INTRAOPERATIVE RADIOTHERAPY (IORT) – A NEW FRONTIER FOR PERSONALIZED MEDICINE AS ADJUVANT TREATMENT AND TREATMENT OF LOCALLY RECURRENT ADVANCED MALIGNANCY

EDITED BY: William Small, Jr. and Tarita O. Thomas

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INTRAOPERATIVE RADIOTHERAPY (IORT) – A NEW FRONTIER FOR PERSONALIZED MEDICINE AS ADJUVANT TREATMENT AND TREATMENT OF LOCALLY RECURRENT ADVANCED MALIGNANCY

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Intraoperative radiotherapy (IORT) is a treatment delivery technique with reports starting in the early 20th century. There are numerous advantages of IORT in oncology including delivery of a tumoricidal radiation dose in a single treatment, direct visualization of the treatment area of interest, decreasing dose to surrounding tissues, among others. In this series we focus on the clinical application, radiobiology and physics of IORT with an emphasis on the Intrabeam system. As medicine and health care continue to evolve the new frontier of personalized medicine must continue to rigorously evaluate and implement technologies that limit costs and provide meaningful therapeutic benefit.

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EDITORIAL
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Editorial: Intraoperative Radiotherapy (IORT)—A New Frontier for Personalized Medicine as Adjuvant Treatment and Treatment of Locally Recurrent Advanced Malignancy

Tarita O. Thomas and William Small Jr*

Loyola University Medical Center, Maywood, IL, United States

Keywords: intraoperative radiotherapy, personalized medicine, Kv, breast cancer, physics

Editorial on the Research Topic

Intraoperative Radiotherapy (IORT)—A New Frontier for Personalized Medicine as Adjuvant Treatment and Treatment of Locally Recurrent Advanced Malignancy

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Intraoperative radiotherapy (IORT) is a treatment delivery technique with reports starting in the early twentieth century with the use of orthovoltage energy with limited applicability due to the energy characteristics (1). This technology had a resurgence in approximately the 1960s with the use of electron energy in Japan (2) and subsequently the literature is replete with numerous other publications. Initially, the use of IORT was restricted by the cumbersome nature of treatment delivery as a shielded operating room was needed requiring large capital expenditure as well as expertise of staff with limited patient applicability. Over time the technology has evolved from requiring a shielded room to the development of a mobile device that can move into a standard operating room with minimal shielding requirements. Various current technologies exist that deliver electron or photon energies intraoperatively including Novac7 (Hitesys SPA, Aprillia, Italy; 7–10 MeV), Mobetron (IntraOp Medical Corporation, Sunnyvale, CA, USA; 4–12 MeV), Axxent system (Xoft, San Jose, CA, USA; 20–50 kV), and Intrabeam system (Carl Zeiss Meditec, Dublin, CA, USA; 30–50 kV).

There are numerous advantages of IORT in oncology. IORT has the benefit of delivering a tumoricidal radiation dose in a single treatment, while targeting the therapy to the region of highest risk of disease recurrence with direct visualization in the operating room. This provides a high relative biological effectiveness while limiting dose to normal tissue *via* tumor bed devascularization, elimination of inter-fraction tumor cell repopulation, and possibly providing a systemic immune effect (3). In addition, there are practical benefits to the patient by elimination or reduction in outpatient treatment visits that routinely last for 5–6 weeks for conventional postoperative radiotherapy, such as improved quality of life, decreased side effects and financial advantages.

In this series we focus on the use, radiobiology, and physics of IORT with an emphasis on the Intrabeam system. Sethi et al. describe the technical and dosimetric considerations for the various applicators now available to treat patients with disease intraoperatively in various locations including with flat, spherical, and even a needle applicator. Valente et al. discuss their experience with IORT from the surgical perspective and how their group decreased operative times in patients receiving breast IORT with increased utilization. Paunesku and Woloschak provide a review of the history of IORT as well as an engaging discussion of how IORT can be used in the future. Herskind et al.

extend this discussion into the theoretical usage of large radiation fraction size in brain metastasis and the potential combination with immunotherapy. The series then reviews the use of IORT in various malignancies, including head and neck cancer, pancreas cancer, and brain metastasis. Three articles finally review the use of IORT in breast cancer a highly prevalent cancer with numerous radiation treatment options available. Jacobson and Sochi provide a review of the various types of partial breast therapy and the toxicities associated. Chin et al. describe their experience using IORT for patients with prior thoracic radiation exposure. Harris and Small provide a comprehensive review of the data in support of the use of breast IORT as well as the toxicities, cosmesis, and quality of life with use of this treatment modality touching on both the use of electron and photon-based IORT.

The Organization for Economic Cooperation and Development evaluated the spending, supply, utilization, and price of health care across 13 high income countries and found that as a percent of GDP from 1980 to 2013 health care spending is approximately 17% in the United States versus 10% in the other countries evaluated (4). In the United States, health care spending consumes on average 1/5 of a households' income. It has been estimated that the use of breast IORT could provide at least $1.2 billion in saving to the health care system in the United States over 5 years (5). Currently breast IORT using the IntraBeam system is being used in 35 countries in more than 300 major hospitals with more than 200,000 women treated. Here, we provide a series of articles that discuss the usage of IORT in various malignancies as well as the technical aspects of this technology. As medicine and health continue to evolve the new frontier of personalized medicine must continue to rigorously evaluate and implement technologies that limit costs to the health care system and provide meaningful therapeutic benefit.

AUTHOR CONTRIBUTIONS

Both authors contributed to the editorial.

REFERENCES

1. Beck C. On external roentgen treatment of internal structures (eventration treatment). *N Y Med J* (1909) LXXXIX(13):621–2.
2. Abe M, Takahashi M, Yabumoto E, Onoyama Y, Torizuka K. Techniques, indications and results of intraoperative radiotherapy of advanced cancers. *Radiology* (1975) 116:693–702. doi:10.1148/116.3.693
3. Emami B, Woloschak G, Small W Jr. Beyond the linear quadratic model: intraoperative radiotherapy and normal tissue tolerance. *Transl Cancer Res* (2015) 4(2):140–7. doi:10.3978/j.issn.2218-676X.2015.04.06
4. Squires D, Anderson C. U.S. health care from a global perspective: spending, use of services, prices and health in 13 countries. *Issue Brief (Commonw Fund)* (2015) 15:1–15.
5. Alvarado MD, Mohan AJ, Esserman LJ, Park CC, Harrison BL, Howe RJ, et al. Cost-effectiveness analysis of intraoperative radiation therapy for early-stage breast cancer. *Ann Surg Oncol* (2013) 20(9):2873–80. doi:10.1245/s10434-013-2997-3

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ORIGINAL RESEARCH
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Intraoperative Radiotherapy With INTRABEAM: Technical and Dosimetric Considerations

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Purpose: We evaluate dose characteristics and clinical applications of treatment accessories used in intraoperative radiotherapy (IORT) and make site-specific recommendations for their optimal use.

Methods and materials: Dose measurements were performed for a low energy (50 kV) X-ray INTRABEAM source. For spherical, flat, surface, and needle applicators, the following dosimetric parameters were measured: depth-dose (DD) profiles, surface dose (Ds), output factors (OF), and target dose homogeneity (DH). Optical density versus exposure calibration films were employed to obtain 2-dimensional dose distributions in planes parallel and perpendicular to beam direction. Film results were verified *via* repeat dose measurements with a parallel-plate ionization chamber in a custom water tank. The impact of applicator design on dose distributions was evaluated.

Results: Spherical applicators are commonly used for treating the inner-surface of breast lumpectomy cavity. Flat and surface applicators provide uniform planar dose for head and neck, abdomen, and pelvis targets. Needle applicators are designed for kypho-IORT of spinal metastasis. Typically, larger applicators produce a more homogeneous target dose region with lower surface dose, but require longer treatment times. For 4-cm diameter spherical, flat, and surface applicators, dose rates (DR) at their respective prescription points were found to be: 0.8, 0.3, and 2.2 Gy/min, respectively. The DR for a needle applicator was 7.04 Gy/min at 5 mm distance from the applicator surface. Overall, film results were in excellent agreement with ion-chamber data.

Conclusion: IORT may be delivered with a variety of site-specific applicators. Appropriate applicator use is paramount for safe, effective, and efficient IORT delivery. Results of this study should help clinicians assure optimized target dose coverage and reduced normal tissue exposure.

Keywords: intrabeam, spherical, flat, surface applicators, dosimetry

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INTRODUCTION

Intraoperative radiotherapy (IORT) delivers a large tumoricidal dose to a well-defined target at the time of surgery while simultaneously minimizing exposure to nearby normal structures (1, 2). Compared to external beam radiotherapy, the advantages of IORT are: potential for dose escalation, reduced overall treatment time, and enhanced patient convenience. IORT may be delivered with

either an external beam of low-energy electrons (3), kV X-rays (4, 5), or *via* a miniaturized X-ray tube used as radiation source in electronic brachytherapy (6).

The IORT investigated in this report is based on an INTRABEAM X-ray source, PRS 500 (INTRABEAM, Carl Zeiss Surgical, Oberkochen, Germany) emitting low-energy (50 kV) photons at a high dose-rate (**Figure 1**) (4, 5, 7–12). The IORT's appeal lies in its ability to deliver a large dose (10–20 Gy) to the target volume with rapid dose fall-off and hence limited exposure to adjacent organs at risk. Furthermore, with appropriate precautions, the low energy X-rays result in minimal radiation risk to the operating room personnel. Recent IORT advances, such as the availability of novel treatment applicators to shape radiation dose to a desired target volume have resulted in tremendous gains in its clinical applications (13). Currently, some of the more common treatment sites for IORT include: breast, head and neck, brain, abdomen, pelvis, rectum, sarcoma, and spine.

At Loyola University Medical Center, we have commissioned and clinically used the INTRABEAM system with spherical, flat, surface, and needle applicators. Owing to their symmetric shape, spherical applicators are used to deliver a uniform dose at the inner-surface of the breast lumpectomy cavity. The surface and flat applicators are used when a constant dose is desired at a given tissue-depth: 0 and 5 mm, respectively. The needle applicator is designed for kypho-IORT (spine metastasis). These applicators are available in a range of sizes (diameter: 0.5–6 cm).

Although spherical applicators have been in use for a long time for breast IORT, the flat, surface, and needle applicators have recently become available and their clinical applications are becoming more popular. However, at present, there is a lack of available data for these applicators, which may limit their clinical use. Having a thorough understanding of IORT dose distribution is essential for safe, effective, and efficient treatment delivery. In this paper, we report on the dosimetric characteristics of each applicator, including, dose rate (DR), depth-dose (DD), dose homogeneity (DH), and treatment time. In addition, practical guidelines are provided for the optimal use of each applicator for various treatment sites. However, it is our recommendation that each institution intending to practice IORT must validate the dosimetric data of their equipment prior to clinical use.

MATERIALS AND METHODS

All measurements were performed for an INTRABEAM 50-kV X-ray source fitted with either a spherical, flat, surface, or needle applicator to produce desired spherical or planar dose (**Figure 1**) (10). At our institution, the physician performing IORT may choose from any of the following treatment accessories: five spherical applicators (diameter: 3–5 cm in 0.5 cm increment), six flat applicators (diameter: 1–6 cm in 1 cm increment), and four surface applicators (diameter: 1–4 cm in 1 cm increment). For

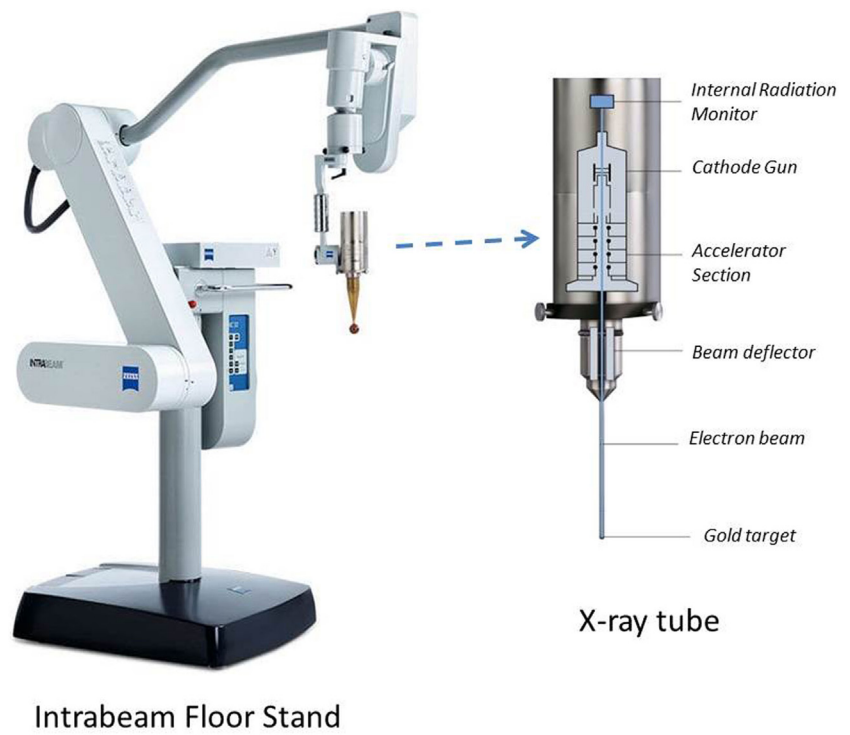

FIGURE 1 | Intrabeam stand and X-ray source shown with spherical applicator attachment. The floor stand provides full flexibility of movement for the X-ray tube with millimeter precision in six dimensions. The floor stand weighs 275 kg and has dimensions of 74 cm × 194 cm × 150 cm (W × H × L) in transport position. Also shown are internal components of the X-ray source (dimensions: 7 cm × 11 cm × 17 cm; weight: 1.6 kg).

each applicator, DD profiles, surface dose, output factors (OFs), and DH were measured:

(a) DD profiles are measured as change in DR with depth in a phantom.
(b) Surface dose (Ds) is defined as the dose at the target surface in contact with applicator tip.
(c) Output factor (OF) refers to the delivered dose at the prescription point in 1 min (Gy/min). The prescription point depends on the applicator type selected: surface of spherical applicator, 5 mm depth in phantom for flat applicator, phantom surface for surface applicator, and 5 mm from the tip for needle applicator.
(d) DH is defined as the variation in dose (D_{max}/D_{min}) in the beam direction in the target region of interest.

Output factors in terms of absolute DR (Gy/min) and DD profiles were measured in a water tank (**Figure 2A**) with a suitable thin-window parallel plate ion chamber (PTW 34013A, Physikalisch Technische Werkstaetten, Freiburg, Germany) (**Figure 2B**) (14). The ion chamber was connected to a PTW UNIDOS electrometer T10010 to record measured charge. The water-phantom available from Zeiss (Carl Zeiss Surgical, Oberkochen, Germany) allows precise positioning of applicator tip relative to ion chamber for accurate dose output and dose distribution measurements.

The measured DR (*Gy/min*) at a specific depth z in water can be written as:

$$\mathrm{DR}(z) = N_k Q(z) C_{TP} k_Q k_{elec} \quad (1)$$

where N_k is the ion chamber calibration factor (*Gy/nC*), $Q(z)$ is the ionization charge (C) collected in 60 s for the chamber located at depth z in water, C_{TP} is the correction factor for room temperature (T) and pressure (P) at the time of dose measurement, k_Q is the beam quality correction factor, and k_{elec} is the electrometer calibration factor. The measured DR is plotted as a function of depth z to obtain depth dose profiles (DD).

DH data were obtained from the measured DD profiles. Surface-dose (Ds) data were acquired with a film dosimeter. Whenever possible, film data were confirmed with ion-chamber measurements.

The spherical applicator's isotropic dose distribution is easily mapped with an ion chamber. The dose characteristics and treatment times for a needle applicator are available from a look-up table available with Zeiss, Inc. (Carl Zeiss Surgical, Oberkochen, Germany). Dose distributions generated with flat and surface applicators, on the other hand, are more intricate, requiring the use of a 2-dimensional film dosimeter. Films are an efficient tool to measure planar dose distribution. We used Gafchromic EBT3 films (International Specialty Products - ISP, Wayne, NJ, USA) sandwiched between slabs of water equivalent phantom (Plastic water, CIRS, Norfolk, VA, USA) (15) (**Figure 3A**). The films were aligned in both parallel and perpendicular orientations relative to the radiation beam (only films in perpendicular orientation are shown in **Figure 3A**). For each measurement, the X-ray source was oriented vertically with the end of the applicator in contact with the phantom surface (**Figure 3A**).

First, we established a film characteristic or sensitometric curve (also known as Hurter and Driffield or H&D curve), which relates film optical density with film exposure or dose (**Figures 3B,C**). This was done by irradiating several films from the same batch to a known dose (range: 0–4 Gy) delivered at 5 mm depth from the phantom surface (**Figure 3B**). Absolute calibration of IORT source was validated *via* Eq. 1 given above. Since the EBT3 film response is known to be highly sensitive to environmental conditions, all necessary film precautions were

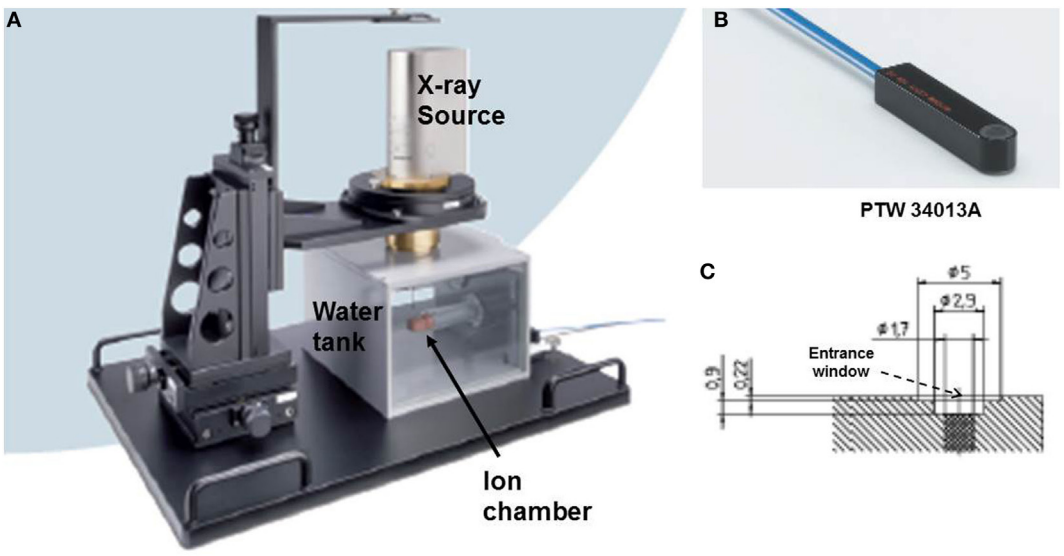

FIGURE 2 | Measurement setup for dose output factor, OF and depth dose profiles, DD. **(A)** Water tank showing positions of ion chamber and X-ray source; **(B)** PTW34013A thin-window parallel plate ion chamber used for dose measurements; **(C)** a schematic diagram of the parallel plate ion chamber showing beam entrance window (thickness = 0.22 mm).

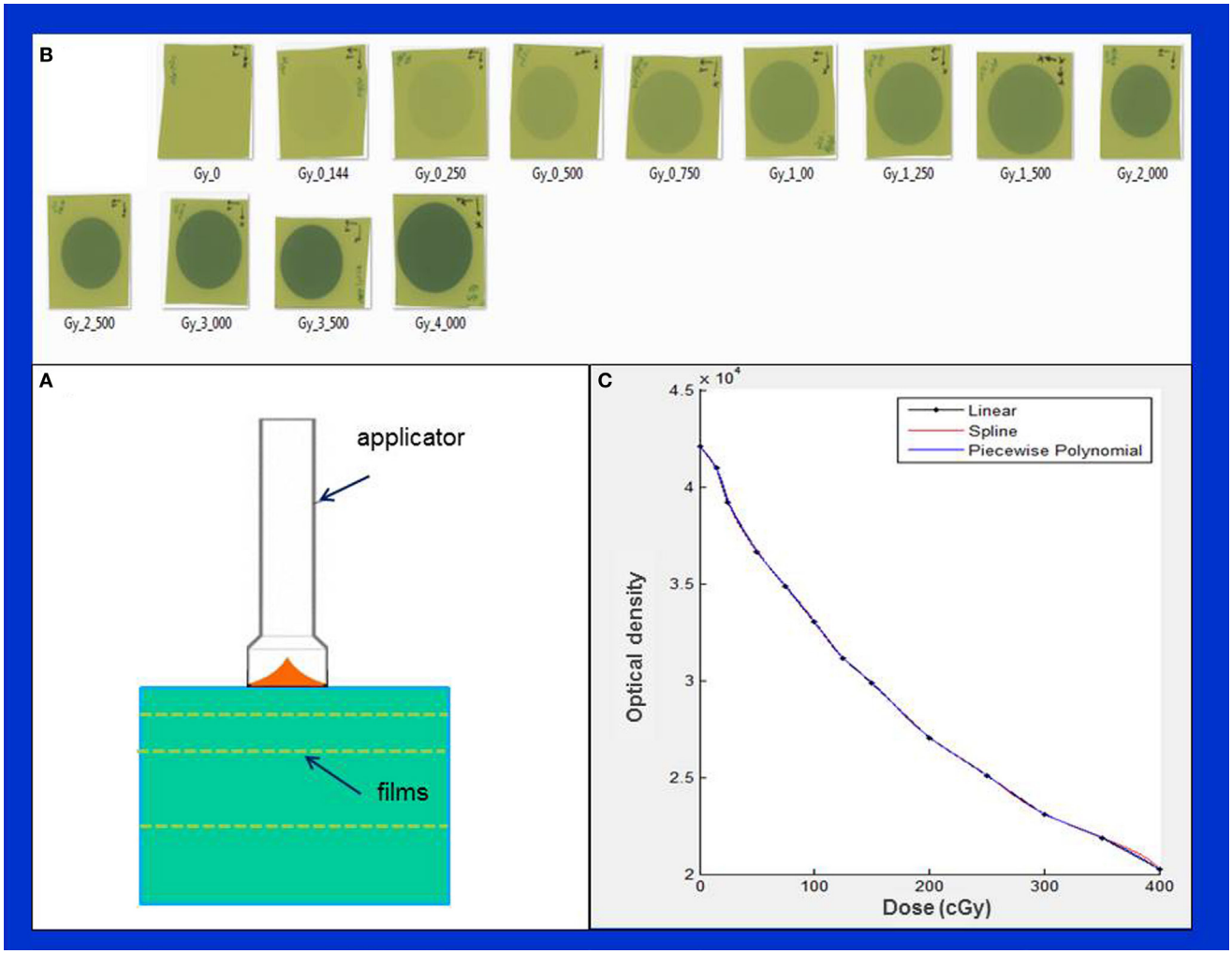

FIGURE 3 | Determination of film sensitometric (H&D) curve. **(A)** Measurement setup showing X-ray source, phantom slabs, and EBT3 films; **(B)** a batch of EBT3 films irradiated in the dose range: 0–400 cGy; **(C)** H&D curve showing variation of film optical density with dose.

observed, for example, handling of films with tweezers and latex gloves (15–19). Furthermore, following each irradiation, films were allowed to self-develop for at least 24 h to stabilize dose response. An EPSON 11000XL PRO flatbed scanner was used with films placed at its center in the portrait orientation. The red color channel was used and film pixel values were converted to dose using the sensitometric (H–D) curve. Film scanning and analysis software, RIT ver. 6.4 (Radiological Imaging Technology, Colorado Springs, CO, USA) was used to generate 2-dimensional dose distributions. With each applicator, films were irradiated to deliver 1 Gy dose at the prescription depth. All film results (DD profiles, OF, etc.) were verified with parallel-plate ion chamber measurements in the water phantom.

RESULTS

Spherical Applicators

Figure 4 shows typical dose distribution produced by a 4 cm diameter spherical applicator. A 20 Gy dose was prescribed at the applicator surface (or the lumpectomy cavity-inner surface). For effective skin sparing, the applicator surface must be at least 1 cm depth from the skin-surface. In the present case, the 20 Gy dose at the applicator surface would result in 5.7 Gy skin dose. Target DH, defined as the ratio of maximum and minimum doses (D_{max}/D_{min}), was evaluated in the radial direction within a 1 cm thick spherical shell surrounding the applicator (as indicated in the figure). For the 4 cm spherical applicator, the measured DR at the applicator surface was 0.8 Gy/min, which resulted in a treatment time of 25 min. At 1 cm from the applicator surface, the DR was 0.23 Gy/min, corresponding to a DH = 3.5. In general, larger applicators require longer treatment time due to lower surface DR, but yield superior target dose homogeneity (DH values closer to unity) or a slower dose fall-off in the target region. Due to its unique design features, the 3-cm diameter spherical applicator has a lower surface dose and slower dose fall-off compared to the 3.5 cm applicator. This results in somewhat longer than expected treatment times with the 3 cm applicator (**Table 1**). **Figure 5** shows the surface DRs and dose fall-off with depth (DD

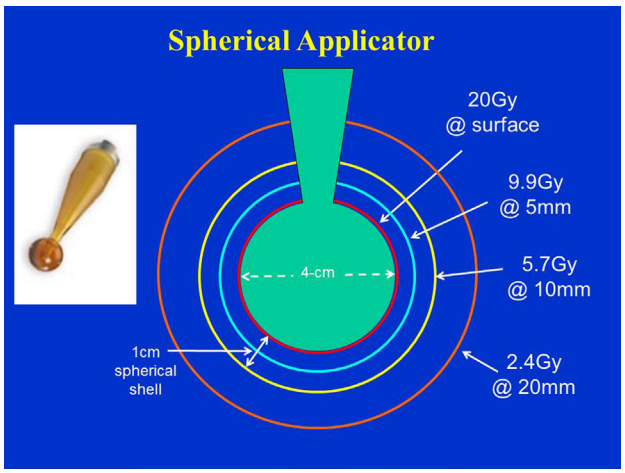

FIGURE 4 | Dose distribution produced by a 4 cm diameter spherical applicator. Doses are shown at the applicator surface and at 5, 10, and 20 mm distance from it. Dose homogeneity was evaluated in a 1 cm thick spherical shell surrounding the applicator. Applicator shown in inset.

