel},k} = \sum_{h=0}^{M} \widetilde{A}_{\mathrm{voxel},h} \cdot S_{\mathrm{voxel},k \leftarrow \mathrm{voxel},h} \tag{4}$$

where $D_{\mathrm{voxel},k}$ is the absorbed dose to a given target voxel,$k$ due to irradiation from $M$ surrounding source voxels; $\tilde{A}_{\mathrm{voxel},h}$ is the time-integrated activity in any voxel $h$; $S_{\mathrm{voxel},k \leftarrow \mathrm{voxel},h}$ is the voxel $S$ factor specific for any voxel,$h$ contributing to the absorbed dose to voxel,$k$. As the SPECT voxel size is equal to

4.4 mm for any source voxel,*h*, the surrounding cubic array of 7×7×7 voxels (including the source voxel) was considered for convolution. The maximum distance from the source voxel was 13.2 mm, a choice related to the maximum range of the $^{90}$Y particles (about 11 mm). The voxel *S* factors for $^{90}$Y and 4.4 mm side were evaluated by Monte Carlo simulation with PENELOPE code [13, 14; www.df.unibo.it/medphys]. The BED for each voxel, $\mathrm{BED}_{\mathrm{voxel},k}$, was evaluated by Eq. 2 with $D_{\mathrm{voxel},k}$ replacing *D*.

$D_{\mathrm{voxel},k}$ and $\mathrm{BED}_{\mathrm{voxel},k}$ were used to generate absorbed dose histograms (DVH) and BVH, as well as the mean absorbed dose among voxels ($\overline{D}_{vox}$) and the mean BED among voxels ($\overline{BED}_{vox}$).

In order to assess the possible radiobiological effects of heterogeneity in the absorbed dose and dose rate, the EUBED [15] and the EUD were calculated. The EUBED represents the biological absorbed dose which would result from a uniform absorbed dose delivered to the same volume and which would produce the same number of surviving cells. The EUBED was calculated as follows:

$$EUBED = \frac{1}{\alpha}\left[-\ln\frac{\sum_{i=0}^{N_{voxels}}\exp(-\alpha\cdot BED_i)}{N\ voxels}\right] \quad (5)$$

where $N_{\mathrm{voxels}}$ is the total number of voxels constituting the region where EUBED is being calculated; and $\exp(-\alpha\cdot \mathrm{BED}_i)$ is the expression of the fraction of surviving cells (SF) in each target voxel; the value of $\alpha$ was set at 0.3 $\mathrm{Gy}^{-1}$ [11].

For evaluation of EUD we considered that homogeneous and heterogeneous absorbed dose distributions were equivalent from a radiobiological perspective if leading to the same fraction of surviving clonogens:

$$\mathrm{SF}_{\mathrm{heterogeneity}} = \mathrm{SF}_{\mathrm{uniformity}} \quad (6)$$

$$\exp(-\alpha\mathrm{EUBED}) = \exp\left(-\alpha\mathrm{EUD}\left(1+\frac{\lambda}{(\mu+\lambda)\cdot\alpha/\beta}\mathrm{EUD}\right)\right) \quad (7)$$

$$\mathrm{EUBED} = \mathrm{EUD} + \frac{\lambda}{(\mu+\lambda)\cdot\alpha/\beta}\mathrm{EUD}^2 \quad (8)$$

$$\mathrm{EUD} = \frac{-1+\sqrt{1+4\frac{\lambda}{(\mu+\lambda)\cdot\alpha/\beta}\mathrm{EUBED}}}{2\frac{\lambda}{(\mu+\lambda)\cdot\alpha/\beta}} \quad (9)$$

The ratio $\overline{D}_{vox}/EUD$ was considered to be representative of the absorbed dose heterogeneity, whereas the ratio $D_{\mathrm{standard}}/\mathrm{EUD}$ directly compares the 3D SDM and VDM results. Similarly, the ratio $\overline{BED}_{vox}/EUBED$ is representative of the heterogeneity of the radiobiological effect, whereas the difference between BED and EUBED compares the radiobiological effects derived by the two dosimetric methods.

