Intraoperative Avidination for Radionuclide Therapy: A Prospective New Development to Accelerate Radiotherapy in Breast Cancer

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Abstract Purpose: In a continuous effort to seek for anticancer treatments with minimal side effects, we aim at proving the feasibility of the Intraoperative Avidination for Radionuclide Therapy, a new procedure for partial breast irradiation.

Experimental Design: To assess doses of 90Y-DOTA-biotin to target (i.e., breast tumor bed) and nontarget organs, we did simulation studies with 111In-DOTA-biotin in 10 candidates for conservative breast surgery. Immediately after quadrantectomy, patients were injected with 100-mg avidin in the tumor bed. On the following day, patients were given 111In-DOTA-biotin (~111 MBq) i.v. after appropriate chase of biotinylated albumin (20 mg) to remove circulating avidin. Biokinetic studies were done by measuring radioactivity in scheduled blood samples, 48-h urine collection, and through scintigraphic images. The medical internal radiation dose formalism (OLINDA code) enabled dosimetry assessment in target and nontarget organs.

Results: Images showed early and long-lasting radioactive biotin uptake in the operated breast. Rapid blood clearance (<1% at 12 h) and urine excretion (>75% at 24 h) were observed. Absorbed doses, expressed as mean ± SD in Gy/GBq, were as low as 0.15 ± 0.05 in lungs, 0.10 ± 0.02 in heart, 0.05 ± 0.02 in red marrow, 1.30 ± 0.50 in kidneys, 1.50 ± 0.30 in urinary bladder, and 0.06 ± 0.02 in total body, whereas in the targeted area, they increased to 5.5 ± 1.1 Gy/GBq (50% ISOROI) and 4.8 ± 1.0 Gy/GBq (30% ISOROI).

Conclusion: Our preliminary results suggest that Intraoperative Avidination for Radionuclide Therapy is a simple and feasible procedure that may improve breast cancer patients’ postsurgical management by shortening radiotherapy duration.

Breast conservative surgery, with sentinel node biopsy and postoperative regional radiotherapy, represents the treatment of choice in patients with early breast cancer (1, 2). Unfortunately, the duration of a standard course of whole-breast external beam radiation therapy (EBRT), followed by a boost to the tumor bed, is usually 6 to 8 weeks. This can represent a logistics problem for many patients, particularly those who are far from a radiation treatment facility (3). Alternative modalities of accelerated partial breast irradiation, such as MammoSite, breast brachytherapy, three-dimensional Conformal External Beam Radiotherapy, interstitial brachytherapy, and single fraction intraoperative radiotherapy, are currently under clinical evaluation (4–8).

Based on our previous clinical experience in locoregional treatment of peritoneal carcinomatosis and recurrent high-grade glioma using the avidin-biotin pretargeting technique (9–11), we foresaw a potential application of 90Y-DOTA-biotin radionuclide therapy in breast cancer. We developed the Intraoperative Avidination for Radionuclide Therapy (IART) that relies on the avidin-biotin binding system. In fact, the “avidination” of the anatomic area of the tumor with native avidin, directly injected by the surgeon into and around the tumor bed, provides a target for the radiolabeled biotin i.v. injected 1 day later.

To prove the feasibility of this new procedure, we first did a pilot study to optimize the chase of biotinylated albumin to bind circulating avidin, thus restricting the presence of free avidin in the tumor bed. Consequently, 10 patients with early breast cancer, candidates for breast conservative surgery, were enrolled in a phase I trial specifically designed to study dosimetry and biodistribution of 90Y-DOTA-biotin in target and nontarget organs through simulation studies based on 111In-DOTA-biotin. Tumor resection was followed by avidin injection in the tumor bed. On the following day, patients were given 111In-DOTA-biotin i.v. after appropriate chase of biotinylated albumin. Biokinetic studies were based on measured radioactivity in timed blood samples, 48-h urine collection, and through scintigraphic images. Our preliminary results