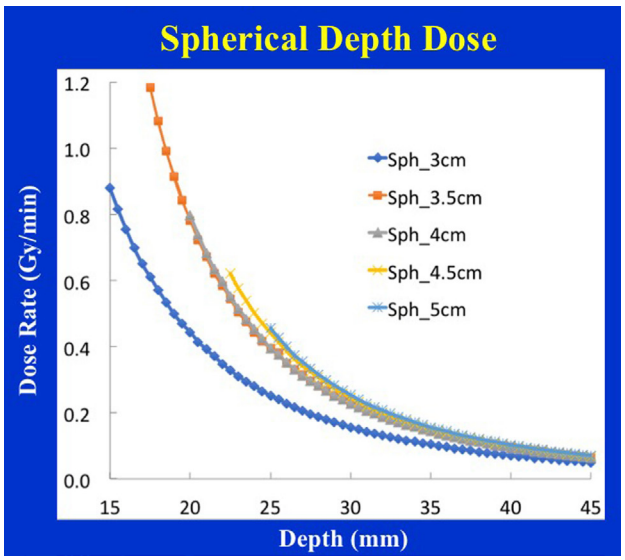

FIGURE 5 | Spherical applicator depth-dose (DD) profiles for a range of diameters (3–5 cm) plotted as a function of the distance from the X-ray source. Note that each depth dose profile begins at the applicator surface, for example, DD profile for the 3 cm applicator begins at 1.5 cm from the X-ray source, etc.

TABLE 1 | Dosimetric characteristic of various intraoperative radiotherapy applicators used with INTRABEAM.

Dosimetric comparison of applicators

Applicator type and diameter	Rx dose (Gy)	Surface dose, Ds (Gy)	Dose homogeneity (DH) (D_{max}/D_{min})	Treat time (min)
Sphere 3 cm	20	20	3.5	23
Sphere 4 cm	20	20	3.5	25
Sphere 5 cm	20	20	2.9	44
Flat 2 cm	10	25.1	2.5	13
Flat 4 cm	10	19.4	1.9	32
Flat 6 cm	10	18.7	1.9	51
Surface 4 cm	10	D5 = 3	3.3	4.5
Needle	D8 = 8	D13 = 2.2	3.6	1.1

profiles) for spherical applicators with diameters ranging from 3 to 5 cm (treatment times: 17–44 min). For each applicator, the DD curve starts at the applicator surface, for example, 15 mm from the X-ray source for a 3 cm applicator, 20 mm from the X-ray source for a 4 cm applicator, etc. Radial DH, in the 1 cm spherical shell surrounding each applicator (presumed target region) ranged between 3 and 4.

Flat Applicators

Figure 6 shows the dose distribution produced by a 4 cm diameter flat applicator. The dose uniformity (or flatness) perpendicular to the beam direction is greatest at the prescription depth of 5 mm with the dose being less uniform at other depths. At shallower depths (<5 mm from the skin-surface), "horns" in dose profiles corresponding to higher dose values are seen at points away from the central axis. For deeper depths (>5 mm), the opposite effect is observed: the measured dose is greatest along the central axis but tapers-off away from it. For a prescription dose of 10 Gy at 5 mm depth, 19.4 Gy would be delivered to the skin-surface corresponding to a dose-homogeneity, DH of 1.94 along the beam direction within 5 mm thick surface layer. Typical treatment time is approximately 30 min. Larger applicators require longer treatment times, but result in a lower surface dose (Ds) and superior dose-homogeneity. **Figure 7** shows the dose fall-off with depth (DD) in water for various flat applicators ranging in diameter from 1 to 6 cm. Several interesting features of this figure are worth noting. First, small applicators are associated with (a) large surface (or skin) dose, (b) shorter treatment times, and (c) lower DH. Second, **Figure 7** shows a lack of measured data for depths <2 mm. This is caused by the design of the parallel-plate ion-chamber used for dose measurements. The effective point of measurement for this chamber is located at its entrance (inner) wall, which is ~2 mm below the chamber's outer surface. As shown in **Figure 2C**, the chamber wall thickness is 0.22 mm and the chamber is protected inside a 1 mm thick waterproof sleeve (**Figure 2A**) with an air gap of 0.5 mm between the sleeve and the chamber wall. Thus, a separation of 1.72 mm between the inner wall of the chamber and its outer surface represents the region where dose cannot be measured. To obtain missing data points in the superficial region, we repeated DD measurements with EBT3 films oriented parallel to the beam direction. **Figure 8** shows excellent agreement between film and ion chamber results for a 4 cm flat applicator.

Surface Applicators

Figure 9 shows dose distribution from a 4 cm diameter surface applicator. The prescription dose in this case is at the

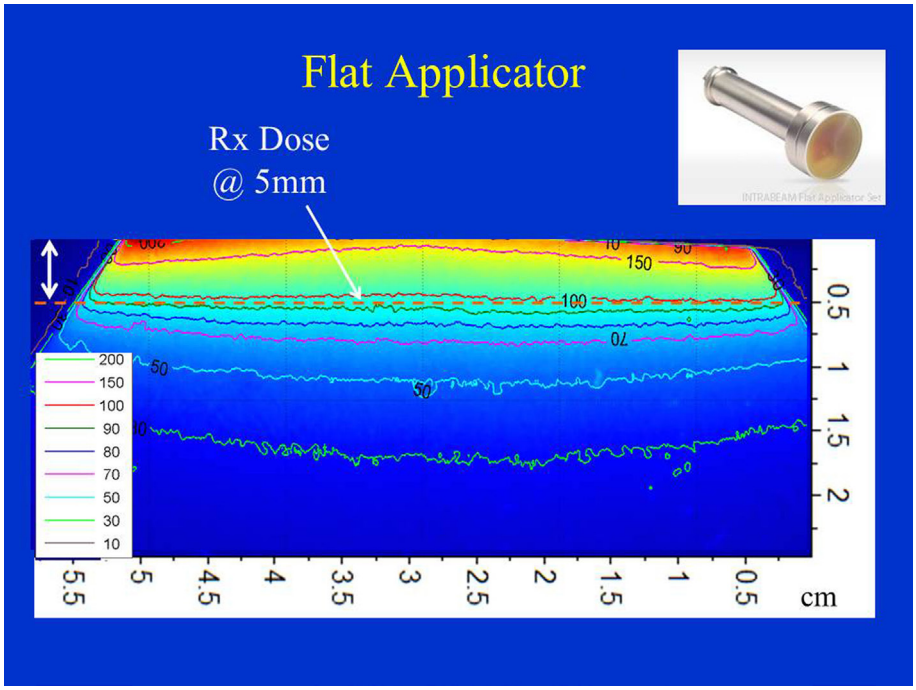

FIGURE 6 | Dose distribution produced by a 4 cm flat applicator. Dose is prescribed at 5 mm depth in phantom. Also indicated is 5 mm superficial layer used to evaluate dose homogeneity. Applicator shown in inset.

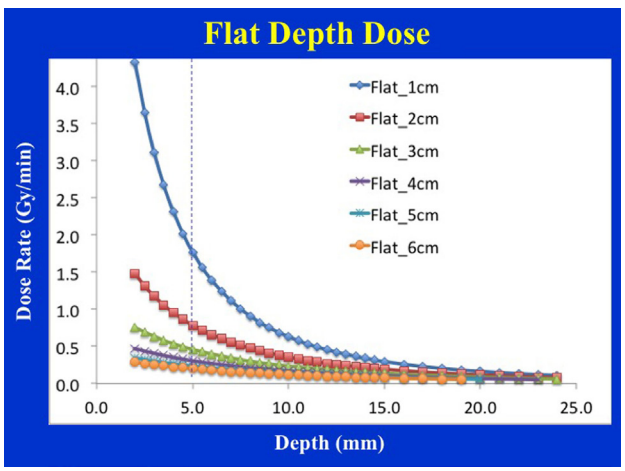

FIGURE 7 | Flat applicator depth-dose (DD) profiles for a range of diameters (1–6 cm) as measured with an ion chamber. Larger applicators are characterized by superior dose homogeneity, lower surface dose, smaller output factor, and longer treatment times. Notice a lack of measured data at shallow depths (<2 mm) due to the chamber design.

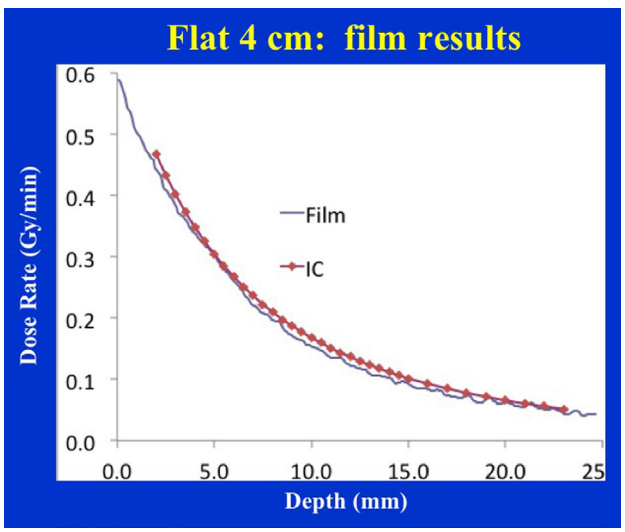

FIGURE 8 | Film vs. ion chamber depth dose comparison for a 4 cm diameter flat applicator.

applicator surface and a rapid dose fall-off is observed with depth. The dose is highest along the central-axis and tapers off-axis. For a prescription dose of 10 Gy at the applicator (or skin) surface, a treatment time of 4.5 min is required. This corresponds to a surface dose-rate (Ds) of approximately 2.2 Gy/min. At a depth of 5 mm, the dose reduces to only 3 Gy for a DH = 3.33. Again, larger diameter surface applicators will require longer treatment times but produce superior DH and lower Ds. **Figure 10** shows the dose fall-off with depth for various surface applicators. To recover missing

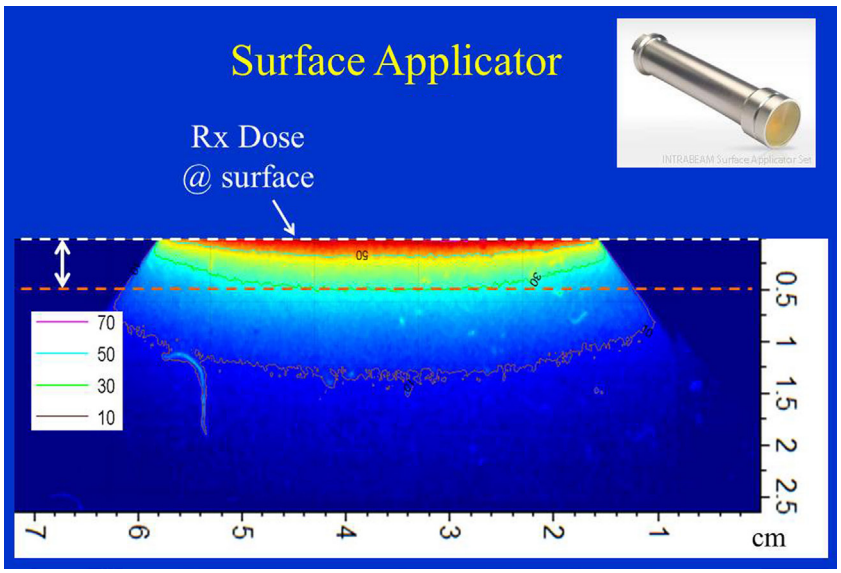

FIGURE 9 | Dose distribution from a 4 cm surface applicator. Dose is prescribed at the surface of the phantom. Also indicated is 5 mm superficial layer used to evaluate dose homogeneity. Applicator shown in inset.

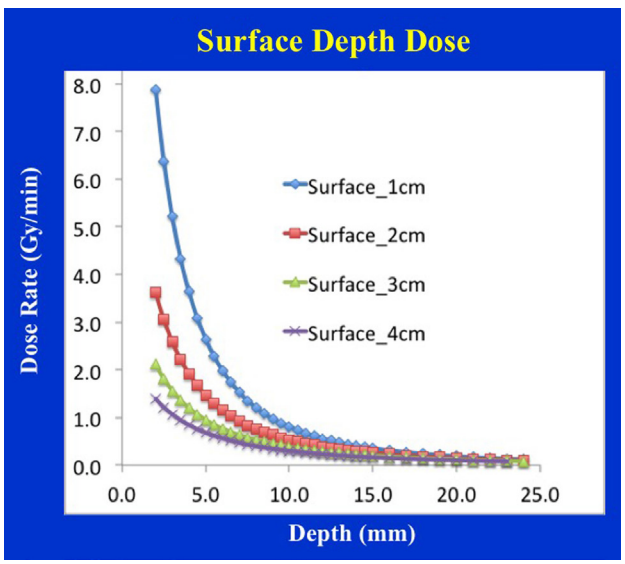

FIGURE 10 | Surface applicator depth-dose (DD) profiles for a range of diameters (1–4 cm). Larger applicators are characterized by superior dose homogeneity, smaller output factor, and longer treatment times. Notice a lack of measured data at shallow depths (<2 mm) due to the chamber design.

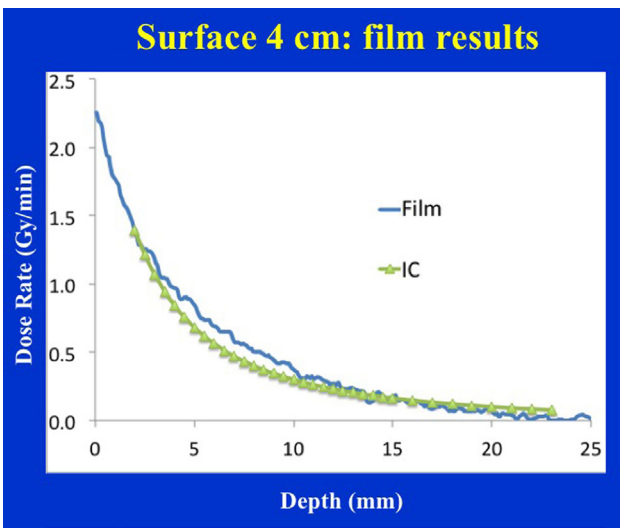

FIGURE 11 | Film vs. ion chamber depth dose comparison for a 4 cm diameter surface applicator. Discrepancy between film and ion chamber data could be related to X-ray spectral changes resulting from steep dose gradient associated with surface applicators.

dose data points at the shallower depths (<2 mm), doses were re-measured with calibrated EBT3 films and the results are shown for the 4 cm-surface applicator. Good agreement between ion-chamber and film doses is seen (**Figure 11**). The discrepancy between film and chamber dose is probably due to X-ray spectral changes and rapid dose fall-off with surface applicators.

Needle Applicators

Figure 12 shows dose distribution produced with a needle applicator. Typically, 8 Gy prescription dose is given at 5 mm distance from the needle applicator surface to spine metastases for a treatment time of over a minute. Owing to the close-proximity of the prescription dose point to the XRS source, a rapid dose fall-off with depth is observed (**Figure 13**).

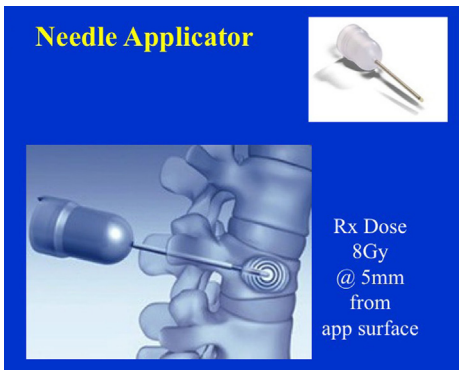

FIGURE 12 | Dose distribution from a needle applicator. Dose is prescribed at 5 mm from the applicator surface or 8 mm from the source. Needle applicator shown in inset.

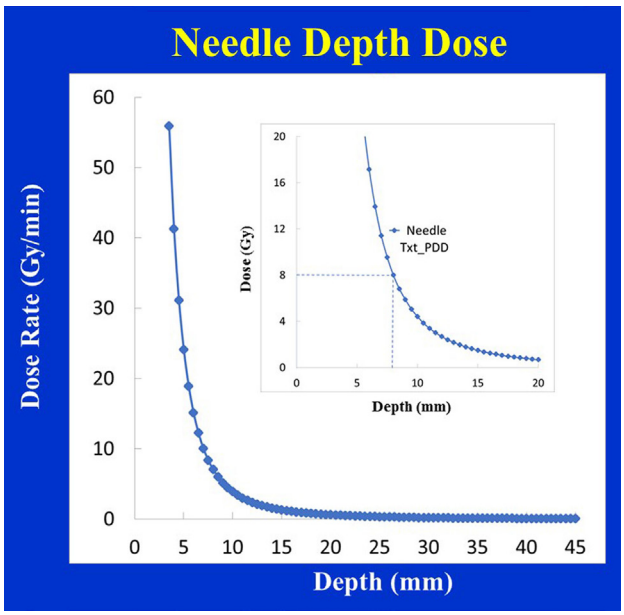

FIGURE 13 | Depth-dose (DD) profiles for the Needle applicator (diameter 4.4 mm). Inset figure shows a prescribed dose of 8 Gy delivered at 8 mm from the source.

A look-up table (available from Zeiss, Inc.) is used to determine treatment time for desired prescription dose.

Table 1 summarizes main dosimetric results for various IORT applicators.

DISCUSSION

Intraoperative radiotherapy has shown clinical utility in a variety of treatment sites outside breast: intracranial (20), head and neck (21, 22), abdomen (23), pelvis (24, 25), spine (26, 27), and skin (28). Compared to 3-d conformal radiotherapy, the main advantages of IORT lie in its steep dose-fall off and the ability to give a large dose to target volume while limiting dose to nearby organs-at-risk (OARs). Successful IORT requires a multi-disciplinary team of nurses, anesthesiologists, radiation oncologists, surgeons, and medical physicists. Also needed are quality assurance checks for safe and effective IORT delivery and a detailed understanding of each applicator's dose distribution. Since April 2014, our group has treated 73 IORT patients for a variety of treatment indications: breast (35 patients), H&N (23 patients), abdomen/pelvis (13 patients), and spine metastasis (2 patients).

The choice of IORT applicator depends on the treatment site and the extent of the disease. For example, breast IORT is commonly delivered using a spherical applicator with the prescription dose at the outer surface of the applicator (or inner-cavity surface). Flat and surface applicators provide a uniform planar dose as in the H&N and abdomen/pelvis regions. At our institution, H&N IORT has been delivered with flat applicators; however, both flat and surface applicators have been used in the treatment of abdomen/pelvis targets. The needle applicator has been designed for kypho-IORT of spine metastasis.

Each IORT applicator presents a unique dosimetric challenge and learning curve, due attention to which is essential for safe and effective treatments. Prior to their clinical use, dosimetric parameters: surface dose (Ds), depth dose profiles (DD), treatment times, etc., for each applicator must be measured and validated. These data, as a lookup table, can be helpful in performing quality assurance or independent checks of treatment times used for patient treatments. In addition, room survey measurements must be performed for each applicator to assess doses received by the OR personnel during IORT and to ensure they are within safe-limits.

The maximum dose with a spherical applicator is at the applicator surface. In general, radial dose fall-off with depth is sharper with smaller applicators. The use of small applicators may, therefore, result in greater skin sparing but a less uniform target dose. Small applicators are also associated with shorter treatment times. Using too small an applicator size, however, could cause air-gaps between the applicator and the surrounding cavity, thereby compromising treatments. Studies have shown significant attenuation of low energy photon spectrum in the presence of tissue inhomogeneities (29). These may produce unacceptably large variation in PTV dose. Based on film and ion chamber measurements, our group showed a 16% dose enhancement when a 2 mm layer of tissue is replaced by air and a 58% dose reduction when it is replaced by bone (29). This is further exacerbated by the above noted rapid variation in target dose with depth; for example, a 3.5 times reduction in dose within 1 cm thick shell surrounding a 4 cm diameter breast applicator. Therefore, Bouzid et al. have recommended CT-based treatment planning with Monte Carlo dose calculations for improved prescription and assessment of delivered IORT dose (30). With CT based planning, any concerns related to a lack of target coverage and/or OAR sparing can be addressed by the planner.

A flat applicator is used when a uniform dose at a given depth is desired in tissue (typically 5 mm depth from skin-surface). With an increase in applicator diameter, the dose-rate decreases, the treatment time increases, but the DH is improved in the

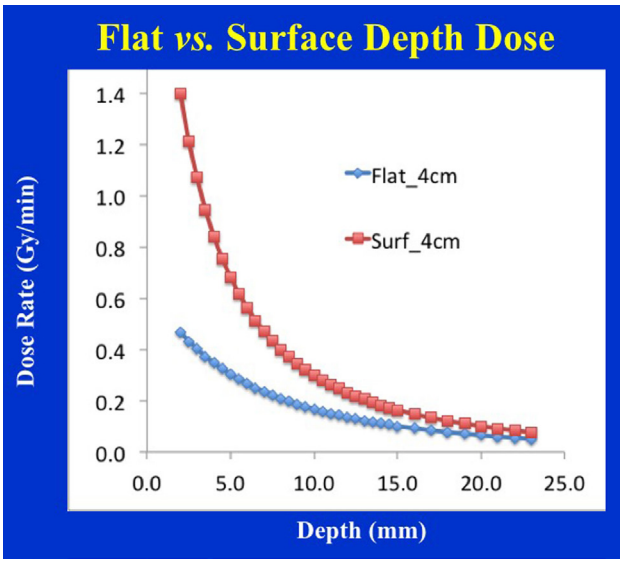

FIGURE 14 | Depth-dose profile comparison for 4 cm diameter flat vs. surface applicators. Notice the steep dose-fall of with depth for the surface applicator resulting in inferior dose homogeneity, larger output factor, and shorter treatment times.

shallow regions. These changes are most dramatic for smaller applicators (<3 cm diameter). In general, larger applicators produce the most homogeneous dose. Similar depth-dose variation is observed for surface applicators but the effect is more pronounced (**Figure 14**). A concern with the use of flat/surface applicators is the skin/surface dose, which could be a limiting factor in some treatments. It is important to note that very small applicators (≤2 cm diameter) may yield relatively high surface dose; therefore, one must select the largest possible applicator size that is compatible with the treatment area.

Due to large prescription doses used with IORT, skin-toxicity can be a big concern. We have investigated the use of SURGICEL® (Ethicon, Inc., Johnson and Johnson Health Care, Somerville, NJ, USA) to reduce surface dose. A 1 or 2-mm layer of SURGICEL® may be used to reduce skin toxicity (lower skin dose by up to 30%).

In summary, the dosimetric results presented here pertain to INTRABEAM IORT and associated applicators only. Furthermore, the results reported in this study are for guidance purposes only and must be validated by each institution with their own equipment prior to the clinical implementation of IORT.

CONCLUSION

Intraoperative radiotherapy may be delivered with a variety of treatment applicators. Selection of appropriate applicator is important for safe, efficient, and effective delivery of IORT. The dosimetric results from this study should help design IORT treatments to assure optimized target coverage and reduced normal tissue exposure. These results may also be used in designing an effective IORT QA program including secondary check of treatment times.

AUTHOR CONTRIBUTIONS

AS participated in study design, data measurement, and manuscript preparation. BE, WS, and TT contributed clinical data and recommended applications and reviewed manuscript.