Finally, the corresponding absorbed dose delivered with EBRT in a standard scheme of 2 Gy per fraction that would

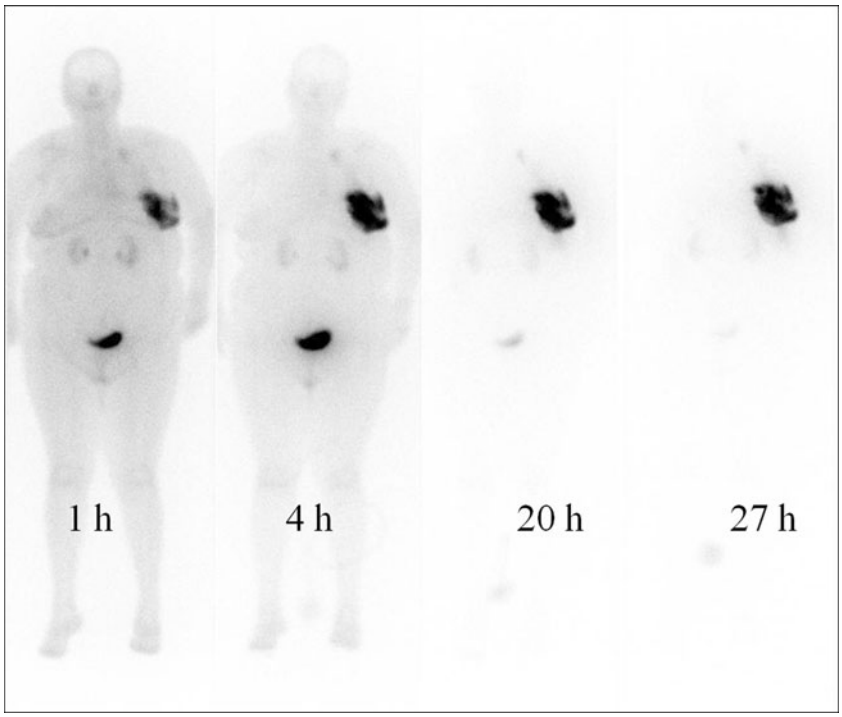


**Fig. 1** Anterior whole-body scintigraphic images of patient 4, acquired 1, 4, 20 and 27 h after injection

**Table 1** Breast region areas characteristics. The data are presented are medians (ranges)

| Uptake area | Volume (ml) | Fraction of injected activity (%) | $\tilde{a}$ (h) |
|---|---|---|---|
| HU (target) | 220 (120–450) | 2.9 (1.3–5.4) | 2.6 (1.2–4.7) |
| MU | 380 (140–490) | 2.6 (1.0–4.5) | 2.3 (0.9–3.7) |
| LU | 815 (340–1,015) | 2.6 (1.1–5.1) | 2.2 (1.0–3.1) |

produce the biological effect associated with a certain EUBED was derived from:

$$\mathrm{EUBED_{IART}} \equiv \mathrm{BED_{EBRT}} = D_{2\mathrm{Gy/fr}}\left(1+\frac{D_{2\mathrm{Gy/fr}}}{n\cdot\alpha/\beta}\right) = 2n\left(1+\frac{2}{\alpha/\beta}\right) \tag{10}$$

where $n$ is the number of EBRT fractions and $D_{2\mathrm{Gy/fr}} = n \cdot 2$ Gy is the total prescribed absorbed dose with EBRT. This allowed EUD values from IART® to be compared with absorbed doses uniformly released with $\mathrm{EBRT_{2Gy}}$ (at 2 Gy per fraction) and the number of EBRT fractions that would be required to cover the equivalent radiobiological effect produced by IART® to be extrapolated. Explicitly:

$$n = \frac{EUBED_{IART}}{2\cdot\left(1+\frac{2}{\alpha/\beta}\right)} \tag{11}$$

## Results

Whole-body scintigraphic images (Fig. 1) showed rapid and intense uptake of radioactivity in the surgically treated breast in all patients. The shape of the whole breast region did not change over time. The activity uptake in the surgically treated breast, evaluated in all patients, ranged from 4 % to 12 % of the total injected activity, with a median value of 8 %. The median value of the effective dose rate constant $\lambda$ was 10.5 $h^{-1}$ (range 6.7–37.2 $h^{-1}$), leading to an $\tilde{a}$ value for the whole breast of 7.0 h (3.4–10.1 h). For the HU, MU and LU areas, the volumes, the $\tilde{a}$ values and the corresponding $\tilde{A}$ values were derived from analysis of the SPECT images. The values are presented in Table 1.