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suggested to remove 20 mg of biotinylated albumin as the optimal chase dose to remove circulating avidin. The $^{111}$In-DOTA-biotin simulation studies to predict dosimetry with $^{90}$Y-DOTA-biotin showed that the mean absorbed dose in nontarget organs was <0.15 Gy/GBq, with the exception of kidneys and urinary bladder, where the doses ($\pm$ SD) were 1.20 $\pm$ 0.42 and 1.39 $\pm$ 0.10 Gy/GBq, respectively. Interestingly, such absorbed dose reached 5.5 Gy/GBq (50% ISOROI) and 4.8 Gy/GBq (30% ISOROI) in the target area. Images showed early and long-lasting radioactive biotin uptake in the operated breast. Rapid blood clearance and urine excretion were observed. Such findings led to apply IART with $^{90}$Y-DOTA-biotin for the first time in a patient with local breast cancer recurrence, showing an objective response to this new targeted locoregional therapy.

**Materials and Methods**

**Reagents**

Native avidin (10 mg/mL), biotinylated human serum albumin (HSA-biot; 20 mg/mL), and DOTA-biotin ligand (2 mg/mL, product code ST2210) dissolved in saline were supplied by Sigma-Tau S.p.A. i.f.r. Anhydrous sodium acetate (NaAc), acetic acid, and diethylene triaminepentaacetic acid were purchased from Sigma-Aldrich Italy at the highest available purity. A NaAc buffer at 1 mol/L (pH 5.0) was prepared using MilliQ water ($\phi$= 18 MQ/cm) as previously described (12). Indium-111 chloride ($^{111}$InCl$_3$) in 0.05 N HCl was purchased from Perkin-Elmer, Inc. Yttrium-90 chloride ($^{90}$YCl$_3$) was prepared using MilliQ water ($\phi$= 18 MQ/cm), whereas yttrium-90 chloride ($^{90}$YCl$_3$) in 0.04N HCl was obtained from Mallinckrodt Medical B.V., whereas yttrium-90 chloride ($^{90}$YCl$_3$) in 0.04N HCl was obtained from Mallinckrodt Medical B.V., whereas yttrium-90 chloride ($^{90}$YCl$_3$) in 0.04N HCl was obtained from Mallinckrodt Medical B.V., whereas yttrium-90 chloride ($^{90}$YCl$_3$) in 0.04N HCl was obtained from Mallinckrodt Medical B.V., whereas yttrium-90 chloride ($^{90}$YCl$_3$) in 0.04N HCl was obtained from Mallinckrodt Medical B.V.

**Radiolabeling**

The radiolabeling of DOTA-biotin was carried out following a previously described procedure (12). Briefly, a volume of NaAc buffer, equal to that of the radionuclide MCl$_3$ (M = $^{111}$In or $^{90}$Y) solution, was mixed with a molar excess of avidin and diethylene triaminepentaacetic acid were purchased from Sigma-Aldrich Italy at the highest available purity. A NaAc buffer at 1 mol/L (pH 5.0) was prepared using MilliQ water ($\phi$=$\phi$ MQ/cm) as previously described (12). Indium-111 chloride ($^{111}$InCl$_3$) in 0.05 N HCl was purchased from Perkin-Elmer, Inc.

**Patients**

Fifteen patients with breast cancer at stage T$_2$N$_0$O$_1$, suitable for a quadrantectomy and axillary dissection (or sentinel lymph node biopsy), gave signed, written informed consent to participate in our study. In particular, 5 patients were randomly selected for a pilot study for B-HSA chase optimization and 10 were enrolled in a phase I trial. Inclusion criteria were performance status (Eastern Cooperative Oncology Group), 0-2; age, 18 to 75 years; life expectancy, $>$1 year; and general clinical conditions adequate for comprehension of informed consent and study compliance. Exclusion criteria were performance status (Eastern Cooperative Oncology Group) $>$2, previous biopsy or surgically removed tumor, severe psychiatric disorders, pregnancy, and breast-feeding.

The study was approved by the Local Ethics Committee (IEO 208/504). The patient undergoing the pilot therapeutic study had advance breast cancer with bone and lung metastases and local cancer recurrence, characterized by little lumps under the skin of the right thorax and reddish-pink rashes and swelling of the left breast area.