REFERENCES

1. Hensley FW. Present state and issues in IORT physics. *Radiat Oncol* (2017) 12:37. doi:10.1186/s13014-016-0754-z
2. Eaton DJ. Electronic brachytherapy – current status and future directions. *Br J Radiol* (2015) 88:20150002. doi:10.1259/bjr.20150002
3. Beddar AS, Biggs PJ, Chang S, Ezzell GA, Faddegon BA, Hensley FW, et al. Intraoperative radiation therapy using mobile electron linear accelerators: report of AAPM radiation therapy committee task group No. 72. *Med Phys* (2006) 33:1476–89. doi:10.1118/1.2194447
4. Armoogum KS, Parry JM, Souliman SK, Sutton DG, Mackay CD. Functional inter-comparison of intraoperative radiotherapy equipment – photon radiosurgery system. *Radiat Oncol* (2007) 2:11. doi:10.1186/1748-717X-2-11
5. Eaton DJ. Quality assurance and independent dosimetry for an intraoperative x-ray device. *Med Phys* (2012) 39:6908–20. doi:10.1118/1.4761865
6. Park CC, Yom SS, Podgorsak MB, Harris E, Price RA Jr, Bevan A, et al. American Society for Therapeutic Radiology and Oncology (ASTRO) emerging technology committee report on electronic brachytherapy. *Int J Radiat Oncol Biol Phys* (2010) 76:963–72. doi:10.1016/j.ijrobp.2009.10.068
7. Beatty J, Biggs PJ, Gall K, Okunieff P, Pardo FS, Harte KJ, et al. A new miniature X-ray device for interstitial radiosurgery: dosimetry. *Med Phys* (1996) 23:53–62. doi:10.1118/1.597791
8. Dinsmore M, Harte K, Sliski A, Smith D, Nomikos O, Dalterio MJ, et al. A new miniature x-ray source for interstitial radiosurgery: device description. *Med Phys* (1996) 23:45–52. doi:10.1118/1.597790
9. Ebert MA, Carruthers B. Dosimetric characteristics of a low-kV intraoperative x-ray source: implications for use in a clinical trial for treatment of low-risk breast cancer. *Med Phys* (2003) 30:2424–31. doi:10.1118/1.1595611
10. Vaidya JS, Baum M, Tobias JS, Morgan S, D'Souza D. The novel technique of delivering targeted intraoperative radiotherapy (TARGIT) for early breast cancer. *Eur J Surg Oncol* (2002) 28(4):447–54. doi:10.1053/ejso.2002.1275
11. Vaidya JS, Joseph DJ, Tobias JS, Bulsara M, Wenz F, Saunders C, et al. Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial. *Lancet* (2010) 376:91–102; Erratum in: *Lancet* (2010) 376:90. doi:10.1016/S0140-6736(10)60837-9
12. Vaidya JS, Baum M, Tobias JS, Wenz F, Massarut S, Keshtgar M, et al. Long-term results of targeted intraoperative radiotherapy (TARGIT) boost during breast-conserving surgery. *Int J Radiat Oncol Biol Phys* (2011) 81:1091–7. doi:10.1016/j.ijrobp.2010.07.1996
13. Schneider F, Clausen S, Thölking J, Wenz F, Abo-Madyan Y. A novel approach for superficial intraoperative radiotherapy (IORT) using a 50 kV X-ray source: a technical and case report. *J Appl Clin Med Phys* (2014) 15:4502. doi:10.1120/jacmp.v15i1.4502
14. Biggs PJ, Beatty J, Yasuda T. Distance-dose curve for a miniature x-ray tube for stereotactic radiosurgery using an optimized aperture with a parallel-plate ionization chamber. *Med Phys* (1999) 26:2550–4. doi:10.1118/1.598792
15. Steenbeke F, Gevaert T, Tournel K, Engels B, Verellen D, Storme G, et al. Quality assurance of a 50-kV radiotherapy unit using EBT3 GafChromic film: a feasibility study. *Technol Cancer Res Treat* (2015) 15(1):163–70. doi:10.1177/1533034614565910
16. Lynch BD, Kozelka J, Ranade MK, Li JG, Simon WE, Dempsey JF. Important considerations for radiochromic film dosimetry with flatbed CCD scanners and EBT GafChromic film. *Med Phys* (2006) 33:4551–6. doi:10.1118/1.2370505

17. Paelink L, De Neve W, De Wagter C. Precautions and strategies in using a commercial flatbed scanner for radiochromic film dosimetry. *Phys Med Biol* (2007) 52:231–42. doi:10.1088/0031-9155/52/1/015
18. Butson MJ, Cheung T, Yu PKN, Metcalfe P. Assessment of large single-fraction, low energy x-ray dose with radiochromic film. *Int J Radiat Oncol Biol Phys* (2000) 46:1071–5. doi:10.1016/S0360-3016(99)00465-4
19. Avanzo M, Rink A, Dassie A, Massarut S, Roncardin M, Borsatti E, et al. In vivo dosimetry with radiochromic films in low-voltage intraoperative radiotherapy of the breast. *Med Phys* (2012) 39:2359–68. doi:10.1118/1.3700175
20. Giordano FA, Wenz F, Petrecca K. Rationale for intraoperative radiotherapy in glioblastoma. *J Neurosurg Sci* (2016) 60(3):350–6.
21. Munter MW, Koppen U, Ramuscak A, Sittel C, Wegner N. Intraoperative radiotherapy (IORT) in the treatment of head and neck cancer. *Transl Cancer Res* (2015) 4(2):178–81. doi:10.3978/j.issn.2218-676X.2015.04.03
22. Chen AM, Budcci MK, Singer MI, Garcia J, Kaplan MJ, Chan AS, et al. Intraoperative radiation therapy for recurrent head-and-neck cancer: the UCSF experience. *Int J Radiat Oncol Biol Phys* (2007) 67(1):122–9. doi:10.1016/j.ijrobp.2006.08.038
23. Ogawa K, Karasawa K, Ito Y, Ogawa Y, Jingu K, Onishi H, et al. Intraoperative radiotherapy for resected pancreatic cancer: a multi-institutional retrospective analysis of 210 patients. *Int J Radiat Oncol Biol Phys* (2010) 77(3):734–42. doi:10.1016/j.ijrobp.2009.09.010
24. Guo S, Reddy CA, Kolar M, Woody N, Mahadevan A, Deibel FC, et al. Intraoperative radiation therapy with the photon radiosurgery system in locally advanced and recurrent rectal cancer: retrospective review of the Cleveland clinic experience. *Radiat Oncol* (2012) 7:110. doi:10.1186/1748-717X-7-110
25. Haddock MG. Intraoperative radiation therapy for colon and rectal cancers: a clinical review. *Radiat Oncol* (2017) 12:11. doi:10.1186/s13014-016-0752-1
26. Schneider F, Greineck F, Clausen S, Mai S, Obertacke U, Reis T, et al. Development of a novel method for intraoperative radiotherapy during kyphoplasty for spinal metastases (Kypho-IORT). *Int J Radiat Oncol Biol Phys* (2011) 81:1114–9. doi:10.1016/j.ijrobp.2010.07.1985
27. Wenz F, Schneider F, Neumaier C, Kraus-Tiefenbacher U, Reis T, Schmidt R, et al. *Kypho*-IORT – a novel approach of intraoperative radiotherapy during kyphoplasty for vertebral metastases. *Radiat Oncol* (2010) 5:11. doi:10.1186/1748-717X-5-11
28. Cognetta AB, Howard BM, Heaton HP, Stoddard ER, Hong HG, Green WH. Superficial x-ray in the treatment of basal and squamous cell carcinomas: a viable option in select patients. *J Am Acad Dermatol* (2012) 67(6):1235–41. doi:10.1016/j.jaad.2012.06.001
29. Sethi A, Chinsky B, Gros S, Diak A, Emami B, Small W Jr. Tissue inhomogeneity corrections in low-kV intra-operative radiotherapy (IORT). *Transl Cancer Res* (2015) 4(2):182–8. doi:10.3978/j.issn.2218-676X.2015.04.08
30. Bouzid D, Bert J, Dupre P-F, Benhalouche S, Predier O, Boussion N, et al. Monte-Carlo dosimetry for intraoperative radiotherapy using a low energy x-ray source. *Acta Oncol* (2015) 54(10):1788–95. doi:10.3109/0284186X.2015.1016623

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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OPINION
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Low-Energy Intraoperative Radiation Therapy and Competing Risks of Local Control and Normal Tissue Toxicity

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Keywords: radiotherapy, breast cancer, breast conserving therapy, accelerated PBI, intraoperative radiation therapy, cardiac toxicity, lung toxicity

INTRODUCTION

Radiotherapy (RT) following breast-conserving therapy has been demonstrated to reduce the risk of breast cancer local recurrence and death (1). The adverse normal tissue effects of radiation have been reduced, but not eliminated, with modern treatment planning techniques. Since the introduction of breast-conserving therapy in the 1980s, analyses of long-term results of randomized trials have identified patients that derive the most benefit in local control and disease-free survival. Partial breast irradiation (PBI) is an option for patients with defined, low-risk features that has the advantage of reduced radiation to the heart, lungs, and soft tissues. Low-energy intraoperative radiation therapy (IORT) is a subset of PBI that shortens the treatment course and reduces the dose to larger volumes of normal tissues compared to other techniques.

Patients with a lower risk of local recurrence are likely to live decades beyond their treatment and are at continued risk of impaired cardiac and pulmonary function. For these patients, it seems prudent to select treatments that reduce the risk of late radiation effects.

WHOLE BREAST IRRADIATION (WBI) AND LOCAL CONTROL

While the proportional benefit of breast radiation in achieving local control is similar for all groups, the absolute benefit is related to patient and tumor characteristics. Data from the Early Breast Cancer Trialists' Collaborative Group showed that the absolute benefit of post-BCS conserving RT was greater in younger women; 10-year risk reduction was 24.6% for women younger than 40 years of age and 8.9% for women 70 years and older (2). An update of the European Organization for Research and Treatment of Cancer Boost or No Boost trial showed a cumulative incidence of breast tumor recurrence (IBTR) at 20 years of 34% in patients younger than 40 years of age and 11% in patients 50 years and older (3). Young age and presence of ductal carcinoma *in situ* were the predominant factors associated with IBTR. Patients with high invasive grade were at high risk for IBTR in the first 5 years posttreatment, but this effect declined with time. Liu et al. showed that breast cancer subtype was related to IBTR in node-negative patients older than 50 years but not associated with response to radiation (4).

In 1985, the reported 5-year ipsilateral breast recurrence rate following lumpectomy and radiation from the National Surgical Adjuvant Breast and Bowel Project B06 trial was 7.7% (5). This level of local control supported the introduction of breast conservation as an acceptable treatment for early breast cancer. Local recurrence rates following conservative surgery and radiation are lower in modern series, probably related to more effective systemic therapy and improved surgical and pathology techniques.

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ACCELERATED PBI

For localized breast cancer, the most common site of recurrence is at or near the index lesion. Recurrence in other quadrants is not impacted by WBI (6). Accelerated PBI (APBI) treats a limited volume surrounding the tumor cavity with larger fractions over a shorter period than WBI. Advantages of APBI include reduced treatment time, fewer patient visits, and reduced normal tissue effects. Several treatment delivery methods are utilized, including interstitial, intracavitary, intensity-modulated radiation therapy or 3-D conformal, proton therapy, and IORT.

A systematic review of eight randomized trials of APBI showed a small difference of local recurrence in favor of WBI but no difference in nodal recurrence, systemic recurrence, overall survival, or mortality (7). A randomized, non-inferiority trial of multicatheter brachytherapy versus WBI reported local recurrence of 1.44% with APBI versus 0.92% with WBI at 5 years, demonstrating non-inferiority with respect to local control and disease-free and overall survival (8). Several studies have identified age as a risk factor for local recurrence with APBI, with lower risk in patients older than 50 years (9, 10). This is reflected in the American Society for Radiation Oncology consensus statement regarding APBI, with age of 50 years or older in the suitable category (11). APBI has been widely used for decades and tested in clinical trials in over 1,000 patients. For appropriately selected patients, outcomes are comparable to WBI. In addition, there is a lower incidence of non-breast cancer mortality. A meta-analysis of randomized trials of PBI versus whole breast radiation reported lower 5-year non-breast cancer and overall mortality rates in patients treated with PBI, amounting to a 25% reduction in relative terms (12).

LOW-ENERGY X-RAY IORT

Intraoperative radiation therapy is a subset of PBI that delivers a single fraction of radiation at the time of lumpectomy, saving patient and facility time and resources. There is a potential therapeutic advantage to delivering radiation to the operative tumor bed, with a steep dose fall-off and minimal dose delivered to non-involved tissues. Several IORT delivery systems are available, most of which use kilovoltage (kV) photons or megavoltage electrons.

The intrabeam IORT device provides a point source of 50 kV X-rays at the center of a spherical applicator. Applicator diameters range from 1.5 to 5.0 cm. HVLs of the Intrabeam device correspond to effective energies of 20.7–36.3 keV. Depending on applicator diameter, the dose is reduced to 5–7 Gy at 1 cm from the applicator and 1 Gy in 2.3–6.4 cm of tissue. An *in vivo* dosimetry study showed a mean skin dose of 2.9 ± 1.6 Gy (13). A separate study demonstrated a skin dose of 0.29 ± 0.17 Gy at 5–10 cm from the applicator and a dose of 0.57 ± 0.23 Gy to the pectoral muscle in left breast patients (14). Based on these characteristics, dose to the heart and lungs from low-energy IORT is minimal. The absence of significant dose to organs at risk is a major difference between external beam radiation (**Figure 1A**) and low-energy, X-ray IORT (**Figure 1B**).

A prospective randomized trial of IORT versus whole breast RT using the Intrabeam device at the time of lumpectomy (TARGIT-A) reported a local recurrence rate at 4 years of 1.2% in the IORT group and 0.95% in the WBI group (15). Five-year results from the trial reported a 2.1% rate of breast recurrence in the IORT group versus 1.1% in the WBI group when IORT was delivered at the time of lumpectomy. When IORT was delayed until pathology was available, local recurrence was higher (5.4%) (16). Overall breast cancer mortality was the same in the TARGIT and WBI groups, but there were significantly fewer non-breast cancer deaths with TARGIT, attributable to fewer deaths from cardiovascular causes and other cancers (16).

LUNG TOXICITY OF WBI

Lung toxicity is a known complication of thoracic radiation that is related to dose and volume. Postmastectomy radiation in the preimage guided 3-D conformal era was associated with a significant risk of radiation pneumonitis. The use of lung constraints in treatment planning has decreased clinical lung complications associated with RT. A Swedish group showed that use of 3-D planning with a lung constraint of V20 <30% reduced the rate of radiation pneumonitis and associated decrease in pulmonary function tests (PFTs) (17). A later report from the same group showed a significant reduction in PFTs compared to pre-RT values and observed that computed tomography (CT) changes observed 4 months after RT were still detectable

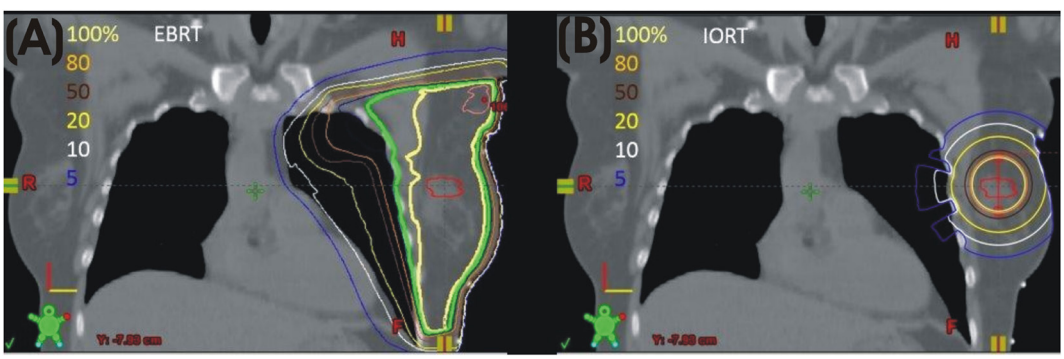

FIGURE 1 | **(A)** Left breast plan with isodose lines. **(B)** Model of calculated isodose plan with 4 cm 50 kV applicator in lumpectomy site.

after 11 years (18). A prospective study of pulmonary sequelae of breast irradiation showed serial changes in lung imaging, with reduction in lung function following radiation. The study included patients receiving postmastectomy and intact breast radiation from 1996 to 1997 using 2-D planning. Lung functioning indices, including forced expiratory volume in 1 s, forced vital capacity, total lung capacity, and diffusing capacity of the lung for carbon monoxide, declined after radiation and were irreversible after 12 months (19).

Contemporary RT is CT-based and incorporates normal tissue constraints that reduce long-term toxicity. A study that coregistered quantitative single photon emission CT (SPECT)/CT of the lung with treatment plans of patients receiving breast/chest wall and regional node irradiation (V20 left lung limited to 33%) showed dose-related decreased perfusion to the lung (20). Although the use of these constraints prevented clinical symptoms of lung toxicity, patients experienced decreased lung perfusion, an indication of lung injury.

While modern radiation techniques can reduce pulmonary toxicity from external beam breast/chest wall irradiation, it occurs, is measurable, and persists long after treatment is completed.

CARDIAC TOXICITY OF WHOLE BREAST RADIATION

Long-term follow-up of early randomized trials for breast cancer demonstrated an increased risk of ischemic heart disease in irradiated patients, with adverse effects on survival (21). Subsequent follow-up showed that the excess of early cardiac deaths was offset by a reduction of death due to breast cancer, particularly in the more recent trials. It was postulated that earlier trials had a higher rate of cardiac toxicity because of dose and radiation techniques (2, 22).

A population-based study of breast cancer patients treated between 1958 and 2001 in Scandinavia showed that radiation to the heart during breast cancer treatment was associated with an increased risk of coronary events. The increase was proportional to mean heart dose (MHD) with no apparent threshold, started within a few years after exposure, and continued for at least 20 years. The authors estimated that a 1 Gy increase in MHD equates to a 7.4% increase in significant coronary events (23). A study of radiation dose response relationship for risk of coronary heart disease (CHD) following radiation for Hodgkin lymphoma (treated 1965–1995) showed that risk of CHD increased linearly with increasing MHD, with a median interval between treatment and expression of CHD of 19 years (24).

Both cohorts of patients were treated in the 2-D era of radiation, before widespread use of CT-based planning and adoption of current cardiac and pulmonary dose constraints. These studies demonstrate that the clinical manifestation of cardiac injury is a late effect and may not be evident until decades after treatment.

Multiple techniques have been developed to decrease cardiac dose, including prone position, intensity-modulated radiation therapy, and deep inspiration breath hold, while dose constraints have been developed to reduce late toxicity. Still, current functional studies provide evidence of measurable cardiac damage following whole breast radiation.

A prospective study of cardiac injury using resting-gated SPECT cardiac perfusion pre- and post-breast/chest wall irradiation, using CT-based planning, showed that radiation therapy caused volume-dependent perfusion defects in about 40% of patients within 6 months to 2 years of treatment. The perfusion defects were more common in patients with a larger volume of the left ventricle within the treatment field and were associated with abnormalities in regional wall motion (25).

A review of published studies of cardiac toxicity demonstrated a decrease in cardiovascular events and cardiac death rate in more modern treatment eras (26). However, the previous example illustrates that measurable cardiac injury occurs with contemporary treatment methods, though symptoms may not be immediately evident. Cardiac injury is related to dose, does not have a threshold, and may become evident years after radiation. This is a relevant concern in the treatment of breast cancer patients who are likely to survive decades after their treatment.

SUMMARY

Selection of radiation modality should consider treatment related-mortality and long-term pulmonary and cardiac toxicity in addition to relative risks of local recurrence and disease-free survival. Multiple techniques have been developed to decrease cardiac and lung dose, and constraints have been developed to reduce late effects. Still, current functional studies provide evidence of measurable cardiac and pulmonary damage following whole breast radiation, which should be considered when selecting treatment.

Discussion of the merits of low-energy (50 kV) IORT has often focused on the issue of local control. Less attention has been directed to potential long-term normal tissue effects. Low-energy IORT has the distinct advantage of minimal dose to the heart and lungs as well as reduced dose to uninvolved soft tissue. In selected patients, local control is not inferior to WBI. In addition, PBI, including IORT, is associated with reduced non-breast cancer mortality.

AUTHOR CONTRIBUTIONS

GJ: conception and design, research of supporting evidence, manuscript writing, and final approval. RS: critical revision of content, editing, creation of dosimetry model, and final approval.

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REFERENCES

1. Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans V, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomized trials. *Lancet* (2005) 366:2087–106. doi:10.1016/S0140-6736(05)67887-7
2. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Darby S, McGale P, Correa C, Taylor C, Arriagada R, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10801 women in 17 randomized trials. *Lancet* (2011) 378:1707–16. doi:10.1016/S0140-6736(11)61629-2
3. Vrieling C, van Werkhoven E, Maingon P, Poortmans P, Weltens C, Fourquet A, et al. Prognostic factors for local control in breast cancer after long-term follow up in the EORTC Boost or No Boost trial: a randomized clinical trial. *JAMA Oncol* (2017) 3:42–8. doi:10.1001/jamaoncol.2016.3031
4. Liu FF, Shi W, Done SJ, Miller N, Pintilie M, Voduc D, et al. Identification of a low-risk luminal A breast cancer cohort that may not benefit from breast radiotherapy. *J Clin Oncol* (2015) 33:1998–2000. doi:10.1200/JCO.2014.57.7999
5. Fisher B, Bauer M, Margolese R, Poisson R, Pilch Y, Redmond C, et al. Five-year results of a randomized clinical trial comparing total mastectomy and segmental mastectomy with or without radiation in the treatment of breast cancer. *N Engl J Med* (1986) 312:665–73. doi:10.1056/NEJM198503143121101
6. Boyages J, Recht A, Connoly JL, Schnitt SJ, Gelman R, Kooy H, et al. Early breast cancer: predictors of recurrence for patients treated with conservative surgery and radiation therapy. *Radiother Oncol* (1990) 19:29–41. doi:10.1016/0167-8140(90)90163-Q
7. Marta GN, Macedo CR, Carvalho Hde A, Hanna SA, da Silva JL, Riera R. Accelerated partial breast irradiation in breast cancer: systematic review and meta-analysis of 8653 women in eight randomized trials. *Radiother Oncol* (2015) 114:42–9. doi:10.1016/j.radonc.2014.11.014
8. Strnad V, Ott OJ, Hildebrandt G, Kauer-Dorner D, Knauerhase H, Major T, et al. 5-year results of accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy versus whole-breast irradiation with boost after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: a randomized, phase 3, non-inferiority trial. *Lancet* (2016) 387(10015):229–38. doi:10.1016/S0140-6736(15)00471-7
9. Ott OJ, Hildebrandt G, Potter R, Hammer J, Lotter M, Resch A, et al. Accelerated partial breast irradiation with multi-catheter brachytherapy: local control, side effects and cosmetic outcome for 274 patients. Results of the German-Austrian multi-centre trial. *Radiother Oncol* (2007) 82:281–6. doi:10.1016/j.radonc.2006.08.028
10. Shah C, Wilkinson JB, Lyden B, Beitsch P, Vicini FA. Predictors of local recurrence following accelerated partial breast irradiation: a pooled analysis. *Int J Radiat Oncol Biol Phys* (2012) 82:e825–30. doi:10.1016/j.ijrobp.2011.11.042
11. Correa C, Harris EE, Leonardi MC, Smith BD, Taghian AG, Thompason AM, et al. Accelerated partial breast irradiation: update of an ASTRO evidence-based consensus statement. *Pract Radiat Oncol* (2017) 7:73–9. doi:10.1016/j.prro.2016.09.007
12. Vaidya JS, Bulsara M, Wenz F, Coombs N, Singer J, Ebbs S, et al. Reduced mortality with partial-breast irradiation for early breast cancer: a meta-analysis of randomized trials. *Int J Radiat Oncol Biol Phys* (2016) 96:259–65. doi:10.1016/j.ijrobp.2016.05.008
13. Eaton DJ, Best B, Brew-Graves C, Duck S, Ghaus T, Gonzalez R, et al. In vivo dosimetry for single-fraction targeted radiotherapy (TARGIT) for breast cancer. *Int J Radiat Oncol Biol Phys* (2012) 82:e819–24. doi:10.1016/j.ijrobp.2011.11.012
14. Avanzo M, Rink A, Dassie A, Massarut S, Roncadin M, Borsatti E, et al. In vivo dosimetry with radiochromic films in low-voltage intraoperative radiotherapy of the breast. *Med Phys* (2012) 39:2359–68. doi:10.1118/1.3700175
15. Vaidya JS, Joseph DJ, Tobias JS, Bulsara M, Wenz F, Saunders C, et al. Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomized, non-inferiority phase 3 trial. *Lancet* (2010) 376:91–102. doi:10.1016/S0140-6736(10)60837-9
16. Vaidya JS, Wenz F, Bulsara M, Tobias JS, Joseph DJ, Keshtgar M, et al. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. *Lancet* (2014) 383:603–13. doi:10.1016/S0140-6736(13)61950-9
17. Blom Goldman U, Anderson M, Wennberg B, Lind P. Radiation pneumonitis and pulmonary function with lung dose-volume constraints in breast cancer irradiation. *J Radiother Pract* (2014) 13:211–7. doi:10.1017/S1460396913000228
18. Blom Goldman U, Svane G, Anderson M, Wennberg B, Lind P. Long term functional and radiological pulmonary changes after radiation therapy for breast cancer. *Acta Oncol* (2014) 53:1373–9. doi:10.3109/0284186X.2014.934967
19. Ooi GC, Kwong DL, Ho JC, Lock DT, Chan FL, Lam WK, et al. Pulmonary sequelae of treatment for breast cancer. *Int J Radiat Oncol Biol Phys* (2001) 50:411–9. doi:10.1016/S0360-3016(01)01438-9
20. Liss AL, Marsh RB, Kapadia NS, McShan DL, Rogers VE, Balter JM, et al. Decreased lung perfusion after breast/chest wall irradiation: quantitative results from a prospective clinical trial. *Int J Radiat Oncol Biol Phys* (2017) 97:296–302. doi:10.1016/j.ijrobp.2016.10.012
21. Cuzick J, Stewart H, Peto R, Fisher B, Kaae S, Johansen H, et al. Overview of randomized trials comparing radical mastectomy without radiotherapy against simple mastectomy with radiotherapy in breast cancer. *Cancer Treat Rep* (1987) 71:7–14.
22. Cuzick J, Stewart H, Rutqvist L, Houghton J, Edwards R, Redmond C, et al. Cause-specific mortality in long-term survivors of breast cancer who participated in trials of radiotherapy. *J Clin Oncol* (1994) 12:447–53. doi:10.1200/JCO.1994.12.3.447
23. Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Bronnum D, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Eng J Med* (2013) 368:987–98. doi:10.1056/NEJMoa1209825
24. van Nimwegen FA, Schaapveld M, Cutter DJ, Janus CP, Krol AD, Hauptmann M, et al. Radiation dose-response relationship for risk of coronary heart disease in survivors of Hodgkin lymphoma. *J Clin Oncol* (2016) 34:235–43. doi:10.1200/JCO.2015.63.4444
25. Marks LB, Yu X, Prosnitz RG, Zhou SM, Hardenbergh PH, Blazing M, et al. The incidence and functional consequences of RT-associated cardiac perfusion defects. *Int J Radiat Oncol Biol Phys* (2005) 63:214–23. doi:10.1016/j.ijrobp.2005.01.029
26. Meattini I, Guenzi M, Fozza A, Vidali C, Rovea P, Meacci F, et al. Overview of cardiac, pulmonary and cutaneous toxicity in patients treated with adjuvant radiotherapy for breast cancer. *Breast Cancer* (2017) 24:52–62. doi:10.1007/s12282-016-0694-3

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REVIEW
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Intraoperative Radiotherapy for Breast Cancer

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Intraoperative radiotherapy (IORT) for early stage breast cancer is a technique for partial breast irradiation. There are several technologies in clinical use to perform breast IORT. Regardless of technique, IORT generally refers to the delivery of a single dose of radiation to the periphery of the tumor bed in the immediate intraoperative time frame, although some protocols have performed IORT as a second procedure. There are two large prospective randomized trials establishing the safety and efficacy of breast IORT in early stage breast cancer patients with sufficient follow-up time on thousands of women. The advantages of IORT for partial breast irradiation include: direct visualization of the target tissue ensuring treatment of the high-risk tissue and eliminating the risk of marginal miss; the use of a single dose coordinated with the necessary surgical excision thereby reducing omission of radiation and the selection of mastectomy for women without access to a radiotherapy facility or unable to undergo several weeks of daily radiation; favorable toxicity profiles; patient convenience and cost savings; radiobiological and tumor microenvironment conditions which lead to enhanced tumor control. The main disadvantage of IORT is the lack of final pathologic information on the tumor size, histology, margins, and nodal status. When unexpected findings on final pathology such as positive margins or positive sentinel nodes predict a higher risk of local or regional recurrence, additional whole breast radiation may be indicated, thereby reducing some of the convenience and low-toxicity advantages of sole IORT. However, IORT as a tumor bed boost has also been studied and appears to be safe with acceptable toxicity. IORT has potential efficacy advantages related to overall survival related to reduced cardiopulmonary radiation doses. It may also be very useful in specific situations, such as prior to oncoplastic reconstruction to improve accuracy of adjuvant radiation delivery, or when used as a boost in higher risk patients to improve tumor control. Ongoing international clinical trials are studying these uses and follow-up data are accumulating on completed studies.