A representative example of activity distribution in a transaxial slice of a SPECT/CT study is shown in Fig. 2a, with iso-ROIs contouring the HU, MU and LU areas

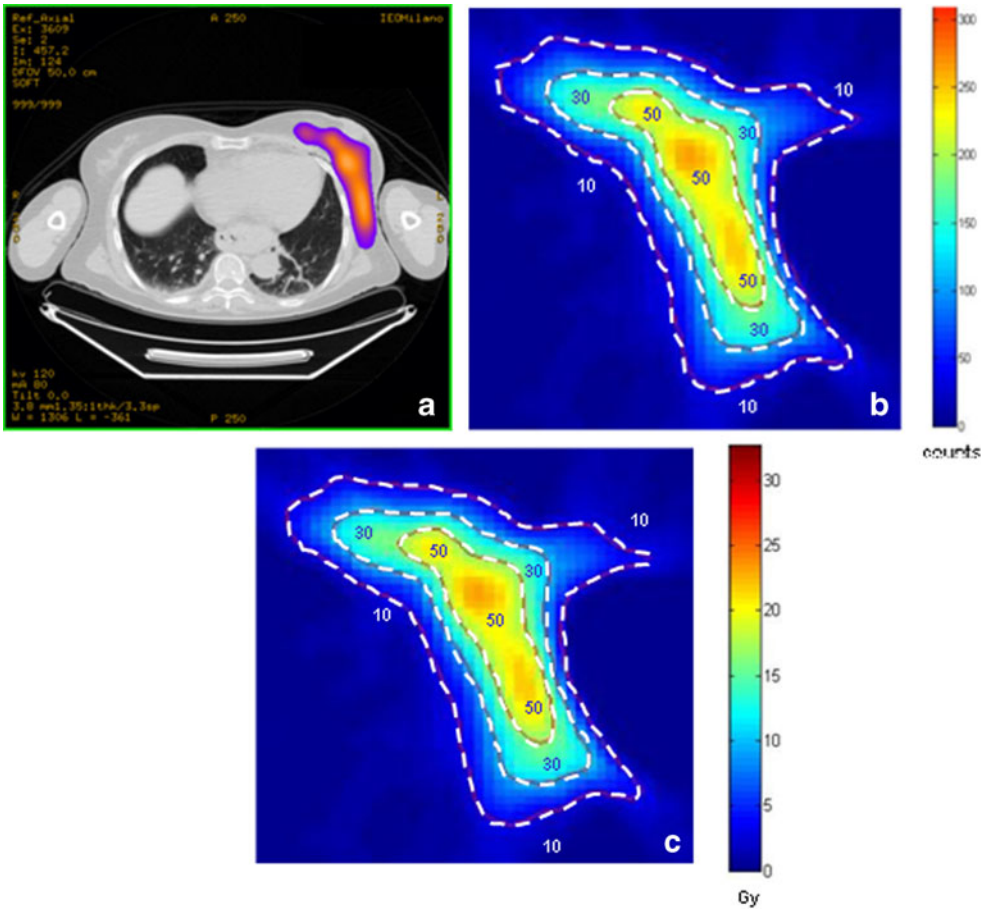


**Fig. 2** SPECT/CT images in patient 13. SPECT and CT scans were acquired on separate systems and fused retrospectively using radioopaque marker. **a** Transaxial slice. **b** Iso-ROI contouring of the HU, MU and LU areas. **c** Isodose contouring