**Pilot study to chase circulating avidin**

To correctly set up the phase I trial, we tested the chase while varying the quantity and volume of administered avidin and the gap time between avidin and biotin injection. In particular, avidin doses ranged from 50 to 150 mg diluted in 20 to 40 mL. One patient was not given biotinylated albumin (HSA-biot), whereas the others received a dose ranging from 15 to 25 mg. 3 to 10 min before $^{111}$In-DOTA-biotin administration. Liver and breast uptake, expressed as percentage of injected radioactivity, were monitored.

**IART procedure**

**Intrasurgical phase.** In the phase I trial, the surgeon administered 100 mg native avidin with three 10 mL syringes as 1 cm-apart multiple injections into the tumoral-peritumoral bed and periareolar site, where necessary, to percolate the index quadrant. Avidin injection occurred after either sentinel node biopsy or axillary dissection. In the pilot therapeutic study, the dose for the subdermal avidinization of the skin lesion was 150 mg.

**Postsurgical phase.** Sixteen to 24 h after surgery, patients were given radiolabeled biotin i.v. as a slow bolus injection. $^{111}$In-DOTA-biotin activity was 108 $\pm$ 9 MBq for patients ($n = 10$) enrolled in the phase I trial. To chase the excess of free avidin, which had been drained overnight by the lymphatic system toward the blood stream, patients were given 20 mg/5 mL of HSA-biot via i.v. injection 10 min before radioactive biotin administration. In the pilot therapeutic study, the patient received 25 mg of HSA-biot as chase and, 10 min later, she was co-injected i.v. with 1.2 GBq $^{90}$Y-DOTA-biotin for therapeutic purposes and 130 MBq $^{111}$In-DOTA-biotin for biodistribution purposes.

**Pharmacokinetic study**

To determine $^{111}$In-DOTA-biotin blood clearance and excretion rate, blood samples were withdrawn at $t = 5$, 10, 30, and 60 min and $t = 3$, 5,

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Avidin mass (mg)</th>
<th>Avidin volume (mL)</th>
<th>HSA-biotin chase (mg)</th>
<th>Gap time (min)</th>
<th>Liver uptake (% injected activity)</th>
<th>Breast uptake (% injected activity)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>150</td>
<td>25</td>
<td>—</td>
<td>—</td>
<td>$-$9</td>
<td>$-$4</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>20</td>
<td>15</td>
<td>1</td>
<td>$-$5</td>
<td>$-$4</td>
</tr>
<tr>
<td>3</td>
<td>100</td>
<td>40</td>
<td>25</td>
<td>3</td>
<td>$-$2</td>
<td>$-$8</td>
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<tr>
<td>4</td>
<td>50</td>
<td>20</td>
<td>10</td>
<td>—</td>
<td>$-$&lt;1</td>
<td>$-$4</td>
</tr>
<tr>
<td>5</td>
<td>100</td>
<td>40</td>
<td>15</td>
<td>10</td>
<td>—</td>
<td>$-$4</td>
</tr>
<tr>
<td>Phase I study</td>
<td>100</td>
<td>30</td>
<td>10</td>
<td>—</td>
<td>$-$&lt;1</td>
<td>$-$6</td>
</tr>
</tbody>
</table>

NOTE: $^{111}$In-DOTA-biotin uptake in breast and liver according to varying data from mass, volume, and time between injection of avidin and HSA-biotin chase in five patients.
maximum counts; the mean-uptake area (i.e., area between 50% and 10% ISOROI); and the low-uptake area (i.e., area between 30% and 10% ISOROI).

SAAM II software (15) was used to depict the kinetics of the radioconjugate by an appropriate compartmental model and to obtain the number of disintegrations [ND(h)] occurring in the source organs for 90Y, on the assumption that the kinetics of biotin with either 111In or 90Y would be identical.

Dose calculations were done for each patient according to the medical internal radiation dose formalism using OLINDA/EXM software (16), entering the ND(h) for all source organs. The absorbed doses were calculated according to the patient/phantom mass ratio.

The self-dose in the breast area was calculated assuming uniform activity distribution in spherical shaped tumors (Spheres Model available in OLINDA/EXM). The ND(h) for the tumor area was derived from the breast area time-activity curves.