Keywords: breast cancer, intraoperative radiotherapy, breast conservation therapy, partial breast irradiation, radiation therapy

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INTRODUCTION

Partial breast irradiation has been established as a suitable treatment option for appropriately selected women with early stage breast cancer by numerous clinical trials dating back to the 1990s. There are several techniques which have been studied to accomplish irradiation of the periphery of the lumpectomy bed as sole therapy after lumpectomy, which is the target volume for any form of partial

breast treatment. Intraoperative radiotherapy (IORT) is one such technique. The major difference between IORT techniques and other forms of APBI is timing of the procedure. IORT is most often performed at the time of breast surgery as a single dose, while other APBI techniques are performed post-operatively, using target volumes are typically based on CT images and delivering multiple fractions. IORT requires specialized radiotherapy equipment, and there are several technologies available to provide IORT partial breast irradiation, which deliver treatment with either electrons or 50 kV X-rays. IORT has the advantage of completing the breast-conserving surgery and, in most cases, the partial breast irradiation as one combined procedure. All forms of APBI treat a smaller volume of normal tissue than whole breast radiation (WBRT), thereby reducing the potential lung and cardiac toxicities of radiation treatment, and reducing the overall treatment time compared with whole breast irradiation. IORT has the additional advantage of delivering a single dose at the time of surgery, potentially reduces non-compliance to post-operative radiation, and mastectomy rates among women without ready access to a radiotherapy center. There are two recently published large prospective randomized controlled trials comparing post-lumpectomy standard whole breast irradiation to IORT, one using electrons and one using 50 kV photons, which have shown low-local recurrence rates for IORT with acceptable toxicity and excellent overall survival outcomes. These trials begin to inform our knowledge of selection criteria for optimal breast IORT candidates and provide the first evidence of outcomes and toxicity when using these techniques. Patient selection is important when recommending IORT, as the final pathology is not available at the time of treatment, so in order to avoid the potential use of subsequent whole breast irradiation, careful pre-operative, and intraoperative assessment can help ensure that high-risk features such as positive margins or positive sentinel nodes are minimized. As all techniques of partial breast irradiation leave some volume of the breast unirradiated, understanding of the selection criteria for each of the various techniques is critical information for clinicians when considering which patients may be appropriately treated with IORT or any other APBI technique. This review will discuss the clinical trial data, patient selection criteria, advantages and disadvantages of partial breast IORT, and published guidelines.

RADIOBIOLOGY AND TUMOR MICROENVIRONMENT

A common calculation for assessing the efficacy of different dose fractionations in radiotherapy is the relative biological effectiveness (RBE = D_x/D). This parameter allows comparisons of radiation-induced cellular damage at a designated dose (D) relative to a reference dose (D_x) for the selected endpoint, such as percentage of cells surviving after 2 Gy (SF2). It is well known that the RBE of photons increases with decreasing energy, explained by a decrease in energy of secondary electrons with an increase in linear energy transfer (1, 2). Cell culture experiments utilizing cell survival methods such as SF2 confirm enhanced biological effects after exposure to lower energy X-rays. Brenner et al. modeled RBE at clinically relevant doses, at which the RBE for 40 kV photons was about 1.4 compared with 4 mV. Since effective RBE increases with depth this creates a less rapid fall-off of the biologically weighted dose at measured depth. A published review summarized RBEs for 10% cell survival established using different systems and tumor cell types for low energy X-rays (10–240 kV) to range from 1.1 and 1.7 (3). The RBE of 50 kV electronic brachytherapy sources has been estimated to exceed biological effectiveness by 40–50% over Co^{60} or Ir^{192} (4). Other investigators have employed a linear-quadratic formula to model the RBE of 50 kV X-rays modeled as an equivalent to a fractionated dose of 2 Gy (EQD2) as a function of depth, with the probability of local control estimated from clinical dose response data (5). This model resulted in a theoretical "sphere of equivalence" to explain the improved tumor control probability in the high-dose cloud near the applicator surface, where residual microscopic disease is most likely to be located, and compensating for a somewhat lower tumor control probability as the distance from the applicator increases. Overall local control patterns thus exhibited a different spatial pattern but were ultimately very similar to conventionally fractionated external beam irradiation. In the example of IORT for breast cancer, higher RBE for low-energy X-rays may result in higher tumor control rates in the breast tissue in closest proximity to the surgical excision bed and effectively eliminating the "marginal miss." In addition, cell culture data suggest that the RBE decreased at increasing distance, potentially reducing the effective dose to adjacent critical structures including heart and lung (6). The tumor bed intraoperatively is better oxygenated, which may also improve cell kill probability. There may also be some radiobiological advantages in using a higher dose per fraction in breast cancer, which has been estimated to have an alpha/beta ratio of around 4, therefore may demonstrate a higher radioresponsiveness to higher doses per fraction (7). The biologically equivalent dose (BED) for an alpha/beta of 4 in the linear-quadratic model for a prescribed single dose of 10 Gy is isoeffective to about 24 in 2 Gy fractions.

The microenvironment of the breast cancer cells likely plays a critical role as well in the risk of tumor recurrence, and this microenvironment is altered by the use of immediate radiation peri-operatively. Belletti et al. collected wound fluid from the lumpectomy cavity over 24 h after surgery, half of whom had IORT at the time of lumpectomy (8). The wound fluid was used to stimulate several breast cancer and control cell lines and analyzed for cell growth and motility. Normal wound fluid stimulated proliferation, migration, and invasion in breast cancer cell lines, while these effects were abrogated by wound fluid from immediately irradiated samples. The radiated wound fluid had altered expression cytokines, suggesting that the radiation had altered protein expression. Fabris et al. collected tissues from irradiated using IORT and non-irradiated tissue from breast cancer patients after surgery, and profiled the tissue for microRNA expression (9). IORT radiation changed the wound response by inducing expression of miRNA 223 in the peri-tumoral tissue, which downregulated expression of epidermal growth factor (EGF) and EGF receptor activation. This downregulation cascade prevented breast cancer cell growth and reduced local recurrence in mice models. A number of other studies have noted the stimulatory effect of wound fluid

on breast cancer cells, suggesting a role of the fluid in cancer cell proliferation and possibly local recurrence, an effect that may be muted by immediate radiation, with its abrogating effect on protein expression. Clinical trial data are clinically consistent with these concepts and investigations of the biological effects of immediate high-dose radiation on the wound fluid and immunologic environment are ongoing.

IO(E)RT TECHNOLOGIES

The Intrabeam® system (Carl Zeiss Meditec, Dublin, CA, USA) uses a 50 kV photon beam mobile X-ray unit that has been in clinical use since 1999 (10). The miniaturized accelerator produces an electron beam that is accelerated to the tip of a drift tube generating an isotropic point source of low-energy X-rays. The source is permanently integrated into the treatment unit, and is calibrated daily and externally yearly. This system has been designed for single fraction IORT and is calibrated at a single dose rate and output factor. IORT is delivered using multiuse solid state spherical applicators of size ranges 1.5–5 cm diameter. Treatment time typically runs 20–45 min depending upon the applicator size used.

The Axxent® System (Xoft Inc., Sunnyvale, CA, USA) is an electronic brachytherapy machine in clinical use since 2009 (11). The radiation source is a miniature, electronic, high-dose rate low-energy X-ray tube integrated into a flexible multi-lumen catheter producing 40–50 Kv X-rays at the catheter tip. The Axxent system was originally designed for fractionated balloon-based partial breast irradiation using variable currents and voltages to allow for changes in dose rates or depths, and can also be used for single fractions. The source is disposable and used for up to 10 fractions, with disposable balloons of spherical and ellipsoidal sizes (3–6 cm spherical and 5–6 × 7 cm elliptical), over treatment times of 10–20 min. Both technologies can be used in a standard operating room with portable shielding only.

Mobile electron accelerators use electrons energies ranging from 3 to 12 MeV. The lumpectomy cavity of the breast is treated with a cone inserted intraoperatively (12). Electrons are more penetrating than low-energy X-rays, requiring breast tissue to be mobilized and for shields to be inserted into the posterior lumpectomy cavity in order to shield tissues inside the thorax. Doses of 20–21 Gy usually delivered at a low-electron energy for the measured depth. This technology is often notated as intraoperative electron radiation therapy (IOERT).

IO(E)RT AS SOLE PARTIAL BREAST RADIATION

To date, there are two large prospective randomized trials published using breast IO(E)RT, the TARGIT-A trial and the ELIOT trial. TARGIT-A compared conventional WBRT (EBRT) to single dose IORT (TARGIT) and enrolled 3,451 patients from 33 centers in 10 countries between the years 2000 and 2012. This study used a non-inferiority statistical design which anticipated a 15% probability of adverse pathologic features on final pathology leading to additional WBRT after initial IORT (13). There were pre-specified strata described as IORT at the time of lumpectomy (pre-pathology), or IORT performed during a subsequent procedure at a different time (post-pathology).

Women enrolled to TARGIT-A were age 45 years or older with operable unifocal invasive ductal carcinoma. Per eligibility criteria pathologic findings requiring subsequent WBRT after IORT included positive excision margins, extensive intraductal component, or the presence of invasive lobular carcinoma. Participating centers could prospectively specify additional other factors. Overall, 22% of women enrolled in the pre-pathology and 3.6% of those in the post-pathology strata received additional WBRT after randomization to IORT. The majority enrolled had lower risk pathologic features, including ≤2 cm (87%), low to intermediate grade (85%), negative nodes (84%), estrogen receptor positive (93%), and mammographic detection (63%). With median follow-up of 2.5 years of the whole cohort and over 1,200 patients with 5-year median follow-up, for the primary endpoint of in-breast recurrence (IBR), the investigators reported 5-year IBR in the EBRT arm of 1.3%, and in the TARGIT arm of 3.3%, a 2% difference which was within the pre-specified 2.5% non-inferiority margin ($p = 0.042$). The impact of the timing of IORT was analyzed between the two strata. For pre-pathology stratum, IBR was 1% in the EBRT arm and 2.1% in the TARGIT arm ($p = 0.31$). For post-pathology stratum, IBR was 1.7% in the EBRT arm and 5.4% in the TARGIT arm ($p = 0.069$). These findings prompted the trialists to conclude that pre-pathology timing was more optimal. Overall survival was higher in the TARGIT arm (3.9%) compared with the EBRT arm (5.3%; $p = 0.099$), mainly due to higher rates of cardiopulmonary deaths. Toxicity comparisons including hematoma requiring treatment, post-operative infection, delayed wound healing, and all major toxicities were similar between the two arms.

The largest series outside of the TARGIT-A trial using 50 kV IORT has been reported by the TARGIT-R North American multi-institutional IORT retrospective registry trial (14). Nineteen institutions participated in this registry and reported outcomes on 822 women treated from 2007 through 2013 with minimum 6 months follow-up and a median follow-up of 2 years. Registrants were treated with IORT without ($n = 537$) or with WBRT ($n = 110$) or IORT as intended boost ($n = 115$). As is typical of APBI studies and registries, patients were mainly lower risk, or meeting American Society for Radiation Oncology (ASTRO) 2009 "suitable" criteria, with a median age of 67, <2 cm (90%), estrogen receptor positive (91%), Her2 non-amplified (89%), grade 1–2 (83%), without lymphovascular invasion (91%), and sentinel node negative (89%). Interestingly, 52% of registrants had a pre-operative breast MRI performed. Post-operative WBRT was recommended in 17% of IORT patients due to unfavorable pathologic findings, and 14% of registrants received IORT as a planned boost. A small number ($n = 60$) had delayed IORT as a second procedure rather than at the time of lumpectomy. Local IBRs were seen in 2.3% ($n = 19$ of 822), and axillary nodal recurrences in 0.2% ($n = 2$), at a median time to recurrence of 19 months. One death was attributed to breast cancer. Local recurrence by type of IORT was reported as follows: IORT alone, 2.4%; secondary IORT, 6.6%; IORT + WBRT, 1.7%; IORT boost, 1.8%. Thirteen of 19 local recurrences occurred >1 cm from the lumpectomy site. Several of these patients had higher risk features

including ER negative tumors or positive sentinel nodes but elected not to undergo WBRT. Complications were low, including post-operative seroma in 9%, hematoma in 1.5%, and infection requiring antibiotics in 2.8%. The early results of this large retrospective registry are similar to those seen in the TARGIT-A randomized trial. There is also an ongoing prospective United States registry study, TARGIT-US (15), which should complete accrual this year.

The ELIOT study had a similar design to the TARGIT-A, but used mobile electron technology to deliver IORT. It was a single institution study completed by the Institute Milan. This trial randomized 1,305 women between the years 2000 and 2007 between external conventional whole breast irradiation (EBRT) (50 + 10 Gy boost) and single dose electron IOERT (21 Gy) with no additional WBRT (16). The study statistical design was an equivalence endpoint, with a pre-specified margin for local recurrence of 7.5% after IOERT. Women eligible for the study had stage I–II invasive breast cancer up to 2.5 cm in size between ages 48 and 75 years old. Lower risk tumors were pre-dominant, with patient characteristics including estrogen receptor positive in 90%, Her2 negative in 97%, and negative nodes in 74%. With median follow-up of 5.8 years, 5 years IBR was recorded in an unexpectedly low percentage in the EBRT arm (0.4%) as well as in the IOERT arm (4.4%), which was within the pre-specified equivalence margin of 7.5% ($p < 0.0001$). There was no difference in overall survival (96.8 and 96.9%, respectively; $p = 0.59$). Cutaneous toxicities were significantly better for all recorded endpoints in the IOERT arm, although a higher incidence of fat necrosis was seen after IOERT, with no overall differences in other side effects including breast fibrosis, retraction, pain, or burning. The ELIOT trialists concluded that the unselected population helped to define stricter selection criteria which could result in a lower IBR rate. They identified risk factors associated with local recurrence after IOERT as tumor size >2 cm, grade 3, 4, or more positive nodes, and triple negative histology.

The published randomized trials and large multi-institutional studies, provide guidance in selecting appropriate patients for breast IORT, and provide the basis for guidelines and consensus statements of selection criteria. The ASTRO consensus guideline was updated in 2017 to include a key question on breast IO(E)RT. The statement notes that IO(E)RT use should be restricted to women who otherwise meet "suitable" criteria for partial breast irradiation, and Coverage with Evidence Development on a registry or trial applies to low-energy X-ray IORT while awaiting longer follow-up on accrued clinical trials (17). The limited follow-up time was a major concern of this panel. There have been published commentary which disagree with some of the conclusions of the ASTRO consensus statement on IORT, including by a group representing other professional societies and IORT users, which highlighted inconsistencies in interpretation of the TARGIT-A data (18). TARGIT investigators advocate use of the study criteria and offering patients WBRT as was done on the study when pathologic features indicative of more diffuse disease are present on final pathology. Similarly, the ELIOT investigators discussed the potential for use of stricter selection criteria for IOERT than used in the trial, with initial use or inclusion of WBRT when those features are present on final pathology. With any type of IO(E)RT, radiation most commonly delivered at the time of surgery when final pathologic features are not yet available, therefore selection criteria should be based on the information available prior to as well as during surgery. Many surgeons and radiation oncologists prefer to have rigorous intraoperative assessment of sentinel nodes and margins to assist in decision making and patient selection.

Toxicity and Cosmesis

In studies using 50 kV X-rays, several have reported acute and late toxicity profiles after IORT ± WBRT. In the original TARGIT-A publication, all clinically significant complications occurred in 3.3% or fewer patients, including hematoma or seroma requiring intervention, infection, wound healing, or any grade 3 toxicity, and were similar between IORT and WBRT arms. In the study update published in 2013, it was noted that complications at 6 months showed no difference between arms for any wound-related complications, with fewer grade 3–4 skin toxicities after IORT. Keshtgar reported cosmesis up to 4 years after IORT on a TARGIT-A subprotocol as assessed by photograph-analyzing software. IORT patients were about twice as likely to have excellent or good cosmetic scores as WBRT treated patients (19). One German institution examined their 48 TARGIT-A enrolled patients in a subgroup analysis of post-treatment mammogram findings (20). They noted a higher rate of radiographic fat necrosis after IORT (56%) than after conventional WBRT (24%), and more scar calcifications as well. Sperk et al. noted no differences between IORT ± WBRT versus WBRT with respect to fibrosis, breast edema, lymphedema, pain, or hyperpigmentation (21). Fibrosis was higher after IORT + WBRT (37.5%) than after IORT alone (6%) or WBRT only (18%) at 3 years. Telangiectasias were not seen in any IORT only patients, compared with 17% of women after WBRT ± IORT. The Copenhagen group conducted a subgroup analysis of post-treatment pain in their enrolled TARGIT-A cohort ($n = 244$) conducted using patient reported outcomes data, and found that persistent pain was reported in 34% of WBRT patients compared with 25% of IORT patients (22).

In studies using electron IOERT, the ELIOT trial reported on the subset of patients in whom toxicity data were available, noting that side effect profiles significantly favored IOERT compared with WBRT, especially as related to skin toxicity, with less erythema, hyperpigmentation, dryness, and pruritis (all $p < 0.04$). No differences were recorded for fibrosis, pain, or burning sensation. Only radiologic presence of necrosis was higher in the IOERT group. The ELIOT group randomly selected 119 patients treated with sole IOERT for further late toxicity assessment using standard rating scales (23). At a median of 6 years, grade 2 fibrosis was noted in 32% and grade 3 fibrosis in 6%. Excellent or good cosmesis was scored by patients in 77% and by physicians in 84%. The Netherlands group compared institutional data for women treated with IOERT ($n = 26$) or conventional WBRT ($n = 45$) based on seven asymmetry features (24). Features favoring IOERT with smaller differences between treated and untreated breast included breast contour, relative breast area, and breast overlap. Excellent and good cosmesis after IOERT was scored as 88% by patients and 96% by physicians.

Quality of Life

Increasingly, study of quality of life accompanies more traditional outcomes endpoints and influences patient preferences and informed consent discussions for patients and their providers facing breast cancer treatment. Investigators in Australia conducted a survey of Western Australia breast cancer health professionals and reported that among those surveyed, 3–7.5% considered breast IORT unacceptable treatment at any risk of local recurrence, 18–21% considered IORT acceptable at risks equivalent to that of WBRT, while 56–59% considered IORT acceptable if associated with a 1–3% increased local recurrence risk (25). In a survey of patient preference considering treatment options of breast IORT or fractionated multi-week whole breast irradiation which described to participants alternative increases in rates of local recurrence risk over 10 years, this survey found that patients accepted a median increase in local recurrence risk for IORT of 2.3% (26). In addition, 91% surveyed would accept IORT if the treatment were equivalent or associated with a slightly higher risk of local recurrence compared with WBRT. Another quality of life study among a subgroup of German patients enrolled in the TARGIT-A trial administered the EORTC QLQ-C30 and BR23 survey instruments (27). Patients in the IORT alone arm indicated significantly less general pain, breast, and arm symptoms and better overall functioning than patients in the WBRT arm.

BREAST IO(E)RT IN OTHER CLINICAL CONTEXTS

Intraoperative radiotherapy, as with all types of APBI, is less well studied in conjunction with breast-conserving surgery for ductal carcinoma *in situ* (DCIS). The recent update of the ASTRO APBI consensus statement now classifies APBI for pure DCIS as "suitable" when meeting certain specific criteria. A California group has published the only series to date using 50 kV IORT for patients with DCIS. In this series, selection criteria included tumor size <4 cm on pre-operative imaging with pure DCIS on biopsy and deemed resectable with breast conservation (28). Thirty-five patients had IORT, with a mean tumor size of 1.5 cm. Five patients had close or positive margins, two of whom had mastectomy due to extent of DCIS in the specimen, and three had re-excision followed by WBRT, for a 14% rate of additional treatment after surgery plus IORT. The 3-year local recurrence rate was 5.7%.

A study from the Milan group used IOERT in conjunction with nipple-sparing mastectomy, comparing 800 patients receiving IOERT to the retroareolar region of the nipple to 201 patients with nipple-sparing mastectomy followed by delayed one-dose radiation later (29). At median follow-up of 20 months, they noted nipple-areolar necrosis in 3.5%, and nipple removal in 5%. Of the 1.4% local recurrences, none were seen in the nipple, but at the site of the primary tumor. No difference in outcomes was noted between the two techniques. This report does not discuss any comparison with patients who have not received any radiation to the nipple-areolar complex. A second series using 50 kV IORT single dose of 16 Gy after nipple-sparing mastectomy describes only seven patients with 7 months follow-up, with no acute toxicity attributable to radiation, no necrosis of the nipple complex or local recurrences (30).

In these special clinical scenarios, further data are needed to define the appropriate role of IORT. The direct visualization and elimination of the possibility of marginal miss makes IORT an attractive technique in situations where accuracy of dose targeting is particularly critical, such as women with higher risk cancers, as being investigated in the TARGIT-B trial of IORT versus conventional boost. Areas for further study of the efficacy and toxicity of IORT may include as sole therapy for lower risk DCIS, as a boost prior to planned oncoplastic reconstruction, and as part of re-treatment after prior whole breast irradiation for limited local recurrence.

IO(E)RT BOOST

A boost dose to the periphery of the surgical lumpectomy bed has been shown to further lower the risk of local recurrence, especially for younger women, women with higher grade, triple negative or larger tumors, and those with positive margins or extensive lymphovascular invasion (31). The tissue in closest proximity to the primary cancer has the highest density of residual microscopic cells and is therefore at highest risk for local recurrence. Several institutional studies have reported using IORT as a boost with planned WBRT to follow. The theoretical advantages of using IORT as a boost include the ability to directly visualize the tumor bed and thereby avoid marginal misses when boosting a CT-based volume. The same BED, oxygenation, and biological advantages theoretically present for single dose IORT may be relevant for IORT boost as well, and are under investigation. Several studies using either IOERT (intraoperative electrons) or 50 kV IORT as a boost have been reported. Ongoing studies going IORT boost include the TARGIT-B(oost) (32) and HIOP trials (33).

Intraoperative electron radiation therapy boost has been reported as a pooled analysis by the International Society of Intraoperative Radiotherapy (34). In this analysis, 1,109 unselected patients from seven European centers, 60% of whom had at least one high risk factor, were treated similarly with IOERT boost at a median dose of 10 Gy and a subsequent whole breast dose of 50–54 Gy. After a median follow-up of 5 years, the local recurrence risk was 0.8%, half seen in the index quadrant. Risk factors for recurrence included high grade, age under 40, and ER negative. Upon examining the impact of delays from IOERT boost to WBRT, no impact on local recurrence of delays up to 140 days was seen. The Salzburg IOERT group conducted a matched-pair analysis of IOERT boost and external electron boost patients, who had IBR rates at 10 years of 1.6 and 7.2%, respectively (35).

Low-energy X-rays IORT as a boost has been reported in two cohort series. One multicenter pilot study treated with 20 Gy to cavity surface intraoperatively followed by 45–50 Gy whole breast in 299 women undergoing lumpectomy. After a median follow-up of 5 years, the observed local recurrence rate was 2.7% (36). A single institution series of 197 patients received an IORT boost of 18–20 Gy then 46–50 Gy whole breast, reporting a 5-year local relapse free survival of 97% (37).

TABLE 1 | Prospective randomized controlled trials of partial breast irradiation compared to whole breast radiation.

Study	Author	PBI technique	Number patients	Med F/U (years)	Age > 50	pT1 %	pTis %	pN0 %	ER+ %	5-Year local recurrence	5-Year overall survival
Hungary	Polgar et al. (47,48)	MC Brachy (69%) or electrons (31%)	128	10.2	77%	100	0	94.5	92	5 years: 4.7%, 10 years: 5.9%	5 years: 94.6%, 10 years: 80%
		WBRT	130		75%	100	0	94.6	88	5 years: 3.4%, 10 years: 5.1%	5 years: 91.8%, 10 years: 82%
Florence	Livi et al. (49)	IMRT	260	5.0	84%	86	9	89	95	1.5%	99.4%
		WBRT	260		83%	82	12	82	96	1.5%	96.6%
GEC-ESTRO	Strnad et al. (50)	MC Brachy	633	6.6	86%	84	6	94	92	1.44%	97.3%
		WBRT	551		83%	86	4	95	91	0.92%	95.6%
TARGIT-A	Vaidya et al. (13)	IORT ± WBRT	1,721	2.5	>45, 98%	96	0	82	90	3.3%	96.1%
		WBRT	1,730		99%	95	0	84	93	1.3%	94.7%
ELIOT	Veronesi et al. (16)	IOERT	651	5.8	93%	87	0	74	90	4.4%	96.8%
		WBRT	654		93%	84	0	73	91	0.4%	96.9%

PBI, partial breast irradiation; MC, multicatheter; Brachy, brachytherapy; WBRT, whole breast radiation; IORT, intraoperative radiotherapy; IOERT, intraoperative electron radiotherapy; IMRT, intensity modulated radiotherapy; F/U, follow-up; ER, estrogen receptor; pTis, pathologic ductal carcinoma in situ; NR, not reported.