**Table 2** Dosimetric and radiobiological results for the HU area in the whole patient group

| Patient | Dosimetric evaluation[a] | | | Radiobiological evaluation[b] | | |
|---|---|---|---|---|---|---|
| | $D_{standard}$ (Gy) | EUD (Gy) | Difference (Gy) | BED (Gy) | EUBED (Gy) | Difference (Gy) |
| 1 | 23.8 | 25.0 | 1.2 | 25.6 | 26.8 | 1.2 |
| 2 | 22.2 | 23.6 | 1.4 | 23.8 | 25.2 | 1.4 |
| 3 | 27.1 | 29.4 | 2.3 | 29.3 | 31.8 | 2.5 |
| 4 | 20.0 | 20.8 | 0.8 | 21.9 | 22.7 | 0.8 |
| 5 | 22.6 | 24.2 | 1.6 | 23.9 | 25.6 | 1.7 |
| 6 | 15.2 | 16.5 | 1.3 | 15.9 | 17.3 | 1.4 |
| 7 | 20.7 | 20.1 | −0.6 | 22.3 | 21.5 | −0.8 |
| 8 | 22.9 | 23.7 | 0.8 | 24.6 | 25.3 | 0.7 |
| 9 | 17.0 | 18.0 | 1.0 | 18.9 | 19.9 | 1.0 |
| 10 | 18.5 | 19.4 | 0.9 | 20.3 | 21.2 | 0.9 |
| 11 | 20.0 | 21.2 | 1.2 | 21.6 | 22.9 | 1.3 |
| 12 | 17.0 | 18.1 | 1.1 | 18.9 | 20.0 | 1.1 |
| 13 | 17.0 | 19.2 | 2.2 | 18.3 | 20.7 | 2.4 |
| 14 | 17.8 | 18.8 | 1.0 | 21.6 | 22.9 | 1.3 |

[a] Average absorbed doses obtained with the hypothesis of uniform activity distribution in spherical volumes (SDM) and the EUD derived from the VDM.

[b] BED obtained from the average absorbed dose (SDM) and the EUBED derived from the VDM.

(Fig. 2b). Figure 2c shows the absorbed dose distribution computed using the VDM.

Table 2 presents the results of the dosimetric and radiobiological evaluations in each patient for the HU area (the therapeutic target) for both the SDM ($D_{standard}$ and BED, respectively) and VDM (EUD and EUBED, respectively), and Table 3 presents the results as medians (ranges) for the three uptake areas. The median value of the mean absorbed dose released to the target (HU) area evaluated with SDM was 20.0 Gy and the median EUD evaluated with VDM was 20.5 Gy. Similarly, for the radiobiological effects predicted by the two dosimetric methods, the median $BED_{standard}$ was 21.8 Gy and the median EUBED was 22.8 Gy (mean difference 1.2 Gy, i.e. about 5 %). Overall, even considering the inaccuracy of image quantification, the differences were negligible, suggesting that the hypothesis of uniformity of SDM was not misleading.

Figure 3a shows the $EUD/\overline{D}_{vox}$ ratios, and Fig. 3b the $EUBED/\overline{BED}_{vox}$ ratios for the HU area. Figure 3 shows that homogeneity was always >90 % (median $EUBED/\overline{BED}_{vox}$ ratio 92 %).

Figure 4 shows the DVH of the HU area in the 14 patients, representing, for each absorbed dose $D$, the percentage of the total volume of the HU area receiving an absorbed-dose higher than $D$. Although the mean absorbed dose varied consistently among patients, the slopes of the distribution curves were quite similar. Figure 4 shows that all the patients received an absorbed dose of at least 13 Gy in the target. Similarly, Fig. 5 shows the BED distribution in terms of BVH, and indicates that all the patients received at least 13 Gy BED in the target.

Table 4 shows the number of $EBRT_{2Gy}$ fractions that should provide the same radiobiological effect (EUBED) as that obtained with IART®. The median value of 9.5 fractions (range 7.2–13.3) corresponds to about 2 weeks of $EBRT_{2Gy}$.

**Table 3** Dosimetric and radiobiological results for the three uptake areas. The data are presented as median (range) values

| Uptake area | Dosimetric evaluation[a] | | | Radiobiological evaluation[b] | | |
|---|---|---|---|---|---|---|
| | $D_{standard}$ (Gy) | EUD (Gy) | Difference (Gy) | BED (Gy) | EUBED (Gy) | Difference (Gy) |
| HU | 20.0 (15.2–27.1) | 20.5 (16.5–29.4) | 1.1 (−0.6–2.3) | 21.8 (15.9–29.3) | 22.8 (17.3–33.0) | 1.3 (−0.8–0.5) |
| MU | 11.3 (8.5–17.7) | 13.0 (10.3–19.1) | 1.9 (−6.1–8.8) | 11.9 (8.7–18.6) | 13.7 (10.8–21.3) | 2.0 (−6.6–10.3) |
| LU | 5.0 (3.7–6.1) | 5.3 (4.3–8.0) | 0.3 (−1.3–3.6) | 5.1 (3.7–6.2) | 5.5 (4.4–8.4) | 0.3 (−1.2–3.6) |

[a] Average absorbed doses obtained with the hypothesis of uniform activity distribution in spherical volumes (SDM) and the EUD derived from the VDM.