The ND(h) in the red marrow was calculated from the ND(h) in blood, assuming that no specific uptake would occur in bone marrow. Uniform activity distribution as well as equivalent clearance in blood and red marrow was also assumed. Due to the small size of the radiolabel, specific activity in red marrow was considered equal to the specific activity in blood (17).

To calculate the absorbed dose to the bladder wall, the ND(h) for bladder contents was calculated according to the dynamic urinary bladder model (18), based on the experimental curve of the cumulative activity eliminated in the urine. The bladder was assumed to void every 1.5 h in the first 8 h after injection (forced diuresis) and at every 4.8-h interval thereafter.

**Biological effective dose: the linear-quadratic model**

The linear-quadratic model enabled a comparison of doses released through EBRT to those from IART and analysis of possible effects on nontarget organs (19, 20). In fact, we adopted the biological effective dose (BED) expression defined by:

\[
BED = \sum_i D_i + \frac{1}{\beta} \left( \frac{T_{1/2 \text{rep}}}{T_{1/2 \text{rep}} + T_{1/2 \text{eff}}} \right) \sum_i D_i^2
\]

where \(D_i\) is the dose delivered per cycle \(i\); \(T_{1/2 \text{rep}}\) is the repair half-time of sublethal damage; and \(T_{1/2 \text{eff}}\) is the effective half-life of the radiopharmaceutical in the specific tissue. The \(\alpha/\beta\) ratio relates the

**Imaging, biodistribution, and dosimetry**

Whole-body transmission scans with 57Co-flood source were done for attenuation correction purposes. At 1, 4, 24, 36, and 48 h after a slow bolus injection of 111In-DOTA-biotin, standard scintigraphic whole-body scans were acquired in anterior and posterior views with a double-head gamma camera (GE Millennium VG) equipped with a medium energy general purpose collimator.

Whole-body images were analyzed by the conjugated view method (14). Regions of interest were drawn manually over the whole body, breast region, and source organs (kidneys, heart, and lungs). The same set of regions of interest was used for all scans. Counts from the gamma-camera images were corrected for background, scatter, and physical decay; biological time-activity curves were obtained.

To further detect 111In-DOTA-biotin uptake and distribution in the mammal gland and surrounding tissues, a single-photon emission computed tomography scan was acquired over the breast region at \(t = 16\) h.

The time-activity curve in the breast gland was created from single-photon emission computed tomography and whole-body images. The breast region was divided into three distinct areas: the high-uptake area (i.e., 50% ISOROI, where all pixels/voxels have more than 50% of maximum counts); the mean-uptake area (i.e., area between 50% and 30% ISOROI); and the low-uptake area (i.e., area between 30% and 10% ISOROI).
intrinsic radiosensitivity ($\alpha$) and the potential sparing capacity ($\beta$) to a specified tissue or effect.

For the breast region, we used $T_{1/2\ rep} = 1.5\ h$, $\alpha/\beta = 10\ Gy$ (21); for the kidneys, we used $T_{1/2\ rep} = 2.8\ h$, $\alpha/\beta = 2.6\ Gy$ (22).

**Results**

**Radiopharmaceutical preparation**

DOTA-biotin was successfully labeled with $^{111}$In/$^{90}$Y, routinely achieving radiochemical purities $\geq 99.0\%$.

**Patients**

Patients ranged in age from 33 to 64 years. All had good performance status (Eastern Cooperative Oncology Group score = 0). Postoperative staging according to tumor-node-metastasis classification showed six T1c (1-2 cm), one T1mic (<0.1 cm), two Tis, and two T1b.

**Pilot study for chase**

Breast and liver uptake of $^{111}$In-DOTA-biotin was calculated as the percentage of injected activity to attain the best combination by associating avidin concentration, HSA-biot mass, and injection time schedule. Table 1 summarizes the variables for each of the five patients. The absence of HSA-biot (case no. 1) led to rather high ($>9\%$) liver uptake (Fig. 1A). Similarly, a short gap time between HSA-biot and $^{111}$In-DOTA-biotin injections led to liver uptake (Fig. 1B; case no. 2: 5% and case no. 3: 2%). A low mass of avidin (50 mg) was associated with inadequate breast uptake (case no. 4: 0.4%) whereas 100-mg avidin seemed to be the optimal dose to reach satisfactory breast uptake with a 20-mg HSA-biot injection 10 min before radiolabeled biotin administration (case no. 5: >4%; Fig. 1C).