Regardless of technique the toxicity of IORT boost appears to be acceptable. The virtual complete skin sparing associated with use of IORT is likely to have a positive impact on any cutaneous toxicity profiles. Acutely there are no reports of increased post-operative infections or delayed wound healing. Late fibrosis has been reported to range from about 0 to 15% for grade 3 toxicity, depending upon technique and dose. Cosmesis does not seem to be compromised in the studies described when compared with conventional boost techniques, although assessment tools have varied. Lemanski has reported the longest term experience in using IOERT boost, reporting 9-year outcomes on 50 women receiving 10 Gy IORT then 50 Gy whole breast, with no grade 3 fibrosis and 14% grade 2 fibrosis (38). Mayo Arizona conducted a prospective study of 10 Gy IOERT then 48 Gy to the whole breast, and reported a 3.8% 6-year local recurrence rate, with excellent or good cosmesis in 87% of patients (39). An Australian group reported that 55 patients treated with 5 Gy at 1 cm IORT boost then 50 Gy whole breast had no local recurrences at 3 years, but grade 3 fibrosis was 15% (40). There is one report of IOERT boost (12 Gy) followed by hypofractionated whole breast (37.05 Gy in 13 daily fractions of 2.85 Gy) in 204 pre-menopausal women. Reporting only acute toxicity, grade 3 skin toxicity was 4%, grade 2 skin toxicity was 29%; late skin toxicity at 12 months was grade 3 and 4 in one patient each (41).

For context in comparison, the EORTC boost trial, the 5- and 10-year rates of moderate to severe fibrosis was reported in 11 and 28% of boost patients compared with 10 and 13% on the no boost arm. In this study, at 3 years, excellent and good cosmesis was somewhat worse in the boost arm compared with no boost, 71 versus 86%, respectively (42, 43).

There are several reports of using IORT boost in conjunction with breast-conserving surgery and WBRT in special patient cohorts. One retrospective series reported on IORT boost after neoadjuvant chemotherapy in 61 patients and a contemporaneous consecutive cohort of 55 patients who received a conventional external beam boost, all receiving WBRT (44). At 4 years follow-up, there was no difference in 5-year local recurrence (9.8% with IORT and 8.3% with external boost), and there was a better overall survival in the IORT arm (97 versus 82%) related to fewer non-breast cancer deaths. The Salzburg group has also reported IORT boost in a retrospective series of triple negative patients undergoing breast conservation, with an 8-year actuarial local recurrence rate of 11%, all of those recurrences occurring in high-grade cancers (45).

A German group has reported on IORT boost in the setting of oncoplastic reconstruction. This is a particularly appealing clinical scenario for the use of an IORT boost, as the oncoplastic reconstruction which immediately follows the definitive oncologic surgery to remove the cancerous cells can eradicate any clear delineation of the tumor bed and preclude the use of external beam boost, causing some patients to be underdosed. Performing IORT after the lumpectomy but prior to the oncoplastic rearrangement eliminates the risk of target volume miss, the possibility of dissemination of microscopic disease during the reconstruction, or inability to identify the boost target on post-operative treatment planning image sets. However, minimal data exist to support the efficacy of this approach. The Cologne group has used IORT boost in 149 patients who also underwent an oncoplastic reconstruction (glandular rotation or mammoplasty), and have reported only post-operative toxicity, with a 2% seroma formation rate. Additional outcome and efficacy data from this and other series will be welcome (46).

CONCLUSION

Breast IO(E)RT is currently primarily a technique for partial breast irradiation which has been well established as an option for patients who are otherwise appropriate candidates for APBI. Two large randomized trials, the TARGIT A trial establishing 50 kV IORT and ELIOT establishing electron based IOERT, both have published excellent results regarding local control and acceptable toxicity. While local recurrence was slightly higher after IORT in both studies, it was within the clinically relevant range seen in numerous other clinical trials of various radiation techniques, including APBI and WBRT approaches (see **Table 1**). Patient preference analyses have shown that some women will accept the risk of a small increase in local recurrence in order to preserve their

breast, to mitigate toxicity or to reduce the burden of lengthier radiation treatment courses. Overall survival in TARGIT-A was significantly better in the IORT group, an intriguing observation that warrants additional investigation. It is appropriate for these considerations to be discussed with patients as part of the clinical decision making and informed consent process for radiation treatment.

When considering use of IO(E)RT techniques for partial breast treatment after lumpectomy, it is recommended to select patients who fall into the low-risk categories among published guidelines, using the "suitable" or "good risk" criteria for patients who are general candidates for APBI. IO(E)RT has potential advantages over external or brachytherapy-based techniques given the direct visualization of and contact with the target tissue and the immediacy of treatment, but has the disadvantage of lacking final pathologic assessment of the margins and sentinel nodes, placing a percentage of women at risk of being recommended to undergo additional external beam irradiation. Therefore, when intended to be used for partial breast treatment, patient selection should focus on clinicopathologic factors predictive of negative nodes and negative margins. Careful assessment of pre-operative mammographic and other imaging studies for features, such as extent of calcifications, may be helpful. Intraoperative techniques can be useful as well, including assessment of margins and sentinel nodes intraoperatively, and careful excision technique to maximize clear margins, such as taking additional shave margins as needed.

Potential emerging indications for breast IO(E)RT under investigation include as a boost in higher risk patients, as a boost in patients undergoing oncoplastic reconstruction, as sole therapy for lower risk DCIS, and as re-treatment for IBR after prior breast irradiation. Longer term follow-up on the completed trials is anticipated and ongoing studies and registries will help define these new modalities.

AUTHOR CONTRIBUTIONS

EH wrote manuscript, created table, completed literature review. WS wrote sections of manuscript and edited entire manuscript.

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REFERENCES

1. ICRU. The quality factor in radiation protection. *ICRU Report 40*. (1986).
2. Brenner DJ, Leu C, Beatty J, Shefer R. Clinical relative biological effectiveness of low energy X-rays emitted by miniature X-ray devices. *Phys Med Biol* (1999) 44:323–33. doi:10.1088/0031-9155/44/2/002
3. Nikjoo H, Lindborg L. RBE of low energy electrons and photons. *Phys Med Biol* (2010) 55:R65–109. doi:10.1088/0031-9155/55/10/R01
4. Reniers B, Liu D, Rusch T, Verhaegen F. Calculation of relative biological effectiveness of a low-energy electronic brachytherapy source. *Phys Med Biol* (2008) 53:7125–35. doi:10.1088/0031-9155/53/24/008
5. Herskind C, Griebel J, Kraus-Tiefenbacher U, Wenz F. Sphere of equivalence—a novel target volume concept for intraoperative radiotherapy using low-energy X rays. *Int J Radiat Oncol Biol Phys* (2008) 72:1575–81. doi:10.1016/j.ijrobp.2008.08.009
6. Liu Q, Schneider F, Ma L, Wenz F, Herskind C. Relative biologic effectiveness (RBE) of 50kV x-rays measured in a phantom for intraoperative tumor-bed irradiation. *Int J Radiat Oncol Biol Phys* (2013) 85:1127–33. doi:10.1016/j.ijrobp.2012.08.005
7. Fowler JF. The linear-quadratic formula and progress in fractionated radiotherapy. *Br J Radiol* (1989) 62:679–94. doi:10.1259/0007-1285-62-740-679
8. Belletti B, Vaidya JS, D'Andrea S, Entschladen F, Roncadin M, Lovat F, et al. Targeted intraoperative radiotherapy impairs the stimulation of breast cancer cell proliferation and invasion caused by surgical wounding. *Clin Cancer Res* (2008) 14(5):1325–32. doi:10.1158/1078-0432.CCR-07-4453
9. Fabris L, Berton S, Citron F, D'Andrea S, Segatto I, Nicoloso MS, et al. Radiotherapy-induced miR-223 prevents relapse of breast cancer by targeting the EGFR pathway. *Oncogene* (2016) 35(37):4914–26. doi:10.1038/onc.2016.23
10. *INTRABEAM System from ZEISS [Internet]*. (2017). Available from: http://www.targit-research.org/clinics/intrabeam/about-intrabeam/
11. *What is Electronic Brachytherapy? [Internet]*. Xoft (2017). Available from: http://www.xoftinc.com/electronic-brachytherapy.html
12. *Meet the Mobetron [Internet]*. IntraOp (2015). Available from: http://intraop.com/mobetron/
13. Vaidya JS, Wenz F, Bulsara M, Tobias JS, Joseph DJ, Keshtgar M, et al. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. *Lancet* (2014) 383:603–13. doi:10.1016/S0140-6736(13)61950-9
14. Valente SA, Tendulkar RD, Cherian S, O'Rourke C, Greif JM, Bailey L, et al. TARGIT-R (retrospective): north American experience with intraoperative radiation using low-kilovoltage X-rays for breast cancer. *Ann Surg Oncol* (2016) 23:2809–15. doi:10.1245/s10434-016-5240-1
15. *Intraoperative Radiation Therapy in Treating Patients with Breast Cancer Undergoing Breast-Conserving Surgery [Internet]*. Clinicaltrials.gov (2017). Available from: https://clinicaltrials.gov/ct2/show/NCT01570998
16. Veronesi U, Orecchia R, Maisonneuve P, Viale G, Rotmensz N, Sangalli C, et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. *Lancet Oncol* (2013) 14:1269–77. doi:10.1016/S1470-2045(13)70497-2
17. Correa C, Harris EE, Leonardi MC, Smith BD, Taghian AG, Thompson AM, et al. Accelerated partial breast irradiation: executive summary for the update of an ASTRO evidence-based consensus statement. *Pract Radiat Oncol* (2017) 7:73–9. doi:10.1016/j.prro.2016.09.007
18. Small W Jr., Thomas TO, Alvarado M, Baum M, Bulsara M, Diaz R, et al. Commentary on "Accelerated partial breast irradiation consensus statement: Update of an ASTRO Evidence-Based Consensus Statement". *Pract Radiat Oncol* (2017) 7(3):e159–63. doi:10.1016/j.prro.2017.01.016
19. Keshtgar MR, Williams NR, Bulsara M, Saunders C, Flyger H, Cardoso JS, et al. Objective assessment of cosmetic outcome after targeted intraoperative radiotherapy in breast cancer: results from a randomised controlled trial. *Breast Cancer Res Treat* (2013) 140(3):519–25. doi:10.1007/s10549-013-2641-8
20. Engel D, Schnitzer A, Brade J, Blank E, Wenz F, Suetterlin M, et al. Are mammographic changes in the tumor bed more pronounced after intraoperative radiotherapy for breast cancer? Subgroup analysis from a randomized trial (TARGIT-A). *Breast J* (2013) 19:92–5. doi:10.1111/tbj.12049
21. Sperk E, Welzel G, Keller A, Kraus-Tiefenbacher U, Gerhardt A, Sutterlin M, et al. Late radiation toxicity after intraoperative radiotherapy (IORT) for breast cancer: results from the randomized phase III trial TARGIT A. *Breast Cancer Res Treat* (2012) 135:253–60. doi:10.1007/s10549-012-2168-4
22. Andersen KG, Gartner R, Kroman N, Flyger H, Kehlet H. Persistent pain after targeted intraoperative radiotherapy (TARGIT) or external breast radiotherapy for breast cancer: a randomized trial. *Breast* (2012) 21:46–9. doi:10.1016/j.breast.2011.07.011
23. Leonardi MC, Ivaldi GB, Santoro L, Lazzari R, Ferrari A, Morra A, et al. Long-term side effects and cosmetic outcome in a pool of breast cancer patients treated with intraoperative radiotherapy with electrons as sole treatment. *Tumori* (2012) 98:324–30. doi:10.1700/1125.12400
24. Struikmans H, Snijders M, Mast ME, Fisscher U, Franssen JH, Immink MJ, et al. Single dose IOERT versus whole breast irradiation: cosmetic

results in breast-conserving therapy. *Strahlenther Onkol* (2016) 192:705–13. doi:10.1007/s00066-016-1029-1
25. Corica T, Joseph D, Saunders C, Bulsara M, Nowak AK. Intraoperative radiotherapy for early breast cancer: do health professionals choose convenience or risk? *Radiat Oncol* (2014) 9:717X–9X. doi:10.1186/1748-717X-9-33
26. Alvarado MD, Conolly J, Park C, Sakata T, Mohan AJ, Harrison BL, et al. Patient preferences regarding intraoperative versus external beam radiotherapy following breast-conserving surgery. *Breast Cancer Res Treat* (2014) 143:135–40. doi:10.1007/s10549-013-2782-9
27. Welzel G, Hofmann F, Blank E, Kraus-Tiefenbacher U, Hermann B, Sutterlin M, et al. Health-related quality of life after breast-conserving surgery and intraoperative radiotherapy for breast cancer using low-kilovoltage X-rays. *Ann Surg Oncol* (2010) 17(Suppl 3):359–67. doi:10.1245/s10434-010-1257-z
28. Rivera R, Banks A, Casillas-Lopez A, Rashtian A, Lewinsky B, Sheth P, et al. Targeted intraoperative radiotherapy for the management of ductal carcinoma in situ of the breast. *Breast J* (2016) 22:63–74. doi:10.1111/tbj.12516
29. Petit JY, Veronesi U, Orecchia R, Rey P, Martella S, Didier F, et al. Nipple sparing mastectomy with nipple areola intraoperative radiotherapy: one thousand and one cases of a five years experience at the European institute of oncology of Milan (EIO). *Breast Cancer Res Treat* (2009) 117:333–8. doi:10.1007/s10549-008-0304-y
30. Pan L, Zheng W, Ye X, Chen L, Ke Y, Wan M, et al. A novel approach of INTRABEAM intraoperative radiotherapy for nipple-sparing mastectomy with breast reconstruction. *Clin Breast Cancer* (2014) 14:435–41. doi:10.1016/j.clbc.2014.04.002
31. Bartelink H, Maingon P, Poortmans P, Weltens C, Fourquet A, Jager J, et al. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial. *Lancet Oncol* (2015) 16:47–56. doi:10.1016/S1470-2045(14)71156-8
32. *A Comparison of Intra-Operative Radiotherapy Boost with External Beam Radiotherapy Boost in Early Breast Cancer. (TARGIT-B) [Internet]*. ClinicalTrials.gov (2016). Available from: https://clinicaltrials.gov/ct2/show/NCT01792726
33. *Intra-Operative Electron Boost and Hypofractionated Whole-Breast Irradiation during Breast-Conserving Treatment (BCT) (HIOB) [Internet]*. ClinicalTrials.gov (2016). Available from: https://clinicaltrials.gov/ct2/show/NCT01343459
34. Fastner G, Sedlmayer F, Marz F. IORT with electrons as a boost strategy during breast conserving therapy in limited stage breast cancer: long term results of an ISORT pooled analysis. *Radiother Oncol* (2013) 108:279–86. doi:10.1016/j.radonc.2013.05.031
35. Sedlmayer F, Reitsamer R, Fussl C, Ziegler I, Zehentmayr F, Deutschmann H, et al. Boost IORT in breast cancer: body of evidence. *Int J Breast Cancer* (2014) 2014:472516. doi:10.1155/2014/472516
36. Vaidya JS, Baum M, Tobias JS, Wenz F, Massarut S, Keshtgar M, et al. Long-term results of targeted intraoperative radiotherapy (Targit) boost during breast-conserving surgery. *Int J Radiat Oncol Biol Phys* (2011) 81:1091–7. doi:10.1016/j.ijrobp.2010.07.1996
37. Blank E, Kraus-Tiefenbacher U, Welzel G, Keller A, Bohrer M, Sutterlin M, et al. Single-center long-term follow-up after intraoperative radiotherapy as a boost during breast-conserving surgery using low-kilovoltage x-rays. *Ann Surg Oncol* (2010) 17(Suppl 3):352–8. doi:10.1245/s10434-010-1265-z
38. Lemanski C, Azria D, Thezenas S, Gutowski M, Saint-Aubert B, Rouanet P, et al. Intraoperative radiotherapy given as a boost for early breast cancer: long-term clinical and cosmetic results. *Int J Radiat Oncol Biol Phys* (2006) 64:1410–5. doi:10.1016/j.ijrobp.2005.10.025
39. Wong WW, Pockaj BA, Vora SA, Halyard MY, Gray RJ, Schild SE. Six-year outcome of a prospective study evaluating tumor bed boost with intra-operative electron irradiation followed by whole-breast irradiation for early-stage breast cancer. *Breast J* (2014) 20:125–30. doi:10.1111/tbj.12235
40. Chang DW, te Marvelde L, Chua BH. Prospective study of local control and late radiation toxicity after intraoperative radiation therapy boost for early breast cancer. *Int J Radiat Oncol Biol Phys* (2014) 88:73–9. doi:10.1016/j.ijrobp.2013.09.049
41. Ivaldi GB, Leonardi MC, Orecchia R, Zerini D, Morra A, Galimberti V, et al. Preliminary results of electron intraoperative therapy boost and hypofractionated external beam radiotherapy after breast-conserving surgery in premenopausal women. *Int J Radiat Oncol Biol Phys* (2008) 72:485–93. doi:10.1016/j.ijrobp.2007.12.038
42. Bartelink H, Horiot JC, Poortmans PM, Struikmans H, Van den Bogaert W, Fourquet A, et al. Impact of a higher radiation dose on local control and survival in breast-conserving therapy of early breast cancer: 10-year results of the randomized boost versus no boost EORTC 22881-10882 trial. *J Clin Oncol* (2007) 25:3259–65. doi:10.1200/JCO.2007.11.4991
43. Vrieling C, Colette L, Fiyrquet A. The influence of the boost in breast conserving therapy on cosmetic outcome in the EORTC "boost versus no boost" trial. *J Radiat Oncol Biol Phys* (1999) 45(3):677–85. doi:10.1016/S0360-3016(99)00215-1
44. Kolberg HC, Loevey G, Akpolat-Basci L, Stephanou M, Fasching PA, Untch M, et al. Targeted intraoperative radiotherapy tumour bed boost during breast-conserving surgery after neoadjuvant chemotherapy. *Strahlenther Onkol* (2017) 193:62–9. doi:10.1007/s00066-016-1072-y
45. Fastner G, Hauser-Kronberger C, Moder A, Reitsamer R, Zehentmayr F, Kopp P, et al. Survival and local control rates of triple-negative breast cancer patients treated with boost-IOERT during breast-conserving surgery. *Strahlenther Onkol* (2016) 192:1–7. doi:10.1007/s00066-015-0895-2
46. Malter W, Kirn V, Richters L, Fridrich C, Markiefka B, Bongartz R, et al. Intraoperative boost radiotherapy during targeted oncoplastic breast surgery: overview and single center experiences. *Int J Breast Cancer* (2014) 2014:637–898. doi:10.1155/2014/637898
47. Polgar C, Fodor J, Major T, Nemeth G, Lovey K, Orosz A, et al. Breast-conserving treatment with partial or whole breast irradiation for low-risk invasive breast cancer-5-year results of a randomized trial. *Int J Radiat Oncolo Biol Phys* (2007) 69(3):694–702. doi:10.1016/j.jirobp.2007.04.022
48. Polgar C, Fodor J, Major M, Sulyok Z, Kasler M. Breast-conserving therapy with partial or whole breast irradiation: ten year results of the Budapest randomized trial. *Radiother Oncol* (2013) 108:197–202. doi:10.1016/j.radonc.2013.05.008
49. Livi L, Meattini I, Marrazzo L, Simontacchi G, Pallotta S, Saieve C, et al. Accelerated partial breast irradiation using intensity modulated radiotherapy versus whole breast irradiation: 5-year survival analysis of a phase 3 randomised controlled trial. *Eur J Cancer* (2015) 51:451–63. doi:10.1016/j.ejca.2014.12.013
50. Strnad V, Ott O, Hildebrandt G, Kauer-Dorner D, Knaserhase H, Major T, et al. 5-Year results of accelerated partial breast irradiation using sole multicatheter brachytherapy versus whole-breast irradiation with boost after breast conserving surgery for low risk invasive and in situ carcinoma of the female breast: a randomized, phase 3 non-inferiority trial. *Lancet* (2016) 387:229–38. doi:10.1016/S0140-6736(15)00471-7

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ORIGINAL RESEARCH
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Intraoperative Radiation for Breast Cancer with Intrabeam™: Factors Associated with Decreased Operative Times in Patients Having IORT for Breast Cancer

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Introduction: Intraoperative radiation with Intrabeam™ (IORT) for breast cancer is a newer technology recently implemented into the operating room (OR). This procedure requires time and coordination between the surgeon and radiation oncologist, who both perform their treatments in a single operative setting. We evaluated the surgeons at our center, who perform IORT and their OR times to examine changes in OR times following implementation of this new surgical procedure. We hypothesized that IORT is a technique for which timing could be improved with the increasing number of cases performed.

Methods: A prospectively maintained IRB approved database was queried for OR times (incision and close) in patients who underwent breast conserving surgery (BCS), sentinel lymph node biopsy with and without IORT using the Intrabeam™ system at our institution from 2011 to 2015. The total OR times were compared for each surgeon individually and over time. Next, the OR times of each surgeon were compared to each other. Continuous variables were summarized and then a prediction model was created using IORT time, OR time, surgeon, and number of cases performed.

Results: There were five surgeons performing IORT at our institution during this time period with a total of 96 cases performed. There was a significant difference observed in baseline surgeon-specific OR time for BSC ($p = 0.03$) as well as for BCS with IORT ($p < 0.05$), attributable to surgeon experience. The average BCS times were faster than the BCS plus IORT procedure times for all surgeons. The overall mean OR time for the entire combined surgical and radiation procedure was 135.5 min. The most common applicator sizes used were the 3.5 and 4 cm, yielding an average 21 min IORT time. Applicator choice did not differ over time ($p = 0.189$). After adjusting for IORT time and surgeon, the prediction model estimated that surgeons decreased the total BCS plus IORT OR time at a rate of −4.5 min per each additional 10 cases performed.

Conclusion: Surgeon experience and applicator size are related to OR times for performing IORT for breast cancer. OR time for IORT in breast cancer treatment can be improved over time, even among experienced surgeons.

Keywords: intraoperative radiation therapy, surgery, operation, time, applicator, experience, radiation oncology, breast surgery

INTRODUCTION

Adjuvant intraoperative radiation with the Intrabeam™ system (IORT) is an excellent therapeutic option for selected patients with breast cancer. Evidence to support the use of IORT comes from the TARGIT-A randomized trial showing that for early stage breast cancer, risk of local recurrence with IORT performed at the time of lumpectomy surgery is not statistically different than whole breast radiation (WBRT) (2.1% with IORT compared to 1.1% with WBRT, $p = 0.31$) (1, 2). This was confirmed with the large North American TARGIT-Retrospective Study supporting similar low local recurrence rates and showing utilization of IORT for breast cancer treatment is growing in North America and globally (3).

In the treatment of breast cancer, IORT has been shown to have many advantages for patients including convenience, improved quality of life (4), and lower cost compared to more traditional treatments (5). However, the use of IORT as adjunct for breast cancer treatment does prolong operating room (OR) times for patients having breast-conserving surgery. OR time is a costly and precious resource within health-care systems (6). There is increasing pressure on value-based health-care delivery and efficient care (7). Little is known about the impact of performing IORT with Intrabeam™ on OR times and factors associated with decreased operative times (8).

We hypothesized that the time to perform IORT in combination with breast conserving surgery (BCS) can be decreased with the increasing number of cases performed. In this study, we sought to document OR times associated with performance of BCS and IORT and analyze factors associated with operative time. This information is critical for assigning appropriate resources, OR allocations, and for optimizing efficient use of ORs within centers offering IORT for the treatment of breast cancer.

MATERIALS AND METHODS

A prospectively maintained database was queried for OR times (incision and close) in patients who underwent lumpectomy, sentinel lymph node biopsy with and without IORT using the Intrabeam™ system (Carl Zeiss AG: Oberkochen, Germany) at our institution from 2011 to 2015. Only IORT cases performed as a unilateral procedure at the time of initial lumpectomy were included. OR time was defined from incision to closure in this study. OR times included combined performance of lumpectomy, sentinel node biopsy, and IORT. In our practice, frozen section analysis was performed on axillary sentinel nodes in patients having IORT. The size applicator used for IORT can vary at our institution from 2.5 to 5 cm. Surgeons choose an applicator size based on the size of the lumpectomy cavity, which is a result of the size tumor removed. IORT was performed by 1 of 2 radiation oncologists who were present in the OR for these procedures. IORT delivery time was calculated based on the size applicator used.

Surgeons who performed conserving surgery (BCS) operation with IORT at our institution during this time period were identified. The IORT applicator sizes used and total OR times for all the identified surgeons were then analyzed. As a baseline control for OR time, surgeons individual OR times for BCS alone during the study period were averaged and compared. Then, their individual OR times for BCS with IORT were analyzed and compared. Next, the OR times for each surgeon who had performed greater than 10 IORT cases during the study period were evaluated. Statistical analysis was performed using the Kruskal–Wallis test and repeated measures ANOVA. Continuous variables were summarized and then a prediction model was created using IORT time, OR time, surgeon, and number of cases performed. Since IORT time is a standard prescribed time based on the size applicator used, this was controlled for in the prediction model. A p-value < 0.05 was considered statistically significant. This study was carried out in accordance with the recommendations of the Cleveland Clinic Foundation Institutional Review Board, under which it was reviewed and approved. A waiver of informed consent was granted, as all patient data were de-identified.

TABLE 1 | Applicator sizes used for IORT cases with Intrabeam™ in this series.

Applicator size	Percentage (%) of cases	Number of cases performed $N = 96$
2.5	3	3
3	9	9
3.5	33	32
4	35	34
4.5	13	12
5	6	6

TABLE 2 | Operating room times for five different surgeons performing BCS IORT with Intrabeam™ in this series.