[b] BED obtained from the average absorbed dose (SDM) and the EUBED derived from the VDM.

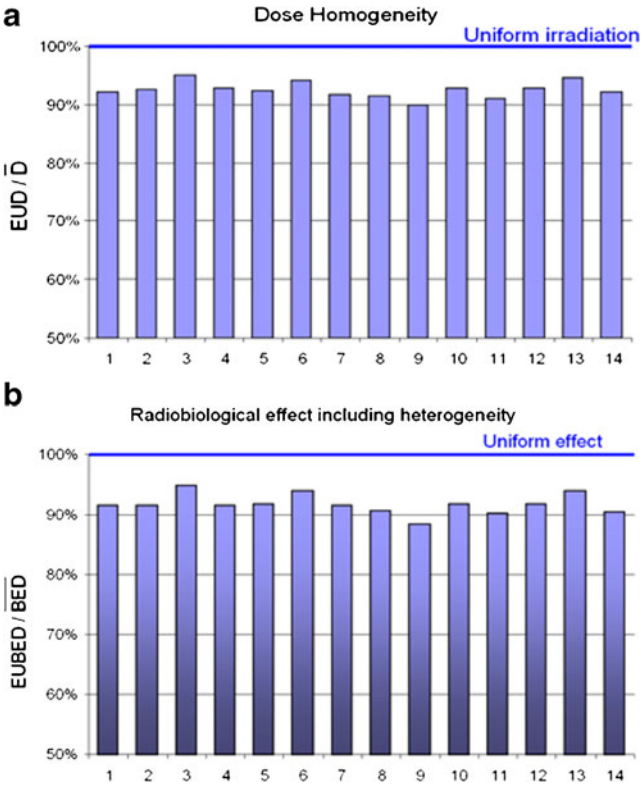


**Fig. 3** $\overline{D}_{vox}/EUD$ ratio (**a**) and the $\overline{BED}_{vox}/EUBED$ ratio (**b**) for the HU area in each patient

## Discussion

Postsurgical radiation treatment of early breast cancer aims at preventing local recurrences, consequently improving overall survival of patients [16, 17]. Recently, intraoperative radiotherapy followed by accelerated EBRT has shown encouraging results and an excellent rate of local tumour control [18]. In an effort to find a simple and convenient method for accelerated EBRT after quadrantectomy, our team at the European Institute of Oncology in Milan developed the IART® method, a targeted radionuclide therapy based on the high affinity between avidin and biotin. Avidin intraoperatively injected into the tumour bed is retained at the injection site for several days acting as "new receptor" for $^{90}$Y-radiolabelled biotin, which is intravenously administered 16–24 h after surgery. IART® is a novel approach to breast irradiation acting as an adjuvant boost immediately after surgery.

Over the last decade, the potential of 3D dosimetry at the voxel level has been shown to improve the dose estimation for several targeted radionuclide therapies [19–21]. He et al. [22] conclude that "methods such as the simple planar method are inadequate for nuclear medicine therapy treatment planning. More sophisticated methods, such as the hybrid SPECT/planar method, are likely to be better predictors of organ dose and, as a result, organ toxicities". SDM does not provide information on the uniformity of irradiation. This lack may reduce the possibility of a correlation with the radiobiological effects. Being IART® an innovative approach, a deeper analysis switching from SDM to VDM appears mandatory. Evaluation of the pharmaceutical distribution may help to reach the therapeutic goal in sequentially combined IART® and EBRT.

The VDM introduced in the present paper permitted us to bypass a number of simple hypotheses and to focus on the observed activity distribution and actual geometry. Moreover, we aimed to investigate radiobiological parameters to achieve better integration of IART® and EBRT using a rationale that would take into account differences in radiation modality (dose rate, uniformity, time schedule).