An avidin dose ratio of 5:1 was considered appropriate for a successful chase and led to 20 mg of HSA-biot.

**Phase I trial**

Patients enrolled in the phase I trial showed no clinical adverse reactions: the intrasurgical injection of avidin was well tolerated and no side effects were observed after the i.v. injection of $^{111}$In-DOTA-biotin.

**Imaging and biodistribution.** The scintigraphic images showed that the radiolabeled compound remained well localized within the operated breast area with very negligible background in other tissues (Fig. 2). The blood clearance was fast, the IA% in the blood at $t = 24\ h$ was 0.15 $\pm$ 0.10%, whereas the cumulative activity excreted in the urine was 81.4 $\pm$ 12.2% IA 24 h after injection.

**Dosimetry and biological effective dose.** Using SAAM II software, the ND(h) that occurred in the source organs for $^{90}$Y was extrapolated (Table 2). The highest absorbed doses were in the urinary bladder wall (1.4 $\pm$ 0.1 Gy/GBq) and kidneys (1.2 $\pm$ 0.4 Gy/GBq). The estimated absorbed dose to the red marrow was 0.05 $\pm$ 0.02 Gy/GBq.

In seven patients, the maximum uptake in breast area was at $t = 4\ h$. The other three had maximum uptake within 24 h after injection. The breast area time-activity curve revealed an early and stable radioactive uptake in the target area (Fig. 3). The mean value of the ND(h) for the mean-uptake region of the target tissue was 1.77 h, ranging from 1.27 to 2.41 h; the mean value of the absorbed dose to the mean-uptake breast region was 5.1 (1.4) Gy/GBq, ranging from 3.3 to 6.2 Gy/GBq.

For the breast region, the mean $T_{1/2\ eff}$ equaled 47.3 $\pm$ 6.7 h, and therefore, the biological effective dose was 4.8 $\pm$ 1.1 Gy/GBq: for the kidneys, the mean $T_{1/2\ eff}$ was 8.6 $\pm$ 4.1 h with biological effective dose at 1.3 $\pm$ 0.5 Gy/GBq.

**Pilot therapeutic study**

From the data of the pilot therapeutic case treated by i.v. co-injection of 1.2 GBq of $^{90}$Y-DOTA-biotin and 130 MBq of $^{111}$In-DOTA-biotin (Fig. 4A), we extrapolated that the

<table>
<thead>
<tr>
<th>No. disintegrations [ND(h)]</th>
<th>Absorbed doses (Gy/GBq)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Heart</td>
<td>0.07 (0.05)</td>
</tr>
<tr>
<td>Kidneys</td>
<td>0.68 (0.28)</td>
</tr>
<tr>
<td>Lungs</td>
<td>0.11 (0.07)</td>
</tr>
<tr>
<td>Red marrow</td>
<td>0.12 (0.03)</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>0.80 (0.06)</td>
</tr>
<tr>
<td>Remainder of the body</td>
<td>5.14 (2.43)</td>
</tr>
<tr>
<td>Other organs</td>
<td>1.42 (1.01)</td>
</tr>
<tr>
<td>High-uptake region</td>
<td>1.77 (0.46)</td>
</tr>
<tr>
<td>Mean-uptake region</td>
<td>2.09 (1.13)</td>
</tr>
</tbody>
</table>

**Table 2.** Dosimetric results

Note: Number of disintegrations and absorbed doses throughout the body in 10 patients after $^{111}$In-DOTA-biotin injection.
absorbed dose was 1.8 Gy in kidneys and 2.5 Gy in urinary bladder wall. The target area received a dose ranging from 8 to 10 Gy. The patient had an objective local response to IART therapy (Fig. 4B), documented by clinical inspection lasting more than a year. Moreover, the patient had complete pain remission in the chest with consequent withdrawal of pain relief drugs (morphine).

Discussion

In an attempt to provide quality of life improvement through investigating patient-customized anticancer therapies, we propose IART as a new procedure for partial breast irradiation in candidates for conservative breast surgery.