Surgeon	No. procedures in series	Minimum time (min)	Mean time (min)	Maximum time (min)
A	2	170	185	200
B	5	117	184	218
C	14	65	139	228
D	26	127	176	261
E[a]	49	83	131	210

[a]*The surgeon with prior significant experience performing IORT.*

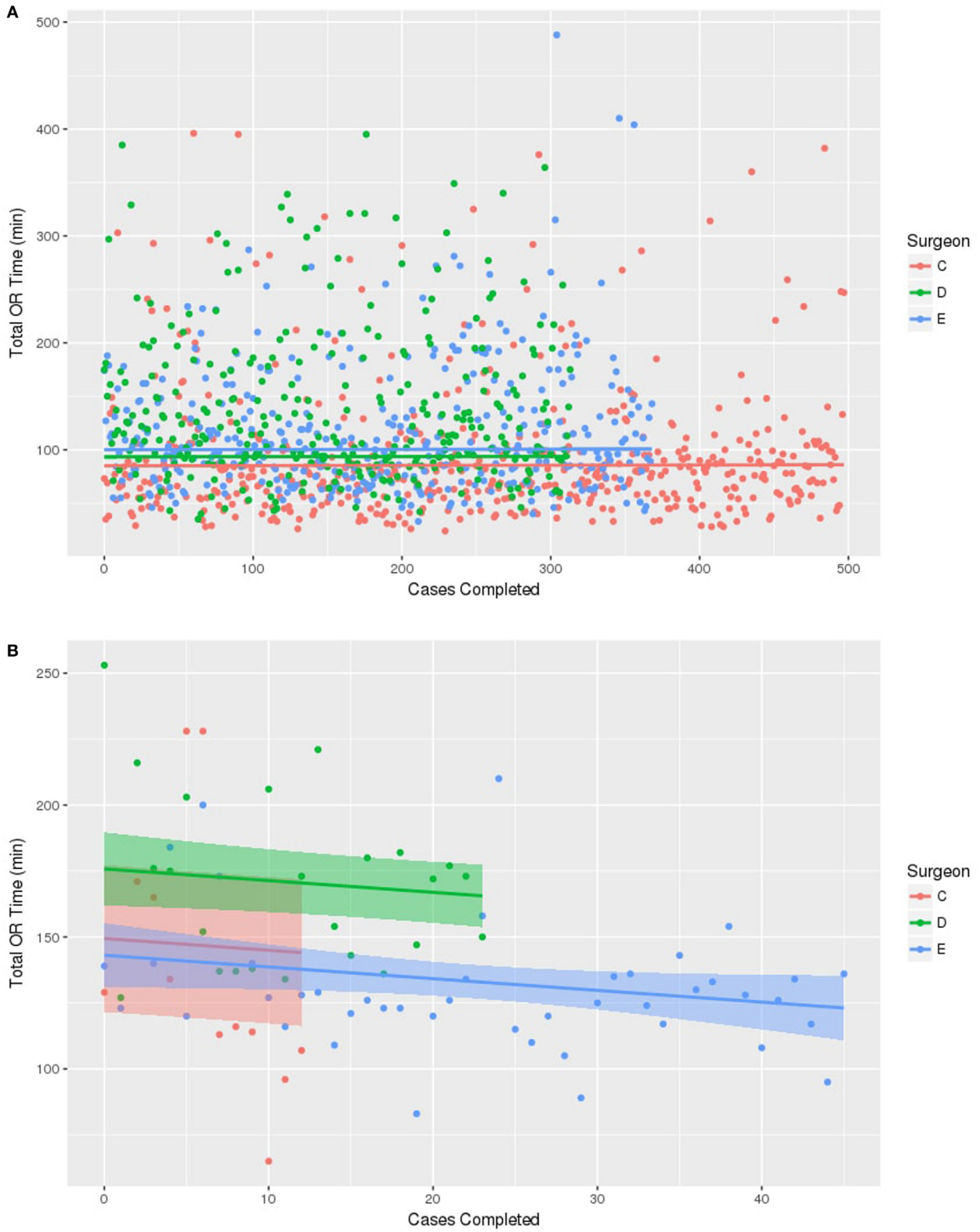

FIGURE 1 | Prediction line graphs for surgeon operating room (OR) time for cases completed. The model includes the three surgeons who had performed greater than 10 cases. **(A)** No change in time observed among any of the three surgeons in OR time for breast conserving surgery without IORT. **(B)** Reduction in OR time is associated with increasing surgeon number of cases with IORT using Intrabeam™ system. Every surgeon decreased OR time by −4.5 min for each 10 cases performed.

RESULTS

There were five surgeons identified performing IORT at our institution during this time period with a total of 96 cases performed. The most common applicator sizes used were the 3.5 cm (33%) and the 4 cm (36%), yielding an average 21-min IORT time (**Table 1**). Applicator size did not differ over time ($p = 0.189$). Longer OR times were significantly associated with use of larger applicator sizes, as a longer time is required to deliver the prescribed dose of radiation ($p < 0.0001$).

The overall mean OR time for all surgeons for the entire combined BCS and IORT procedure was 135.5 min (102–173 min). There was a significant difference observed in surgeon specific mean OR time for BCS with IORT (131 vs 185 min, $p = 0.03$) (**Table 2**). Only one of the five surgeons had significant prior experience with performing IORT (Surgeon E). This surgeon with the greatest IORT experience had the lowest mean operating time (131 min), which was significantly lower than the surgeon with least IORT experience (185 min, $p = 0.02$).

For the purpose of prediction modeling, only surgeons with at least 10 operations performed were used, giving a total of three surgeons evaluated in this analysis (**Figure 1**). First, a control group was created using the BCS only OR times for the three surgeons during 2011–2015. **Figure 1A** shows that at baseline, the three surgeons did differ significantly in their average overall BCS only OR times [(Surgeon C 86.8 min, D 95.2 min, E 101.8 min), $p < 0.001$] and this difference was maintained over the study period without significant improvement in OR time over time. Next, BCS with IORT times for the three surgeons were analyzed (**Figure 1B**). This demonstrates that there were baseline differences among surgeons in total OR time for BCT with IORT (131 vs 176 min, $p < 0.001$). Surgeon E, with the prior IORT experience, had the fastest average BCS with IORT time (131 min). Similar to the BCS only procedure, the surgeon's individual OR time differences for BCS with IORT were maintained over time. Interestingly, for BCS with IORT, despite differences in individual OR times, all surgeons (C, D, and E) regardless of prior IORT OR experience were found to have significantly decreasing operating time with an increasing number of cases performed over the study period ($p = 0.02$). After adjusting for IORT time and surgeon, the prediction model estimated that each surgeon decreased the total OR time for BCS with IORT at a rate of −4.5 min per each additional 10 cases performed.

DISCUSSION

This study documents that total OR time with IORT Intrabeam™ does decrease with increasing experience with the technique. The decreased time is likely related to surgeons and operating teams becoming more familiar with the procedure and improved coordination of the required steps to complete the breast conserving surgery, sentinel node biopsy, and IORT. It is noteworthy that even a highly experienced IORT surgeon (**Table 2**, Surgeon E) can improve OR times as experience with an operating team and radiation oncology team grows. The reported times in this series compare favorably to operating times reported utilizing an alternative form of IORT, which was reported to be 140 min (9). We hypothesize that while the delivery of radiation is longer with Intrabeam™ compared to other systems, the reproducible simplicity of setup and cavity preparation of Intrabeam™ accounts for the lower overall observed OR times with Intrabeam™.

We did not investigate the specific time of each step as it relates to the observed decrease in operative times. However, there are several specific areas in the procedure where efficiencies can be realized to decrease total operation time such as: surgeon technique including performance of intraoperative radiation and purse-string suture placement; equipment setup and having the proper equipment in the OR by OR staff (shielding drapes, ultrasound, etc.); and coordination of the arrival of the radiation oncologist and physicist to coincide with the start of the IORT portion of the case.

In this series, all patients had frozen section performed as part of the procedure as our programmatic approach during the time of the study was to not perform IORT in patients with axillary metastasis. There is a potential to reduce OR times further if this step was eliminated and patients were treated with IORT regardless of nodal status. IORT has been shown to be an effective boost replacement for patients requiring WBRT therapy (10). Other opportunities to improve OR times include: having standard operating teams and nursing teams who are familiar with the procedure, use of anticipatory paging of radiation oncology team members to avoid delays waiting for their arrival, and performing procedures at standard time and in a standard location.

The data in this report are important, as this is the first documentation of time associated with the performance of BCS and IORT using the Intrabeam™ system. These data can be used for planning operating time and resource allocation and serve as a benchmark for planning operating days for new teams adopting the Intrabeam™ system. Importantly, this series shows us that surgeons and treatment teams can become more efficient over time with IORT delivery as experience with the technique grows.

AUTHOR CONTRIBUTIONS

Each author has collaborated together to make contributions to conception and design, with the acquisition of data, and the analysis and interpretation of data. Each author has offered revisions and input on the manuscript. Each author gave their final approval of the submitted manuscript.

REFERENCES

1. Vaidya JS, Wenz F, Bulsara M, Tobias JS, Joseph D, Baum M. Radiotherapy for breast cancer, the TARGIT-a trial – authors' reply. *Lancet* (2014) 383:1719–20. doi:10.1016/S0140-6736(14)60830-8
2. Vaidya JS, Wenz F, Bulsara M, Tobias JS, Joseph DJ, Keshtgar M, et al. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. *Lancet* (2014) 383:603–13. doi:10.1016/S0140-6736(13)61950-9
3. Valente SA, Tendulkar RD, Cherian S, O'Rourke C, Greif JM, Bailey L, et al. TARGIT-R (retrospective): north American experience with intraoperative radiation using low-kilovoltage X-rays for breast cancer. *Ann Surg Oncol* (2016) 23:2809–15. doi:10.1245/s10434-016-5240-1

4. Welzel G, Hofmann F, Blank E, Kraus-Tiefenbacher U, Hermann B, Sutterlin M, et al. Health-related quality of life after breast-conserving surgery and intraoperative radiotherapy for breast cancer using low-kilovoltage X-rays. *Ann Surg Oncol* (2010) 17(Suppl 3):359–67. doi:10.1245/s10434-010-1257-z
5. Alvarado MD, Mohan AJ, Esserman LJ, Park CC, Harrison BL, Howe RJ, et al. Cost-effectiveness analysis of intraoperative radiation therapy for early-stage breast cancer. *Ann Surg Oncol* (2013) 20:2873–80. doi:10.1245/s10434-013-2997-3
6. Sandberg WS, Daily B, Egan M, Stahl JE, Goldman JM, Wiklund RA, et al. Deliberate perioperative systems design improves operating room throughput. *Anesthesiology* (2005) 103:406–18. doi:10.1097/00000542-200508000-00025
7. Fong AJ, Smith M, Langerman A. Efficiency improvement in the operating room. *J Surg Res* (2016) 204:371–83. doi:10.1016/j.jss.2016.04.054
8. Grobmyer SR, Lightsey JL, Bryant CM, Shaw C, Yeung A, Bhandare N, et al. Low-kilovoltage, single-dose intraoperative radiation therapy for breast cancer: results and impact on a multidisciplinary breast cancer program. *J Am Coll Surg* (2013) 216:617–23; discussion 623–4. doi:10.1016/j.jamcollsurg.2012.12.038
9. Dickler A, Ivanov O, Syed AMN, Golder S, Prouix GM, Arterberry VE, et al. Five year results of a multicenter trial utilizing electronic brachytherapy to deliver intraoperative radiation therapy in the treatment of early-stage breast cancer. *Int J Radiat Oncol Biol Phys* (2015) 93:E24–5. doi:10.1016/j.ijrobp.2015.07.607
10. Vaidya JS, Baum M, Tobias JS, Wenz F, Massarut S, Keshtgar M, et al. Long-term results of targeted intraoperative radiotherapy (Targit) boost during breast-conserving surgery. *Int J Radiat Oncol Biol Phys* (2011) 81:1091–7. doi:10.1016/j.ijrobp.2010.07.1996

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ORIGINAL RESEARCH
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Evaluation of Partial Breast Reirradiation with Intraoperative Radiotherapy after Prior Thoracic Radiation: A Single-Institution Report of Outcomes and Toxicity

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Introduction: Mastectomy is the current standard of care for ipsilateral breast tumor recurrences after prior whole breast irradiation (WBI). We report our single-institution experience with breast-conserving surgery (BCS) followed by intraoperative radiotherapy (IORT) as an alternative to salvage mastectomy for new or recurrent breast cancers that develop in the setting of prior thoracic radiation.

Methods: We performed an IRB-approved retrospective review of patients treated with breast IORT between September 2013 and November 2016. We identified 12 patients who declined salvage mastectomy for their breast cancer after prior thoracic radiation. IORT was delivered using the Intrabeam™ device (Carl Zeiss, Germany). A dose of 20 Gy was prescribed to the lumpectomy cavity surface using 50 kV X-rays. We graded both acute and late treatment-related breast toxicities using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Local control, mastectomy-free survival, distant metastasis, and overall survival were determined.

Results: Our study included nine patients who developed a new or recurrent ipsilateral breast cancer after prior WBI for early-stage breast cancer, two patients with primary breast cancer after mantle-field radiation for Hodgkin's lymphoma, and one patient with a synchronous stage III non-small cell lung cancer treated with definitive radiation to the ipsilateral lung and mediastinum. The median time from prior radiation to presentation was 18 years (range: 2 months to 46 years). All patients successfully underwent partial breast reirradiation with IORT and were able to preserve their breast. At a median follow-up of 14 months (4–25 months), there were no local or distant recurrences. There was a single non-cancer-related death. In the acute setting, we observed grade 1 toxicity in 58% (n = 7), grade 2 toxicity in 17% (n = 2), and no grade 3 or higher toxicity. In the late setting, at least 3 months after IORT, we observed grade 1 hyperpigmentation and/or fibrosis in 50% (n = 6), symptomatic seroma requiring drainage in 33% (n = 4). A single patient developed an abscess requiring hospitalization and intravenous antibiotic therapy.

Conclusion: BCS with IORT is a feasible salvage option for patients who present with localized breast cancer after prior thoracic radiation treatment. Continued follow-up of these patients is warranted given the incidence of delayed toxicity.

Keywords: breast, accelerated partial breast irradiation, intraoperative radiation therapy, recurrence, reirradiation, toxicity

INTRODUCTION

Based on a number of large randomized trials, the estimated 10-year rate of an isolated ipsilateral breast tumor recurrence (IBTR) after breast-conserving therapy is approximately 10% (1, 2). At the time of local recurrence the current standard of care is salvage mastectomy given the unacceptable toxicity to normal tissues with repeat whole breast irradiation (WBI). Local excision alone of an IBTR results in subsequent local recurrence in approximately 35% of patients based on retrospective series (3–8). Interestingly, in women who develop late local recurrences more than 5 years after treatment of their primary disease, disease-free, and overall survival is not significantly different compared to women who do not experience an IBTR (4, 9, 10). The prolonged interval until recurrence reflects a favorable tumor biology, and retrospective studies report no difference in survival between patients who undergo salvage mastectomy and breast-conserving surgery (BCS) for small, localized recurrences (10, 11). Given that many IBTRs are detected early on surveillance-imaging, many patients desire a breast-conserving option at the time of recurrence. Breast-conserving therapies have therefore become increasingly popular in treating these patients.

Accelerated partial breast irradiation (APBI) is a novel technique that offers the opportunity to limit radiation dose to previously irradiated breast tissue while improving rates of local control after BCS (12–16). There have been a limited number of small retrospective and prospective studies examining the use of APBI after local excision of an IBTR in the setting of prior radiation using various dose fractionations and delivery techniques (17–23). The use of intraoperative radiation therapy (IORT) to deliver a single, high-dose radiation to the lumpectomy surface at the time of surgery has been compared to adjuvant whole breast radiotherapy in the treatment of unifocal, early-stage breast cancers with non-inferior results (13). Its use in the setting of reirradiation has been reported with acceptable toxicity and cosmesis in small retrospective studies (13, 24, 25). Here, we report our single-institution experience with partial breast reirradiation (PBrI) with IORT after BCS in patients who decline salvage mastectomy.

MATERIALS AND METHODS

Patient Eligibility

We performed a retrospective review approved by the Columbia University Institutional Review Board of 228 patients treated with breast IORT between September 1, 2013, and November 31, 2016. Written informed consent was obtained from research participants. Patients were included in this study if they had developed a unifocal IBTR or new primary breast cancer (PBC) in the setting of prior WBI for early-stage breast cancer or a PBC after definitive thoracic radiation for another primary malignancy and declined salvage mastectomy. IBTR was defined as a breast tumor recurrence with the same histology and location as the initial PBC.

Radiation Treatment

Intraoperative radiotherapy was delivered using the Intrabeam™ device (Carl Zeiss, Oberkochen, Germany) at the time of lumpectomy. A spherical applicator was chosen at the radiation oncologist and operating surgeon's discretion to most appropriately fit the lumpectomy cavity. Ultrasound was used to confirm a minimum skin to applicator margin of at least 10 mm. A medical physicist was present to confirm delivery of 20 Gy to the surface of the lumpectomy cavity using 50 kV X-rays.

End Point Analysis

Patients were encouraged to follow-up at 2 weeks after surgery and at least every 6 months for the first year after treatment. End points of local control, mastectomy-free survival, distant metastasis, and overall survival were determined from the time of IORT. Acute and long-term side effects including breast pain, dermatitis, fibrosis, seroma, and infection were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

RESULTS

Patient and Primary Tumor Characteristics

The median age of our patients at the time of recurrence was 65 years old (range: 52–85 years). The median time from prior external beam radiation to biopsy-proven recurrence was 18 years (range: 2 months to 46 years). Nine patients developed an IBTR or new PBC after prior WBI for early-stage breast cancer, 2 patients with a new PBC after mantle-field radiation for Hodgkin's lymphoma, and 1 patient with a synchronous diagnosis of stage III non-small cell lung cancer (NSCLC) treated with definitive radiation to the ipsilateral lung and mediastinum. Only one patient with the synchronous diagnosis of stage III NSCLC and breast cancer underwent breast IORT at an interval of less than 1 year from the time of prior definitive radiation. Further available details of patient primary tumor and treatment characteristics are presented in **Table 1**.

Pathologic Findings

Based on final pathology, the median tumor size was 0.55 cm (range: 0–3.9 cm). All patients with invasive primaries were hormone receptor positive, defined as ≥1% staining of the estrogen

TABLE 1 | Primary tumor and treatment characteristics.

Patient	Age at initial diagnosis (years)	Histology of primary disease	Subtype	Prior radiation details	Prior adjuvant therapy
1	53	IDC	ER/PR+	WBI 50 and 15 Gy boost	CMF, tamoxifen
2	38	Hodgkin's lymphoma	–	Mantle field 40 Gy	–
3	44	DCIS	ER/PR+	WBI dose unknown	Tamoxifen
4	76	IDC	ER/PR+	WBI dose unknown	Anastrazole started but did not tolerate
5	49	DCIS	ER/PR+	WBI 50 and 15 Gy boost	None
6	52	NSCLC	–	Right lung and mediastinum IMRT 66 Gy[b]	–
7	43	IDC	TNBC	WBI 50.4 and 10 Gy boost	ddAC
8	20	Hodgkin's lymphoma	–	Mantle field 40 Gy	–
9	53	DCIS	ER/PR–	WBI 50.4 and 10 Gy boost	None
10	51	IDC	ER/PR+	WBI, 50.4 and 12 Gy boost[a]	A/T/bevacizumab/lupron[b]
11	59	IDC	ER/PR+	WBI dose unknown	Tamoxifen
12	54	IDC	ER/PR+	WBI dose unknown	None

IDC, invasive ductal carcinoma; ER, estrogen receptor; PR, progesterone receptor; NSCLC, non-small cell lung cancer; IMRT, intensity modulated radiation therapy; CMF, cyclophosphamide, methotrexate, fluorouracil; ddAC, dose dense doxorubicin, cyclophosphamide; AT, doxorubicin, paclitaxel.

[a]Patient was treated with neoadjuvant chemotherapy and definitive radiation therapy for her initial primary. [b]Therapy given in the neoadjuvant setting.

[b]Right breast mean dose 10.9 Gy, max point dose 59.6 Gy.

TABLE 2 | Patient treatment characteristics.

Patient	Age at recurrence (years)	Time to recurrence[b] (years)	Histology of breast tumor	Type of recurrence	Subtype	IBTR size (cm)	Lymph node sampling	Adjuvant systemic therapy
1	78	25	IDC	IBTR	ER/PR+	0.2	0/3	Exemestane
2	74	36	IDC	PBC	PR+	0.2	–	Intolerance of AI
3	60	16	DCIS	IBTR	PR+	0[a]	–	None
4	85	9	IDC	IBTR	ER/PR+	0.4	–	None, previous intolerance of AI
5	78	29	DCIS	IBTR	ER/PR+	0.6	–	Tamoxifen
6	52	0.2	IDC	PBC	ER/PR+	3.5	5/20	TC, anastrazole
7	64	21	IDC	SBC	PR+	1.1	0/2	Anastrazole
8	66	46	DCIS	PBC	ER/PR–	0.5	–	None
9	64	11	IDC	SBC	ER/PR+	1.5	0/3	Anastrazole but did not tolerate
10	55	5	Mixed IDC/ILC	IBTR	ER/PR+	1.9	0/14	Letrozole
11	78	19	IDC	SBC	ER/PR+, HER2+	3.9	–	Anastrazole, trastuzumab
12	62	8	IDC	SBC	ER/PR+, HER2+	0.4	0/1	Anastrazole, trastuzumab

IBTR, ipsilateral breast tumor recurrence; SBC, second breast cancer defined as an ipsilateral breast cancer of a different histology from the initial primary breast cancer; PBC, primary breast cancer in the setting of another prior malignancy; AI, aromatase inhibitor; TC, docetaxel and cyclophosphamide.

[a]Patient 3 had no residual disease at the time of lumpectomy.

[b]Interval time from prior diagnosis to biopsy-proven breast recurrence.

and/or progesterone receptor by immunohistochemistry (26). Two patients were HER2/neu positive per American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guideline recommendations (27). One of two patients with ductal carcinoma in situ (DCIS) was hormone receptor negative. Five patients underwent axillary sampling at the time of surgery for their IBTR. One patient was found to have involved sentinel lymph nodes and underwent completion of an axillary lymph node dissection. All patients with invasive primaries were found to have negative margins with no tumor on the final inked margin. One patient with DCIS was found to have a final close margin of 1 mm with no further re-excision. A summary of these findings is shown in **Table 2**.

IORT Details

The median applicator size used in our cohort of patients was 3.0 cm (range: 3.0–3.5 cm). All patients were prescribed 20 Gy to the lumpectomy surface using 50 kV X-rays. The median treatment time was 24.2 min (range: 17.1–24.7 min). The median applicator to skin distance was superiorly 15.3 mm (range: 5.1–23.0 mm), inferiorly 13.9 mm (range: 8.3–21.9 mm), medially 19.4 mm (range: 11.0–29.7 mm), and laterally 13.9 mm (range: 6.3–22.1 mm).

Adjuvant Systemic Therapy

All patients with hormone receptor-positive disease were recommended adjuvant hormonal therapy. All patients were compliant with therapy except three patients due to intolerance. One patient with disease metastasis to the axilla was treated with adjuvant docetaxel and cyclophosphamide chemotherapy. Two patients with HER2-positive invasive disease received adjuvant trastuzumab therapy.

Outcomes and Toxicity

At a median follow-up of 14 months (range: 4–25 months) there were no events of local or distant recurrence, and all women

were able to preserve their breast. There was a single non-breast cancer-related death due to heart failure. In the acute setting, we observed grade 1 dermatitis in 25% ($n = 3$), grade 1 breast pain in 8% ($n = 1$), grade 1 seroma in 25% ($n = 3$), grade 2 seromas requiring drainage in 17% ($n = 2$), and grade 2 infection in 8% ($n = 1$). No grade 3 or higher acute toxicity was observed. In the late setting, defined as 3 months after treatment with IORT, we observed grade 1 hyperpigmentation and/or fibrosis in 50% ($n = 6$), grade 1 seromas in 8% ($n = 1$), persistent grade 2 seromas in 33% ($n = 4$), and grade 2 infection in 17% ($n = 2$). There was a single patient who developed a grade 3 abscess requiring hospitalization and intravenous antibiotic therapy. There were no grade 2 or higher toxicity for the patient who underwent breast IORT within a year of prior definitive RT. Details of patient toxicity regarding breast seroma formation and infection are presented in **Table 3**.

DISCUSSION

In our single-institution experience, all 12 of our patients were able to successfully undergo local excision of their breast cancer followed by IORT with acceptable toxicity and preserve their breast. After a median follow-up of 14 months, there were no events of local or distant recurrence. In the late setting after treatment, we observed a significant incidence of persistent grade 2 seromas requiring drainage and antibiotic therapy. In the current literature, there are conflicting accounts of post-APBI seroma formation using various brachytherapy techniques. Evans et al. reported persistent seromas in about 75% of patients (greater than 6 months after treatment) treated with APBI using MammoSite®. Evaluating various dosimetric, clinical, and treatment-related variables, higher body weight was the only significant variable that correlated positively with seroma formation (28). On the contrary, Kraus-Tiefenbacher reported no difference in the rate of palpable seromas between patients who underwent BCS with or without IORT at the time of lumpectomy. While radiographically detected seromas were higher in the IORT group (81 vs. 52%, $p < 0.001$), the rate of palpable clinically significant seromas was not different. In their analysis, the addition of adjuvant chemotherapy correlated with higher rates of seromas detected on follow-up CT imaging (contingency coefficient 0.22, $p = 0.003$) (29). The higher incidence of seromas we observed in our study may reflect the lower tolerance of normal tissue in the reirradiation setting.

There has been one other published report of PBrI with IORT in a cohort of 17 patients who developed localized breast recurrences after previous external beam radiation (25). Overall, with a median follow-up of 26 months there were no reported local recurrences. Acute toxicity consisted mainly of mild induration of the tumor bed, and there were no instances of grade 3 or 4 toxicity. Interestingly, in comparison to our study, a larger median size applicator was used to treat the lumpectomy cavity (median 4.0 cm, range: 2.5–5.0 cm) and 3 of the 17 patients treated with ≥4.5 cm applicator were prescribed a lower dose of 14.7 Gy to the lumpectomy surface. While both of our cohorts are small, the difference in our reported experiences highlights the importance of applicator selection. Larger applicator selection may help to optimize apposition of the applicator against surrounding breast tissue and improve dose homogeneity at the tissue–applicator interface.

There are a number of single-institution studies that have reported on the toxicity and outcomes of PBrI. Deutsch et al. reported on their experience with PBrI using external beam electrons to cover the involved breast quadrant to 50 Gy in 2 Gy per daily fraction. They reported a recurrence free rate of 77% at 52-month follow-up, and overall good cosmesis with mainly skin pigmentation changes (14). Interstitial brachytherapy has been used by several institutions, reporting late toxicity of grade 3 fibrosis in up to 10–16% of patients (15, 17, 19, 20). Freedom from a second local recurrence at a median follow-up of 5 years was 89–93%. Existing studies support the efficacy and safety of PBrI to treat IBTR. To date, however, there is no clear optimal delivery technique or dose fractionation. RTOG 1014 is the most recent prospective trial examining the safety and efficacy of PBrI for IBTR after prior WBI using 3D-conformal external beam radiation. Their preliminary outcomes were reported at the recent American Society for Radiation Oncology conference, describing a 3-year subsequent IBTR of 3.7%, DMFS and

TABLE 3 | CTCAE graded treatment toxicity.