The absorbed dose and BED distribution maps (summarized in DVHs and BVHs of Figs. 4 and 5) both indicate the lack of cold spots, thus guaranteeing the absence of undertreated regions. Although the integral DVH and BVH curves do not have the abrupt slope associated with complete uniformity, a comparison between $\overline{D}_{vox}$ and EUD in the target region showed median differences of about 1 Gy (about 6 %), and the differences were always less than about 2 Gy (about 11 %). Similarly, the differences between $\overline{BED}_{vox}$ and EUBED indicated radiobiological effects

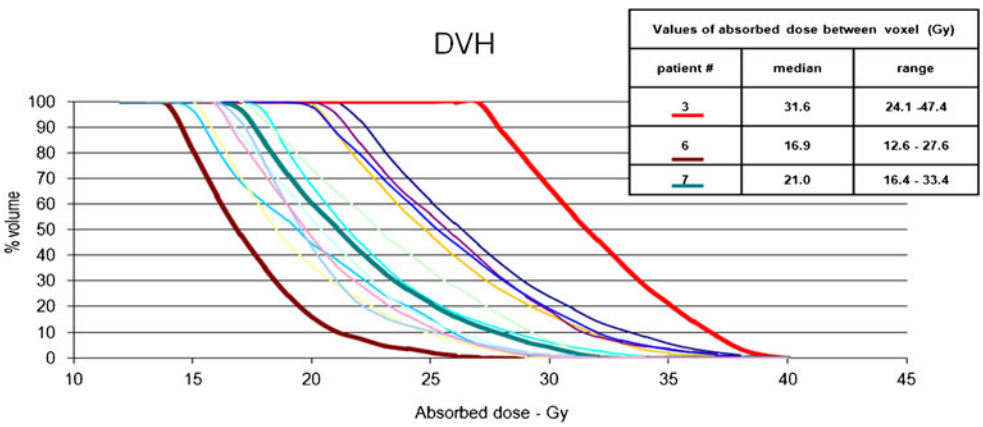


**Fig. 4** Integral DVH of the HU area in all patients, represented as percent of the volume that received a specific absorbed dose. The three highlighted curves (*brown*, *red* and *green*) represent the DVHs of patients 6, 3 and 7 who received the lowest, highest and mean absorbed dose, respectively

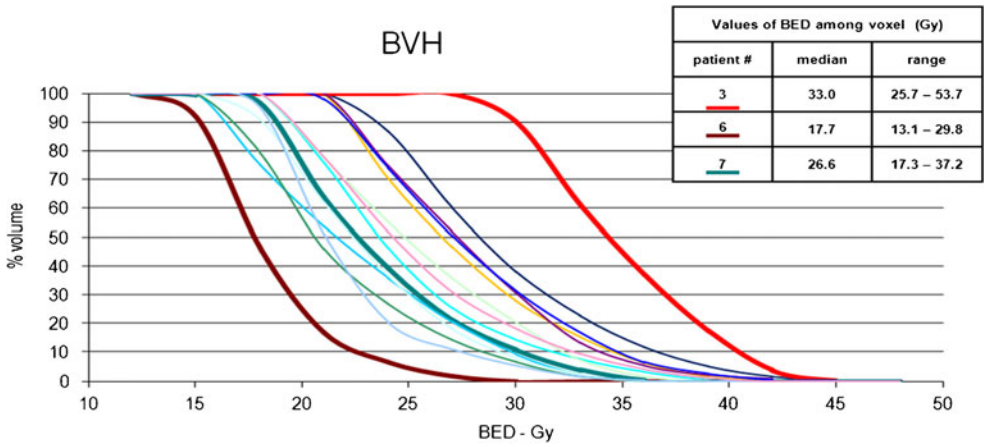


**Fig. 5** Integral BVH of the HU area in all patients, represented as percent of the volume that receives a specific BED. The three highlighted curves (*brown*, *red* and *green*) represent the BVHs of patients 6, 3 and 7 who received the lowest, highest and mean BED, respectively

fairly similar to those related to the average absorbed dose $D$ in the hypothesis of uniformity (Fig. 3).

We are aware that a homogeneous distribution of the absorbed dose may be a false result as a consequence of the relatively low spatial resolution intrinsic to the equipment. Our investigation was based on images of 4.4 mm voxel size, and so we cannot exclude some inhomogeneity at lower dimensions. This issue also involves the dose distribution analysis (DVH) which cannot avoid the activity map alteration due to the partial volume effect. However, the potential of the $^{90}$Y crossfire (95% energy penetration range, $R_{95}$, 5.95 mm [23]) compensates for minor inhomogeneities. Of note, comparison between absorbed dose evaluations obtained with 3D SDM and VDM applied separately in the three breast areas (Table 3), showed small differences with respect to previous results for the HU area. The median differences between $D_{standard}$ and EUD and between $BED_{standard}$ and EUBED were about 6 % (1.1 Gy and 1.3 Gy, respectively). This is not surprising considering the uniform distribution highlighted by the voxel analysis.