The simple two-step method of intraoperative locoregional avidin injection (first step) and $^{90}$Y-DOTA-biotin i.v. administration after 16 to 24 h (second step) relies on avidin-biotin chemical affinity and Yttrium radioisotope properties. In fact, avidin is a 66-kDa glycosylated and positively charged (isoelectric point $\approx$ 10) glycoprotein with extremely high affinity for the 244-Da vitamin H, biotin ($K_d = 10^{-15}$ mol/L; ref. 23). Surgical intervention causes an inflammation reaction that increases capillary permeability and triggers cation-exchanging flows (24). Therefore, at the injection site, avidin is retained for several days and may act as "artificial receptor for radiolabeled biotin" (25, 26). Preclinical animal studies and prior clinical experience show that avidin injection in surgically created cavities is well tolerated (27–30).

On the other hand, biotin can be easily labeled with $^{90}$Y or $^{177}$Lu through the chelating agent $N,N',N'',N'''$-1,4,7,10-tetraazaacyclocodecan-1,4,7,10-tetraacetic acid (DOTA). $^{90}$Y is a high-energy pure $\beta$-emitter ($E_{\beta_{ave}} = 0.935$ MeV), with a relatively short physical half-life ($T_{1/2} = 64.1$ h) and a long penetration range in tissue ($R_{\text{max}} = 11.3$ mm). Thus, $^{90}$Y-DOTA-biotin is particularly suitable for radionuclide therapy, with the likelihood of killing the majority of neoplastic cells related to the so-called cross-fire effect (31), whereas $^{177}$Lu may be particularly suitable for microscopic residual disease or nipple sparing mastectomy, where it is crucial to avoid a high radiation dose to the derma. Avidin-biotin–based pretargeting methods have been used in clinical imaging and experimental therapy trials for more than a decade (11, 30).

This study suggests that the IART procedure succeeds in placing interstitial receptors (tissue avidination) able to bind labeled DOTA-biotin 1 day after breast conservative surgery. The scintigraphic images showed a fast and long-lasting uptake of labeled DOTA-biotin at the operated breast site. This area is therefore suitable for an efficient, targeted therapy. Through simulation studies based on in vivo pharmacokinetics and biodistribution of $^{111}$In-DOTA-biotin, we estimated the absorbed doses and biological effective dose to the breast region and normal organs during treatment with $^{90}$Y-DOTA-biotin.

In the phase I trial, pharmacokinetics of labeled DOTA-biotin showed a rapid renal elimination, which, however, resulted in a moderate dose to the kidney. The absorbed dose to the most involved nontarget organs (urinary bladder and kidneys) was far from the threshold doses of tissue side effects, according to the EBRT experience (32). However, these threshold doses are not suitable for internal radionuclide therapies because the radiation dose delivered during such therapy differs in many aspects from that delivered by external beam irradiation (33). Recently, the linear-quadratic model has been used to quantify the dose-rate sparing concepts expressly for radionuclide therapy, taking into account the different dose rate as compared with EBRT (34–36). In particular, for an injection of 3.7 GBq,
the absorbed dose to the kidneys was 4.4 ± 1.5 Gy, whereas the biological effective dose was 4.8 ± 1.8 Gy, which is clearly lower than the threshold dose for the reported kidney toxicity (22, 37).

The pharmacokinetics herein reported is useful to calculate the optimal injected activity of $^{90}$Y-DOTA-biotin. The radiation dose released to the breast region is ~5 Gy/GBq (biological effective dose, 4.8 ± 1.1 Gy/GBq) suitable for targeted radionuclide therapy. The estimated biological effective dose, according to the linear-quadratic model, would facilitate integration with EBRT treatment planning. IART has the great potential of being applied to any breast cancer treatable with conservative surgery; multifocality, tumor location, and size are not limiting factors. The surgeon injects avidin all around the tumor bed, without margin limitations or constraints. IART can be applied in all institutions where breast surgery is done and a nuclear medicine unit is available.

In our opinion, the combined use of IART followed by reduced EBRT is a valid approach to an easier, patient-tailored accelerated irradiation after breast conservative surgery. Based on the pilot therapeutic study results and dosimetry data herein reported, we consider further clinical development of randomized trials with IART in combination with EBRT fully justified.

References

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