Patient	Dermatitis (acute)	Skin changes (late)	Breast infection (acute)	Breast infection (late)	Seroma (acute)	Seroma (late)	Fibrosis (acute)	Fibrosis (late)	Breast pain (acute)	Breast pain (late)
1	0	0	0	0	0	1	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	1	0	0
4	0	0	0	2	1	2	0	0	0	0
5	1	0	2	0	2	0	0	1	0	0
6	0	0	0	0	0	0	0	0	0	0
7	1	0	2	2	2	2	0	0	1	0
8	1	0	0	0	0	0	0	0	0	0
9	0	1	0	0	1	2	0	1	0	0
10	0	1	0	3	1	2	0	1	0	0
11	0	1	0	0	0	0	0	0	0	0
12	0	0	0	0	0	0	0	1	0	1
Total	25%	25%	17%	25%	42%	42%	0	42%	8%	8%

All toxicity graded per the NCI CTCAE version 4.02; acute defined as within 3 months from intraoperative radiotherapy treatment.

OS of 94.8% in a cohort of 58 patients. Four patients underwent subsequent mastectomy, two for a subsequent IBTR, one for a non-healing wound and another patient who underwent bilateral mastectomy after discovery of contralateral disease (30). They describe grade 1 late toxicity (greater than 1 year from treatment) in 24.1% of patients mainly consisting of breast pain and fibrosis, grade 2 late toxicity in 22.4%, and grade 3 toxicity in 6.9% with one instance of grade 3 infection. Comparable to the 3-year toxicity data from RTOG 1014, we observed a significant number of grade 2 and 3 toxicities in the late setting.

Limitations

The major limitations of this study include the retrospective nature of our data with limited follow-up to observe further delayed toxicities and recurrences. Given the small sample population of our study, it is difficult to draw conclusions regarding the differences in toxicity between our PBrI experience and previously published studies. Finally, we did not report on patient satisfaction and quality of life in our study. The pursuit of breast-conservation was driven mainly by patient preference, and ultimately the low-grade toxicities we observed with breast conservation may be outweighed by the success of breast preservation.

CONCLUSION

Breast-conserving surgery with IORT is a feasible salvage option for patients desiring breast conservation after prior thoracic radiation; however, continued follow-up of these patients is warranted given the incidence of delayed treatment toxicity. Further studies are needed to determine optimal treatment strategy, dose, and dose fractionation for PBrI.

AUTHOR CONTRIBUTIONS

Each of the listed authors contributed to the completion of this submission. Both CC and PJ worked on data collection and drafting of the final manuscript. BT, SF, RH, DH, and EC all contributed to the critical revision of the article with final approval for publication.

REFERENCES

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Darby S, McGale P, Correa C, Taylor C, Arriagada R, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet* (2011) 378:1707–16. doi:10.1016/S0140-6736(11)61629-2
2. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med* (2002) 347:1233–41. doi:10.1056/NEJMoa022152
3. Dalberg K, Mattsson A, Sandelin K, Rutqvist LE. Outcome of treatment for ipsilateral breast tumor recurrence in early-stage breast cancer. *Breast Cancer Res Treat* (1998) 49:69–78. doi:10.1023/A:1005934513072
4. Salvadori B, Marubini E, Miceli R, Conti AR, Cusumano F, Andreola S, et al. Reoperation for locally recurrent breast cancer in patients previously treated with conservative surgery. *Br J Surg* (1999) 86:84–7. doi:10.1046/j.1365-2168.1999.00961.x
5. Abner AL, Recht A, Eberlein T, Come S, Shulman L, Hayes D, et al. Prognosis following salvage mastectomy for recurrence in the breast after conservative surgery and radiation therapy for early-stage breast cancer. *J Clin Oncol* (1993) 11:44–8. doi:10.1200/JCO.1993.11.1.44
6. Voogd AC, van Tienhoven G, Peterse HL, Crommelin MA, Rutgers EJ, van de Velde CJ, et al. Local recurrence after breast conservation therapy for early stage breast carcinoma: detection, treatment, and outcome in 266 patients. Dutch Study Group on Local Recurrence after Breast Conservation (BORST). *Cancer* (1999) 85:437–46. doi:10.1002/(SICI)1097-0142(19990115)85:2<437::AID-CNCR23>3.0.CO;2-1
7. Kurtz JM, Jacquemier J, Amalric R, Brandone H, Ayme Y, Hans D, et al. Is breast conservation after local recurrence feasible? *Eur J Cancer* (1991) 27:240–4. doi:10.1016/0277-5379(91)90505-8
8. Ishitobi M, Okumura Y, Nishimura R, Nakatsukasa K, Tanabe M, Yoshida A, et al. Repeat lumpectomy for ipsilateral breast tumor recurrence (IBTR) after breast-conserving surgery: the impact of radiotherapy on second IBTR. *Breast Cancer* (2014) 21:754–60. doi:10.1007/s12282-013-0454-6
9. Kurtz JM, Spitalier JM, Amalric R, Brandone H, Ayme Y, Jacquemier J, et al. The prognostic significance of late local recurrence after breast-conserving therapy. *Int J Radiat Oncol Biol Phys* (1990) 18:87–93. doi:10.1016/0360-3016(90)90271-K
10. Alpert TE, Kuerer HM, Arthur DW, Lannin DR, Haffty BG. Ipsilateral breast tumor recurrence after breast conservation therapy: outcomes of salvage mastectomy vs. salvage breast-conserving surgery and prognostic factors for salvage breast preservation. *Int J Radiat Oncol Biol Phys* (2005) 63:845–51. doi:10.1016/j.ijrobp.2005.02.035
11. Yoshida A, Takahashi O, Okumura Y, Arima N, Nakatsukasa K, Tanabe M, et al. Prognosis after mastectomy versus repeat lumpectomy in patients with ipsilateral breast cancer recurrence: a propensity score analysis. *Eur J Surg Oncol* (2016) 42:474–80. doi:10.1016/j.ejso.2016.01.011
12. Kuerer HM, Arthur DW, Haffty BG. Repeat breast-conserving surgery for in-breast local breast carcinoma recurrence: the potential role of partial breast irradiation. *Cancer* (2004) 100:2269–80. doi:10.1002/cncr.20257
13. Vaidya JS, Wenz F, Bulsara M, Tobias JS, Joseph DJ, Keshtgar M, et al. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. *Lancet* (2014) 383:603–13. doi:10.1016/S0140-6736(13)61950-9
14. Strnad V, Hildebrandt G, Pötter R, Hammer J, Hindemith M, Resch A, et al. Accelerated partial breast irradiation: 5-year results of the German-Austrian multicenter phase II trial using interstitial multicatheter brachytherapy alone after breast-conserving surgery. *Int J Radiat Oncol Biol Phys* (2011) 80:17–24. doi:10.1016/j.ijrobp.2010.01.020
15. Veronesi U, Orecchia R, Maisonneuve P, Viale G, Rotmensz N, Sangalli C, et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. *Lancet Oncol* (2013) 14:1269–77. doi:10.1016/S1470-2045(13)70497-2
16. Vaidya JS, Vyas JJ, Chinoy RF, Merchant N, Sharma OP, Mittra I. Multicentricity of breast cancer: whole-organ analysis and clinical implications. *Br J Cancer* (1996) 74:820–4. doi:10.1038/bjc.1996.442
17. Deutsch M. Repeat high-dose external beam irradiation for in-breast tumor recurrence after previous lumpectomy and whole breast irradiation. *Int J Radiat Oncol Biol Phys* (2002) 53:687–91. doi:10.1016/S0360-3016(02)02785-2
18. Hannoun-Levi JM, Resch A, Gal J, Kauer-Dorner D, Strnad V, Niehoff P, et al. Accelerated partial breast irradiation with interstitial brachytherapy as second conservative treatment for ipsilateral breast tumour recurrence: multicentric study of the GEC-ESTRO Breast Cancer Working Group. *Radiother Oncol* (2013) 108:226–31. doi:10.1016/j.radonc.2013.03.026
19. Resch A, Fellner C, Mock U, Handl-Zeller L, Biber E, Seitz W, et al. Locally recurrent breast cancer: pulse dose rate brachytherapy for repeat irradiation following lumpectomy – a second chance to preserve the breast. *Radiology* (2002) 225:713–8. doi:10.1148/radiol.2253011913
20. Chadha M, Feldman S, Boolbol S, Wang L, Harrison LB. The feasibility of a second lumpectomy and breast brachytherapy for localized cancer in a

breast previously treated with lumpectomy and radiation therapy for breast cancer. *Brachytherapy* (2008) 7:22–8. doi:10.1016/j.brachy.2007.10.006
21. Guix B, Lejárcegui JA, Tello JI, Zanón G, Henríquez I, Finestres F, et al. Exeresis and brachytherapy as salvage treatment for local recurrence after conservative treatment for breast cancer: results of a ten-year pilot study. *Int J Radiat Oncol Biol Phys* (2010) 78:804–10. doi:10.1016/j.ijrobp.2009.08.009
22. Kauer-Dorner D, Pötter R, Resch A, Handl-Zeller L, Kirchheiner K, Meyer-Schell K, et al. Partial breast irradiation for locally recurrent breast cancer within a second breast conserving treatment: alternative to mastectomy? Results from a prospective trial. *Radiother Oncol* (2012) 102:96–101. doi:10.1016/j.radonc.2011.07.020
23. Polgar C, Major T, Sulyok Z, Frohlich G, Szabo E, Savolt A, et al. [Second breast-conserving surgery and reirradiation with interstitial high-dose-rate brachytherapy for the management of intra-breast recurrences – 5-year results]. *Magy Onkol* (2012) 56:68–74.
24. Keshtgar MR, Vaidya JS, Tobias JS, Wenz F, Joseph D, Stacey C, et al. Targeted intraoperative radiotherapy for breast cancer in patients in whom external beam radiation is not possible. *Int J Radiat Oncol Biol Phys* (2011) 80:31–8. doi:10.1016/j.ijrobp.2010.01.045
25. Kraus-Tiefenbacher U, Bauer L, Scheda A, Schoeber C, Schaefer J, Steil V, et al. Intraoperative radiotherapy (IORT) is an option for patients with localized breast recurrences after previous external-beam radiotherapy. *BMC Cancer* (2007) 7:178. doi:10.1186/1471-2407-7-178
26. Hammond ME, Hayes DF, Dowsett M, Allred DC, Hagerty KL, Badve S, et al. American Society of Clinical Oncology/College Of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. *J Clin Oncol* (2010) 28:2784–95. doi:10.1200/JCO.2009.25.6529
27. Wolff AC, Hammond ME, Hicks DG, Dowsett M, McShane LM, Allison KH, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. *Arch Pathol Lab Med* (2014) 138:241–56. doi:10.5858/arpa.2013-0953-SA
28. Evans SB, Kaufman SA, Price LL, Cardarelli G, Dipetrillo TA, Wazer DE. Persistent seroma after intraoperative placement of MammoSite for accelerated partial breast irradiation: incidence, pathologic anatomy, and contributing factors. *Int J Radiat Oncol Biol Phys* (2006) 65:333–9. doi:10.1016/j.ijrobp.2005.12.045
29. Kraus-Tiefenbacher U, Welzel G, Brade J, Hermann B, Siebenlist K, Wasser KS, et al. Postoperative seroma formation after intraoperative radiotherapy using low-kilovoltage X-rays given during breast-conserving surgery. *Int J Radiat Oncol Biol Phys* (2010) 77:1140–5. doi:10.1016/j.ijrobp.2009.06.008
30. Arthur DW, Moughan J, Kuerer HM, Haffty BG, Cuttino LW, Todor DA, et al. NRG oncology/RTOG 1014: 3 year efficacy report from a phase II study of repeat breast preserving surgery and 3D conformal partial breast re-irradiation (PBrI) for in-breast recurrence. *Int J Radiat Oncol Biol Phys* (2016) 96:941. doi:10.1016/j.ijrobp.2016.09.054

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frontiers in Oncology

CASE REPORT
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Intraoperative Radiation "Boost" to the Surgical Resection Bed following Pancreaticoduodenectomy for a Borderline Resectable Pancreatic Carcinoma: A Case Report

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Neoadjuvant therapy including chemotherapy alone or concurrent chemotherapy with external bream radiation is a standard treatment strategy for borderline resectable pancreatic adenocarcinoma and is also used routinely for primary operable cancers at some institutions (1). The use of intraoperative radiation therapy (IORT) has been limited largely because of the logistical issues in delivery of radiation during surgery (2). This is the first reported case of a borderline resectable pancreas cancer patient who underwent neoadjuvant chemo-radiation therapy followed by resection with the use of IORT using the mobile IntraBeam device to boost the resection bed and improve local control by dose escalation.

Keywords: intraoperative radiation therapy, IORT, pancreas cancer, borderline resectable, neoadjuvant therapy

INTRODUCTION

Surgical resection remains the mainstay therapy for pancreas cancer; however, more than 80% of patients have disease that is not resectable at the time of diagnosis (3). There is a subgroup of patients who are considered potentially resectable following neoadjuvant therapy. This group has been termed borderline resectable pancreas cancer (BRPC) based on the assessment of the association of tumor with the major regional vessels. Generally, neoadjuvant therapy includes chemotherapy followed by concurrent chemo-radiation therapy or in some cases up front chemo-radiation therapy alone (4). Neoadjuvant chemo-radiation has been increasingly used for patients with localized pancreatic carcinoma including resectable or BRPC with improved outcomes (5, 6).

Retrospective studies have shown that adding local radiation to a BRPC leads to improvement in survival at 1 year due to improved local control (7). Phase II data and single institution data support the use of neoadjuvant therapy (8–10). In addition, a meta-analysis has shown that in about one-third of initially unresectable patients can be converted to resectable with the use of neoadjuvant therapy (7). Intraoperative radiation therapy (IORT) had been used in pancreas cancer in the past primarily with the goal of pain reduction and control of locoregional tumor progression (11–14). Formerly IORT was given with an electron energy source that produced promising results but was difficult to implement.

Additionally, further radiation following neoadjuvant radiation after surgery for a close or positive margin is typically prohibited by normal tissue tolerances. Intraoperative radiation has been used as a method to deliver additional radiation boost to areas at risk for residual disease. Here, we describe the use of low-kilovoltage (low-kV) IORT to boost an area at risk for residual disease recognized during the surgical resection.

CASE REPORT

A 50-year-old African-American male presented with a 14-day history of abdominal pain and anorexia in the spring of 2008. Abdominal CT scan revealed a 3.4 cm × 3.7 cm × 4.7 cm hypo-attenuated mass in the region of the uncinate process, contacting directly 50° of the superior mesenteric vein and approximately 25° of the superior mesenteric artery as well as contacting the left renal vein (**Figure 1**). The pancreatic duct was dilated measuring 0.7 cm. An endoscopic ultrasound-guided FNA biopsy was non-diagnostic, and percutaneous CT-guided biopsy confirmed a pancreatic carcinoma. CEA was 14.5 and Ca19-9 was 76. The case was discussed in prospective tumor board and the tumor was deemed to meet NCCN criteria for borderline resectable disease of less than or equal to 180° of contact of major vessels. The patient underwent neoadjuvant chemo-radiation with protracted infusion 5FU and involved field radiation to a dose of 5,040 cGy. Repeat staging showed a good response with the tumor measuring 3.3 cm × 3.1 cm, and the association of the tumor to the SMV and SMA being improved (**Figure 2**). Repeat Ca19-9 was 3. The patient was taken to surgery and underwent pylorus-preserving pancreaticoduodenectomy (**Figure 3**). A boost dose of 1,800 cGy was prescribed to the surface of a 3.5 cm spherical applicator and was administered intraoperatively to the uncinate margin at the superior mesenteric vein, superior mesenteric artery, and inferior vena cava. This area was felt to be at the highest risk for a close or positive margin and formed a concave region making it amendable for treatment with a spherical applicator. Normal tissue was retracted including the left kidney, neck of pancreas, small bowel, and colon which were protected with lead shields and several centimeters of tissue equivalent material in all directions other than the target. Once the radiation dose was delivered, the patient was reconstructed in the standard fashion. Pathology confirmed a 0.5 cm area of tumor over the inferior vena cava. Biopsies of the soft tissues along the right lateral border of the superior mesenteric vein were benign. The patient's final pathology stage was ypT3, N0, M0 with 12 regional nodes negative for metastatic disease, and margins of resection were negative (R0). The patient had a satisfactory postoperative course and was discharged on the 11th postoperative day with the evidence of delayed gastric emptying requiring home TPN. The patient was, over time, able to return to a regular diet, and the TPN was discontinued and then received 6 months of adjuvant chemotherapy with gemcitabine. In our surgical series, we have found ~40% rate of some element of delayed gastric emptying. We have routinely placed patients with clinical manifestation of delayed gastric emptying in the first postoperative week on TPN. This has decreased readmission rates. In this case report, there was no need for vessel resection or reconstruction. This patient did undergo a pylorus-preserving procedure which may have a higher rate of delayed gastric emptying. In addition, it is possible that nerves in the retroperitoneal space could have had radiation exposure. The cause of this patient's delayed gastric emptying is likely multi-factorial including the effects of the surgical technique and radiation exposure.

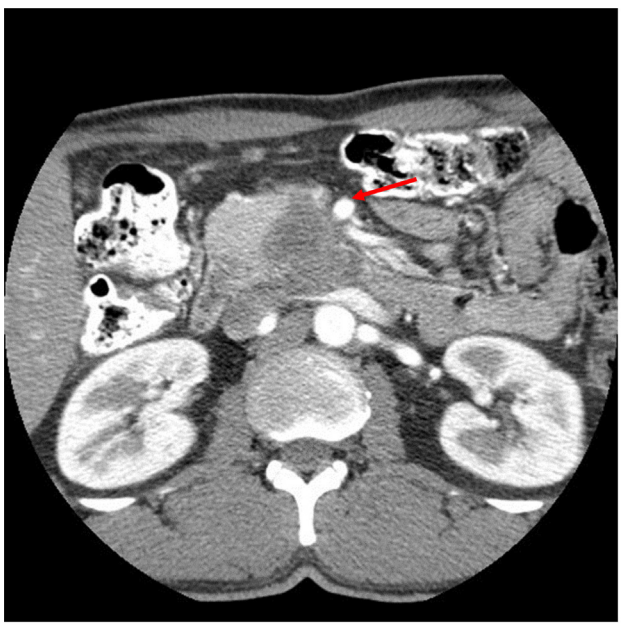

FIGURE 1 | CT abdomen at initial work-up that shows a hypo-attenuated mass in the region of the uncinate process contacting 50% of the superior mesenteric vein, and approximately 25% of the superior mesenteric artery (see arrow) as well as contacting the left renal vein.

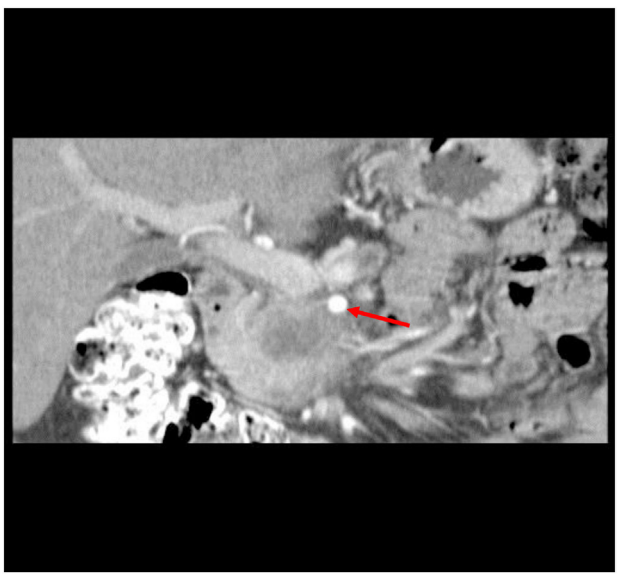

FIGURE 2 | CT abdomen at restaging following neoadjuvant chemo-radiation therapy showed a 3.3 cm × 3.1 cm mass, decreased from initial size with involvement of the SMA (see arrow) and SMV improved.

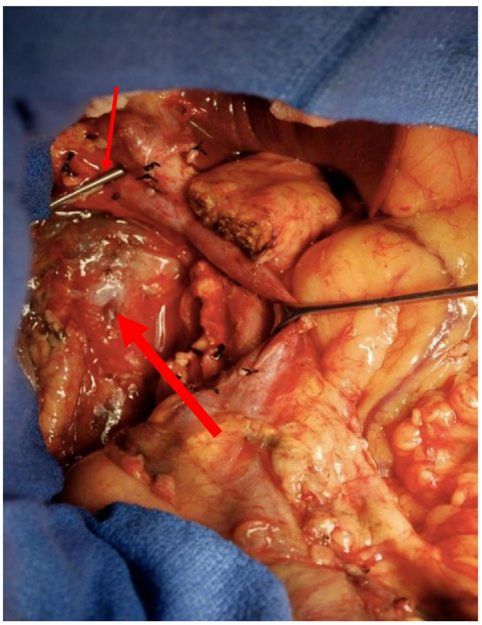

FIGURE 3 | Surgical field at the time of pylorus-preserving pancreaticoduodenectomy in region of the uncinate margin at the superior mesenteric vein (thin arrow), superior mesenteric artery, and inferior vena cava were intraoperative low-kV radiation therapy was administered in retroperitoneal space (thick arrow).

The patient has been followed with repeat three-dimensional imaging at routine intervals (**Figure 4**). Since surgery, the patient has been in surveillance follow-up for over 87 months and is considered free of disease.

DISCUSSION

Intraoperative radiation therapy refers to the delivery of a single dose of radiation therapy directly in the tumor bed at the time of surgery. IORT can be delivered with both electron and low-energy kV X-rays. IOERT requires a specially shielded and approved operating room with a linear accelerator or prior to closing the incision the patient is physically transported to a radiation oncology suite for treatment. In most institutions, this is prohibitive. In addition, electron therapy has more energy scatter and thus is more difficult to spare adjacent normal tissue compared to low-energy kV X-rays (15).

The Intrabeam system offers many potential advantages over IOERT including accessibility, easier patient positioning, rapid dose gradient, and beam characteristics. The system is portable allowing for use in multiple operating rooms. Therefore, no designated operating room is necessary for delivery of treatment. The system has six degrees of freedom permitting the machine to conform to multiple treatment positions. The low-kV X-rays have a steep dose gradient (15). The rapid dose gradient allows for delivery of high dose to the target tissue while relatively sparing the surrounding normal tissues (16). Any tissue at risk can be shielded with tungsten-filled silicone or even wet gauze. The system has minimal radiation protection requirements allowing

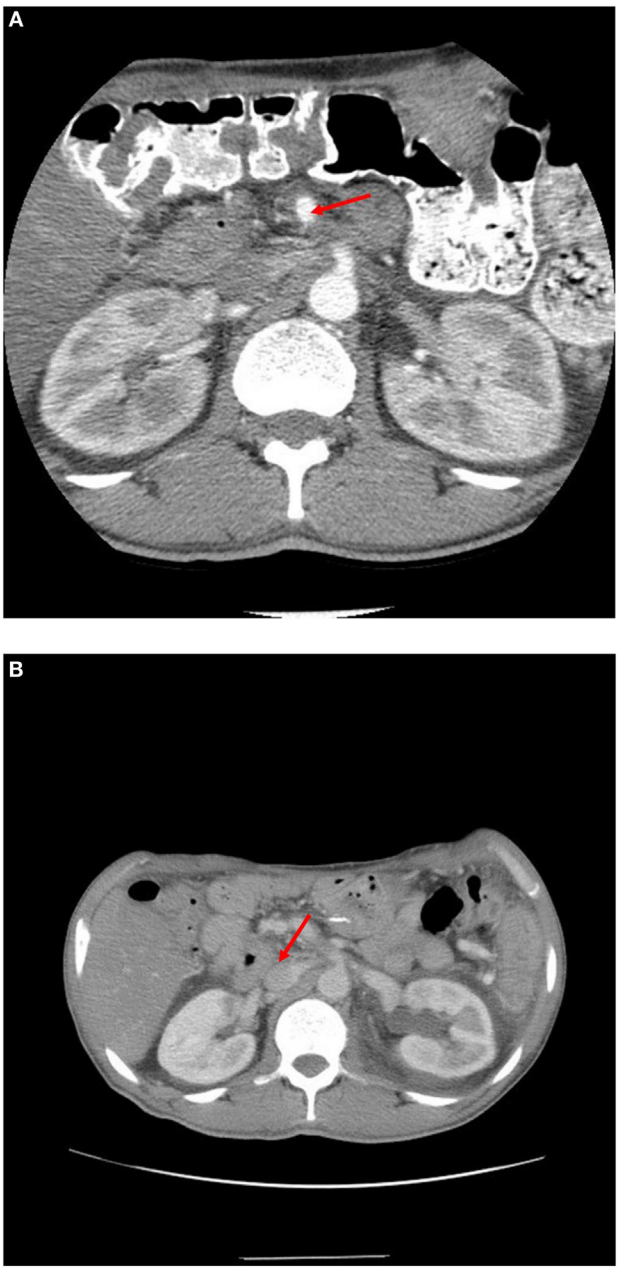

FIGURE 4 | **(A)** 1 year post-operative scan showing SMA (see arrow) is clear of disease. **(B)** 7 year post-operative scan showing renal vein at IVC (see arrow) widely patient and without disease.

essential staff to stay in the room with the anesthetized patient during delivery of the radiation.

In addition to treatment parameters that make the Intrabeam technology easier to deliver, there are also potential radiobiological benefits of IORT. Delivery of a single high-dose treatment to a confined area rather than a fractionated postoperative course of therapy does not allow for tumor cell proliferation between surgery and start of radiotherapy as well as sublethal damage repair between fractions in a standard course of radiation therapy (17, 18).