**Table 4** Correspondence with EBRT fractions

| Patient | Number of 2-Gy fractions[a] |
|---|---|
| 1 | 11.2 |
| 2 | 10.5 |
| 3 | 13.3 |
| 4 | 9.5 |
| 5 | 10.7 |
| 6 | 7.2 |
| 7 | 9.0 |
| 8 | 10.5 |
| 9 | 8.3 |
| 10 | 8.8 |
| 11 | 9.5 |
| 12 | 8.3 |
| 13 | 8.6 |
| 14 | 9.5 |

[a]Number of fractions using the standard EBRT scheme of 2 Gy per fraction that would be required to cover the absorbed dose delivered with IART®.

Conversely, some discrepancies were found in the MU region, which corresponds to the tissue receiving the radiopharmaceutical diffused from the region where avidin was administered (median difference about 14 %, with significant variability ranging 9 % to 46 %). This was probably due to differences in the geometry of the sources considered in the two methods (uniform sphere vs. real geometry, more similar to a hollow cylinder), and especially to the cross-radiation (excluded vs. included) from the HU area. As this region is conceptually associated with the adjacent target tissue potentially harbouring microscopic tumour cells, such a diffusion was not considered a drawback. Finally, negligible differences were observed in the LU area where the contribution from the adjacent MU area was much lower.

The VDM seems to be a useful approach as it is more accurate, capable of confirming that no target regions are undertreated, and provides individual absorbed dose distribution maps. Nevertheless, some improvements and corrections could be applied in the future. A major point of concern is the quality of images. While the planar images used to determine the uptake variation over time were corrected for scatter and attenuation, SPECT images were corrected for scatter only. The use of coregistered SPECT/CT images could improve dosimetric results. At the time of this study, in an attempt to obtain morphofunctional images, radioopaque markers were used during the separate SPECT and CT image acquisitions to reproduce the same patient position. Unfortunately, patients who have recently undergone surgery are often unable to lie on an immobilizing device, and so the alignment of fused images was not accurate enough to allow confident attenuation correction.

The hybrid method applied matches the activity distribution map from one SPECT scan with the uniform effective half-life derived from planar scans. This includes the hypothesis that the whole target tissue follows the same biological kinetics. This premise might be open to criticism, and theoretically the single voxel kinetics could be determined. This would require an optimal voxel-to-voxel alignment of serial SPECT images. However,

considering the anatomical region affected by breath movement and repositioning, and that no SPECT/CT imaging was available, such a sophisticated method would be very difficult to achieve, and overall could introduce more uncertainties.

Finally, the radiobiological model applied in this study is a fundamental starting point for the integration of two radiation therapies with different dose rates and possibly absorbed dose distributions. In the safety assessment phase of such a new therapy, which differs from any other targeted radionuclide therapy approach, this model can be regarded as an attractive guiding rationale, preferable to empirical approaches based on activity escalation.

## Conclusion

IART® is a promising targeted radionuclide therapy for early breast cancer to release a boost of radiation in the tumour bed.

The radiobiological model applied allowed a comparison of the effects of IART® and EBRT and the formulation of hypotheses to match the two irradiation modalities. Accurate IART® dose evaluation would allow the subsequent EBRT to be adequately arranged, choosing the optimal number of fractions needed to complete the treatment and deliver the prescribed therapeutic dose (about 70 Gy BED). The VDM is recommended. Its use highlighted the absence of significant heterogeneity in the target tissues, with a biological efficacy comparable to that of uniform dose distribution.

The present work confirmed previous results and provided valuable information that could be used to optimize future protocols combining IART® and reduced EBRT. On the whole, the flexibility of the combined IART® and EBRT treatment offers the advantage of being able to model and optimize the treatment according to the needs of the individual patient.

**Acknowledgments** This study was supported by grants from the Italian Association for Cancer Research (AIRC).

The authors thank Mrs. Grainne Tierney for her kind assistance in revising the English of this manuscript and Mrs. Deborah Console for the editing.

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