In summary, potential advantages of an intraoperative radiation include direct visualization of the tumor bed, no temporal delay between surgery and radiation not allowing for tumor cell repopulation, and improved displacement and shielding of normal tissues. Loyola University is accruing to a Phase I, 3 × 3 trial of 10, 15, and 20 Gy IORT prescribed to the surface of a flat applicator for patients with resectable pancreas cancer (19). This trial will further establish the dose of kV IORT to increase treatment to the tumor bed and retroperitoneal margin; the areas of highest risk of local recurrence. Currently, flat applicators are available in six sizes ranging from 10 to 60 mm to accommodate patient size and area of concern.

In BRPC, vascular involvement remains an important factor as to whether or not a patient can become resectable. Once respectable, the margin negative rate is a key determinant of local control. This case demonstrates the feasibility of using IORT for target dose escalation while minimizing the normal tissue exposure. This is the first known successful use of intraoperative radiation using the IntraBeam device for a BRPC patient.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of Sentara CarePlex Hospital regulations with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Sentara CarePlex Hospital committee on events related to human subjects.

AUTHOR CONTRIBUTIONS

TT and WS provided intellectual background in analyzing the data for this report and writing the report. MF, SK, and RH were directly involved in the treatment of the patient reported in this case report.

REFERENCES

1. Tsai S, Christians KK, George B, Ritch P, Oshima K, Tolat P, et al. Neoadjuvant therapy for resectable and borderline resectable pancreas cancer. *J Cancer Ther* (2016) 7:24–40.
2. Krishnan S, Ahmad M. Intensifying local radiotherapy for pancreas cancer – who benefits and how do we select them? *J Gastrointest Oncol* (2013) 4(4):337–9. doi:10.3978/j.issn.2078-6891.2013.027
3. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. *CA Cancer J Clin* (2013) 63:11–30. doi:10.3322/caac.21166
4. Small W Jr, Hayes JP, Suh WW, Abdel-Wahab M, Abrams RA, Azad N, et al. ACR appropriateness criteria borderline and unresectable pancreas cancer. *Oncol J* (2016) 619–32.
5. National Comprehensive Cancer Network. *Clinical Practice Guidelines in Oncology, Version 2.2016, 08/16/2016*. National Comprehensive Cancer Network. Fort Washington, PA (2016).
6. Tsai S, Evans DB. Therapeutic advances in localized pancreatic cancer. *JAMA Surg* (2016) 151(9):862–8. doi:10.1001/jamasurg.2016.1113
7. Ishikawa O, Ohigashi H, Imaoka S, Sasaki Y, Iwanaga T, Matayoshi Y, et al. Is the long-term survival rate improved by preoperative irradiation prior to Whipple's procedure for adenocarcinoma of the pancreatic head? *Arch Surg* (1994) 129:1075–80.
8. Landry J, Catalano PJ, Staley C, Harris W, Hoffman J, Talamonti M, et al. Randomized phase II study of gemcitabine plus radiotherapy versus gemcitabine, 5-fluorouracil, and cisplatin followed by radiotherapy and 5-fluorouracil for patients with locally advanced, potentially resectable pancreatic adenocarcinoma. *J Surg Oncol* (2010) 101:587–92. doi:10.1002/jso.21527
9. Katz MH, Pisters PW, Evans DB, Sun CC, Lee JE, Fleming JB, et al. Borderline resectable pancreatic cancer: the importance of this emerging stage of disease. *J Am Coll Surg* (2008) 206(5):833–46; discussion 846–8. doi:10.1016/j.jamcollsurg.2007.12.020
10. Small W Jr, Berlin J, Freedman GM, Lawrence T, Talamonti MS, Mulcahy MF, et al. Full-dose gemcitabine with concurrent radiation therapy in patients with nonmetastatic pancreatic cancer: a multicenter phase II trial. *J Clin Oncol* (2008) 26:942–7. doi:10.1200/JCO.2007.13.9014
11. Gillen S, Schuster T, Meyer Zum Buschenfelde C, Friess H, Kleeff J. Preoperative/neoadjuvant therapy in pancreatic cancer: a systemic review and meta-analysis of response and resection percentages. *PLoS Med* (2010) 7(4):e1000267. doi:10.1371/journal.pmed.1000267
12. Wood WC, Shipley WU, Gunderson LL, Cohen AM, Nardi GL. Intraoperative irradiation for unresectable pancreatic carcinoma. *Cancer* (1982)49(6):1272–5.doi:10.1002/1097-0142(19820315)49:6<1272::AID-CNCR2820490632>3.0.CO;2-E
13. Shipley WU, Wood WC, Tepper JE, Warshaw AL, Orlow EL, Kaufman SD, et al. Intraoperative electron beam irradiation for patients with unresectable pancreatic carcinoma. *Ann Surg* (1984) 200(3):289–96.
14. Reni M, Panucci MG, Ferreri AJ, Balzano G, Passoni P, Cattaneo GM, et al. Effect on local control and survival of electron beam intraoperative irradiation for resectable pancreatic adenocarcinoma. *Int J Radiat Oncol Biol Phys* (2001) 50(3):651–8. doi:10.1016/S0360-3016(01)01470-5
15. Gunderson LL. Electronic brachytherapy/low KV-IORT: physics and techniques. 2nd ed. *Intraoperative Irradiation Techniques and Results*. New York: Springer (2011).
16. *Intrabeam Product Specifications*. Carl Zeiss Meditec Company (2010).
17. Vaidya JS, Joseph DJ, Tobias JS, Bulsara M, Wenz F, Saunders C, et al. Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomized, non-inferiority phase 3 trial. *Lancet* (2010) 376(9735):91–102.
18. Belletti B, Vaidya JS, D'Andrea S, Entschladen F, Roncadin M, Lovat F, et al. Targeted intraoperative radiotherapy impairs the stimulation of breast cancer cell proliferation and invasion caused by surgical wounding. *Hum Cancer Biol* (2008) 14(5):1325–32. doi:10.1158/1078-0432.CCR-07-4453
19. *Intraoperative Radiation Therapy for Resectable Pancreas Cancer (IORT)*. ClinicalTrials.gov identifier NCT02599662.

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REVIEW
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Immunotherapy Combined with Large Fractions of Radiotherapy: Stereotactic Radiosurgery for Brain Metastases—Implications for Intraoperative Radiotherapy after Resection

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Brain metastases (BM) affect approximately a third of all cancer patients with systemic disease. Treatment options include surgery, whole-brain radiotherapy, or stereotactic radiosurgery (SRS) while chemotherapy has only limited activity. In cases where patients undergo resection before irradiation, intraoperative radiotherapy (IORT) to the tumor bed may be an alternative modality, which would eliminate the repopulation of residual tumor cells between surgery and postoperative radiotherapy. Accumulating evidence has shown that high single doses of ionizing radiation can be highly efficient in eliciting a broad spectrum of local, regional, and systemic tumor-directed immune reactions. Furthermore, immune checkpoint blockade (ICB) has proven effective in treating antigenic BM and, thus, combining IORT with ICB might be a promising approach. However, it is not known if a low number of residual tumor cells in the tumor bed after resection is sufficient to act as an immunizing event opening the gate for ICB therapies in the brain. Because immunological data on tumor bed irradiation after resection are lacking, a rationale for combining IORT with ICB must be based on mechanistic insight from experimental models and clinical studies on unresected tumors. The purpose of the present review is to examine the mechanisms by which large radiation doses as applied in SRS and IORT enhance antitumor immune activity. Clinical studies on IORT for brain tumors, and on combined treatment of SRS and ICB for unresected BM, are used to assess the safety, efficacy, and immunogenicity of IORT plus ICB and to suggest an optimal treatment sequence.

Keywords: brain metastases, immune therapy, radiotherapy, stereotactic radiosurgery, intraoperative radiotherapy

INTRODUCTION

Brain metastases (BM) are an advanced-stage manifestation of cancer that affect up to a third of patients with systemic disease. BM predominantly originate from primary lung, breast, or gastrointestinal cancers and melanoma. Given the change in demographics in industrialized countries with increasing cancer frequencies, combined with the increase in numbers of long-term survivors owing

to improved diagnostics and therapy, the incidence is believed to rise further. Depending on the clinical condition, treatment options for BM include surgery, whole-brain radiotherapy (WBRT), stereotactic radiosurgery (SRS), or a combination of these, while chemotherapy has only limited activity owing to low penetration of the blood–brain barrier (BBB). A considerable proportion of patients undergo upfront surgery for debulking the tumor mass or for the determination of histology and/or mutational status. In such cases, local relapse occurs in roughly 60% of patients 1–6 months after surgery alone (1), indicating that tumor stem cells capable of forming recurrent tumors have microscopically invaded the borders of the surgical cavity. While some degree of local control may be achieved by adding WBRT, this is associated with high morbidity and intracranial recurrences are common. Randomized phase III trials did not show improved overall survival by adding adjuvant WBRT (2, 3) and most patients now undergo SRS directed to the tumor bed, a procedure that was proposed and developed even before these trials were done (4, 5). Although level I evidence for this treatment is lacking, initial data suggest a low toxicity profile (6–8). However, even with the best treatment available, the median survival is rarely much longer than 1 year and, thus, there is a strong need for improved treatment beyond the BM and the tumor bed around the excised cavity.

Similar to SRS, intraoperative radiotherapy (IORT) to the cavity and margins treats the tumor site while minimizing dose to the surrounding normal tissue. Early clinical studies on IORT after the resection of glioma were conducted especially in Japan and in Germany, typically applying 15–25 Gy of high-energy electrons in a single fraction. Results were encouraging, with comparable or better local control and overall survival, and less radionecrosis than after fractionated WBRT with external X-ray beams (9–12). A large retrospective study of IORT as a boost combined with external beam WBRT versus WBRT alone did not show any significant improvement by IORT (13). However, failures were found to be associated with insufficient dose coverage (14) and a case of long-term (9 years) survival was indeed observed (15). Because of technical limitations, few centers were able to pursue this treatment at the time, but in the last decade, dedicated mobile machines for delivering IORT by high-energy electrons or low-energy X-rays (LEX) in the operating room have become more widely available.

Compared to SRS for resected metastases, IORT eliminates the healing time between surgery and the beginning of RT during which tumor cells may proliferate and possibly spread beyond the tumor bed. In contrast, IORT requires the total dose to be applied in a single fraction, whereas hypofractionated treatment is optional with SRS (e.g., for larger tumors or cavities). Recently, the potential use of IORT for brain tumors may be supported by encouraging results from a phase I/II trial on IORT with 50 kV X-rays for glioblastoma (16), which was found to be safe in these patients (Giordano et al., submitted) and prompted the initiation of a randomized phase III trial (NCT02685605). The rationale for IORT in glioblastoma has been reviewed by Giordano et al. (17). Notably, the treatment of solitary BM with excision and IORT alone using 50 kV X-rays has been shown to be feasible with disease-specific outcome comparable to other modalities (18).

It has been suggested that in addition to targeted cell killing induced by conventional fraction sizes, vascular, cohort (bystander), and immune effects may contribute to the biological effect of very large doses per fraction (19–22). In contrast, it has been disputed whether additional effects other than the 5R's of radiotherapy (reassortment, repair, reoxygenation, repopulation, and radiosensitivity) need to be invoked to explain the successes of SRS, SBRT/SABR, and IORT (23). Nevertheless, there is a strong case that large radiation doses may act as an adjuvant for immunogenic cell death by releasing tumor antigens and danger signals (24). At the same time, the identification and characterization of immune checkpoints has led to a surge in clinical studies on immune therapy using immune checkpoint blockade (ICB) antibodies (frequently termed "checkpoint inhibitors" although to date no small-molecule inhibitors are available). For example, an early phase II study showed dramatic effects in melanomas, which generally are immunogenic tumors (25). Thus, combining RT and ICB is considered to offer potential synergies, in particular since antitumor immune effects outside the irradiated target volume, so-called abscopal effects (26), might help control microscopic systemic disease.

Although the brain has, for decades, been regarded as a "privileged site" that provided limited scope for antitumor immunity, activated T cells are known to be able to cross the BBB (27). While conventional radiotherapy mildly increases BBB permeability (28), SRS disrupts the BBB within hours after application, allowing cells and substances to easily cross into the CNS for a period of roughly a month (29). In the case of BM, early studies suggested improved overall survival rates when ICB was combined with SRS for unresected metastases (30, 31), reaching levels similar to patients without BM (32). In contrast, a study applying ICB in patients previously treated with SRS found no significant difference to SRS alone (33) and ICB combined with conventionally fractionated WBRT after resection also failed to show an effect (34), suggesting that timing and fractionation may be important.

Whereas a potential interaction between SRS and ICB is readily understandable in the case of non-resected metastases where radiation can release tumor antigens, it is not obvious if the irradiation of residual tumor cells in the tumor bed after resection of the tumor is sufficient to elicit a tumor-directed immune response. Since no systematic studies on resected tumors have been published, a rationale for combining IORT with ICB must be based on an understanding of the mechanisms involved. Therefore, the purpose of the present review is to examine the immunological interaction between radiation and ICB to elucidate whether high single doses to the resection cavity and the residual cancer cells within its margins might act as an immunizing event opening the gate for ICB therapies in the brain. Because of the complexity and dynamic nature of this topic, we first give a brief overview of the antitumor immune response and immune checkpoints for the non-expert. We then present the experimental evidence for the interactions between radiation and the immune system. Finally, we review the clinical studies on SRS combined with ICB and discuss the implications and potential for combining IORT with ICB for BM.

ACTIVATION OF THE IMMUNE RESPONSE

The innate immune system acts as a non-specific first-line defense against infection and foreign antigens but also activates the adaptive immune system to provide an antigen-specific response. Upon infection, trauma (including irradiation), or during tumor initiation and progression (35), an inflammatory cascade is induced. In case of an infection, this is initiated by pathogen-associated molecular pattern (PAMP) molecules such as bacterial liposaccharides. Similarly, trauma release damage-associated molecular pattern (DAMP) molecules including proteins such as nuclear high-mobility group box 1 (HMGB1) and endoplasmatic calreticulin (CRT) as well as non-protein molecules adenosine triphosphate (ATP) and mitochondrial peptides and DNA (in the case of necrotic cell death) (36–38).

Soon after the appearance of PAMP or DAMP molecules, neutrophils enter the tissue secreting a large variety of chemokines and cytokines, including pro-inflammatory interleukin (IL)-12 (39), which in turn recruit monocytes and lymphocytes into the inflamed tissue. Depending on the cytokines, monocytes can differentiate into inflammatory or anti-inflammatory macrophages, and dendritic cells (DC). Phagocytes (neutrophils and macrophages) have pre-formed *pattern recognition receptors* (PRRs), mainly toll-like receptors (TLRs) and *receptors for advanced glycation end-products* (RAGE) that bind to PAMPs on microbial surfaces or to DAMPs from damaged cells. DAMPs are found on cell membranes, released into the extracellular space, or detected in the cytoplasm by intracellular PRR sensors such as TLR-9, which activates the STING [stimulator of interferon (IFN) genes] pathway (40) inducing the expression of type 1 IFN, e.g., IFNβ.

Natural killer (NK) cells are an important component of immune surveillance that remove cells with low expression of major histocompatibility complex (MHC) class I surface molecules. NK cells are $CD3^-$ $CD8^+$ lymphocytes lacking the T-cell receptor (TCR), which $CD3^+$ lymphocytes use for the detection of antigens on MHC. Instead, they express activating receptors belonging to the family of killer-cell immunoglobulin-like receptors (KIRs). The body's own cells are protected by inhibitory KIRs that recognize MHC class I presenting "self" antigens. Combinations of IL-12 or IL-15 with IL-18 stimulate NK cells activated by target cell recognition to secrete chemotactic cytokines, e.g., macrophage inflammatory protein followed by inflammatory cytokines IFNγ and tumor necrosis factor (TNF)-α in different subpopulations (41).

The adaptive immune system reacts to specific antigens and is made up largely of T and B lymphocytes, which are responsible for the cell-mediated and humoral adaptive immune responses, respectively. This part of the system carries a memory of previous antigens with lymphocytes being distributed between lymph nodes and the body tissues. Antigens need to be presented to lymphocytes by antigen-presenting cells (APCs). Most cell types present a small fraction of degraded proteins as peptide antigens on MHC molecules on their surface. Non-professional APCs (essentially all cell types) present 3–18 amino acid (a.a.) peptides from degraded cellular protein on 10^5–10^6 MHC I molecules found on each cell (42), while so-called professional APCs (DC found mainly in superficial tissue, macrophages, and B cells) also present peptides on MHC class II molecules. The peptides presented on MHC class II are generated from antigens taken up by endocytosis and can be longer than 18 a.a. but are often degraded by peptidases to approximately 12 a.a. (42). Tumor cells and dying normal cells translocate CRT to the cell surface acting as an "eat me" signal. If CRT is able to overcome the inhibitory "do not eat me" signal from CD47, it will activate TLRs on phagocytes (43, 44). Together with the release of other DAMP molecules, this stimulates phagocytosis by DC or macrophages which process the antigens and present them on MHC class II leading to activation of these APCs (45). Activated professional APCs migrate to the nearest lymph nodes (or *via* the blood vessels to the spleen) where the MHC:peptide complexes are presented to lymphocytes that recognize specific antigens by their T- or B-cell receptors (BCR). B cells recognize native antigens by their BCR and can internalize, process, and present antigen peptides on their MHC class II molecules to T cells (46). According to the clonal selection theory, the highly variable TCR and BCR give rise to an extremely large number of mature, so-called naive, lymphocytes that each recognize different epitopes made up of antigen peptides presented on MHC molecules. While an adaptive antitumor immune response requires $CD8^+$ and $CD4^+$ T cells, the role of B cells and the humoral adaptive immune response is unclear.

The two major classes of T cells, cytotoxic ("killer") T cells (Tc) and helper T cells (Th), express different co-receptors, CD8 and CD4, respectively. CD8 on Tc bind to MHC class I (on all cells), while CD4 on Th cells bind to MHC class II (on professional APC). The binding between the Th and professional APCs is reinforced by induced expression of co-stimulatory molecules, mainly CD28, which binds to B7.1 (CD80) and B7.2 (CD86) on APCs, and CD40 ligand (CD40L), which binds to the CD40 receptor. Once a specific MHC II antigen-peptide combination binds the TCR and CD4 co-receptor of a naive Th, co-stimulatory binding results in its activation with clonal expansion and differentiation to a secretory effector Th cell releasing different cytokines.

Subsets of differentiated Th cells mediate either a cytotoxic immune response (mainly Th1 cells characterized by secretion of IFNγ) or a humoral immune response (follicular helper, T_{FH}) (47). Th1 cytokine IFNγ stimulates the function of macrophages and the activation of $CD8^+$ T cells, binding to MHC I:peptide complexes. T_{FH} are thought to activate B cells, while Th1, Th2 (characterized by IL-4, IL-5, and IL-13), and Th17 (characterized by IL-17a, IL17b, and IL-22) direct immunoglobulin class switching according to different types of pathogens. Since B cells function as professional APCs they may activate Th cells recognizing the antigen peptides presented on the MHC II molecules of the B cell and the secreted cytokines in turn activate the B cell causing it to proliferate and produce specific antibodies. An overview of the immune activation is shown schematically in **Figure 1** (48, 49).

IMMUNE TOLERANCE AND CHECKPOINTS

Various mechanisms prevent the immune system from attacking its own body cells (autoimmune reactions) and from excessive

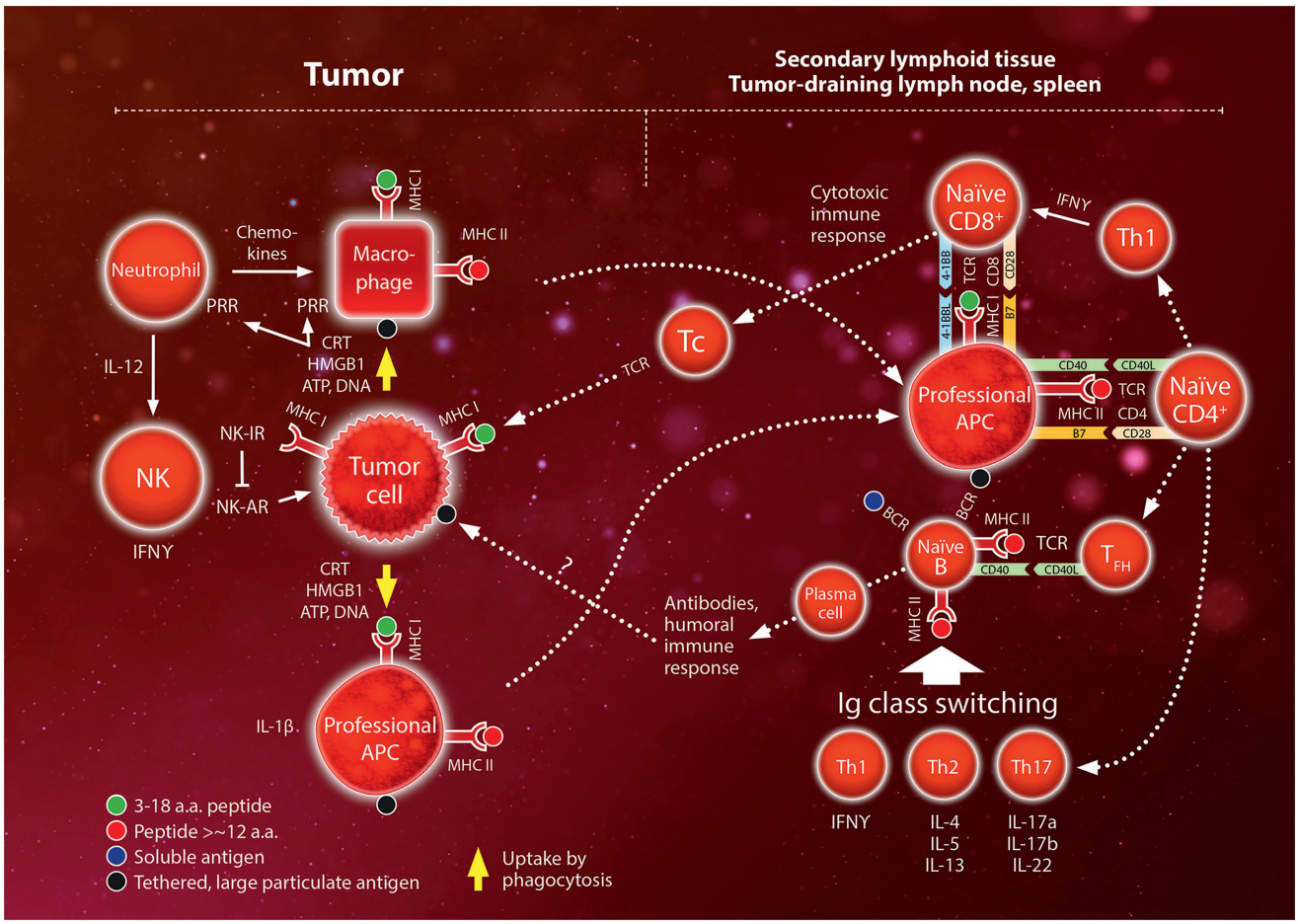

FIGURE 1 | Schematic overview of the interaction between the innate and adaptive immune systems. The innate system initiates the immune response by reacting to pathogens or trauma. Pathogens release pathogen-associated molecular pattern molecules (e.g., liposaccharides) while trauma release damage-associated molecular pattern molecules [mainly calreticulin (CRT); high mobility group box (HMGB)-1; ATP; DNA]. These molecules bind to pattern recognition receptors (PRR) on phagocytes (neutrophils, macrophages). Neutrophils entering the tissue secrete a large variety of chemokines and cytokines which recruit monocytes and lymphocytes. Natural killer (NK) cells remove cells with low expression of major histocompatibility complex (MHC) class I surface molecules *via* a set of activating and inhibiting receptors (AR and IR, respectively). In the adaptive system, antigens are presented to lymphocytes by MHC molecules on antigen-presenting cells (APCs). All cells express MHC class I molecules but only professional APC (mainly dendritic cells, macrophages, and B lymphocytes) express MHC class II molecules. Professional APCs migrate to the secondary lymphoid tissue (lymph nodes and the spleen) where they activate naïve $CD4^+$ and $CD8^+$ T-lymphocytes. Depending on the cytokine expression of $CD4^+$ T helper (Th) cells, these activated cells regulate class switching of naïve B lymphocytes to mediate the humoral immune response. Th1 also stimulate activation of CD8 cells to become cytotoxic ("killer") T cells (Tc) that infiltrate the peripheral inflamed tissue and target specific antigens expressed on MHC class I molecules, e.g., on tumor cells. Interactions between MHC–antigen complexes and T cells are mediated by the T-cell receptor (TCR) and are reinforced by binding between pairs of complementary costimulatory molecules (e.g., B7 and CD28, CD40 and CD40 ligand, 4-1BB ligand and 4-1BB). Please also see text. For more detailed mechanisms, the reader is referred to comprehensive text books, e.g., Ref.(48, 49).

normal immune reactions. Basically, tolerance to "self"-antigens is induced by the deletion of naive Tc recognizing MHC:peptide complexes that present fragments of the individuals own proteins. In addition, a number of other mechanisms help limit the physiological immune response. A special type of $CD4^+$ regulatory T cells (Tregs, characterized by $CD25^{high}$ and the canonical transcription factor FoxP3) limit or modulate the adaptive immune reaction by a variety of mechanisms [reviewed in Ref. (50)]. Tregs secrete inhibitory cytokines IL-10 and TGF-β1 and express CTLA-4 (cytotoxic T-lymphocyte-associated antigen 4) which is a negative regulator competing with CD28 for co-stimulatory binding to the B7 molecule on APCs [reviewed in Ref. (51)]. Tregs constitutively express CTLA-4 (52), but CTLA-4 is also induced during Tc activation, thus providing a feedback mechanism for downregulating APC-mediated Tc activation to prevent an excessive inflammatory reaction (53). Another member of the CD28 family, programmed death-1 (PD-1), is expressed on lymphocytes and inhibits the function of activated T cells, by binding to the B7 family ligand PD-L1. PD-L1 is not expressed in most normal cells but can be induced in tumor cells by IFNγ in the tumor microenvironment (54). PD-L1 can bind to B7.1, and PD-L1 signaling *via* PD-1 mediates immune suppression by stimulating apoptosis of T cells, inducing IL-10 and inducible Tregs, which contributes to a dysfunctional state

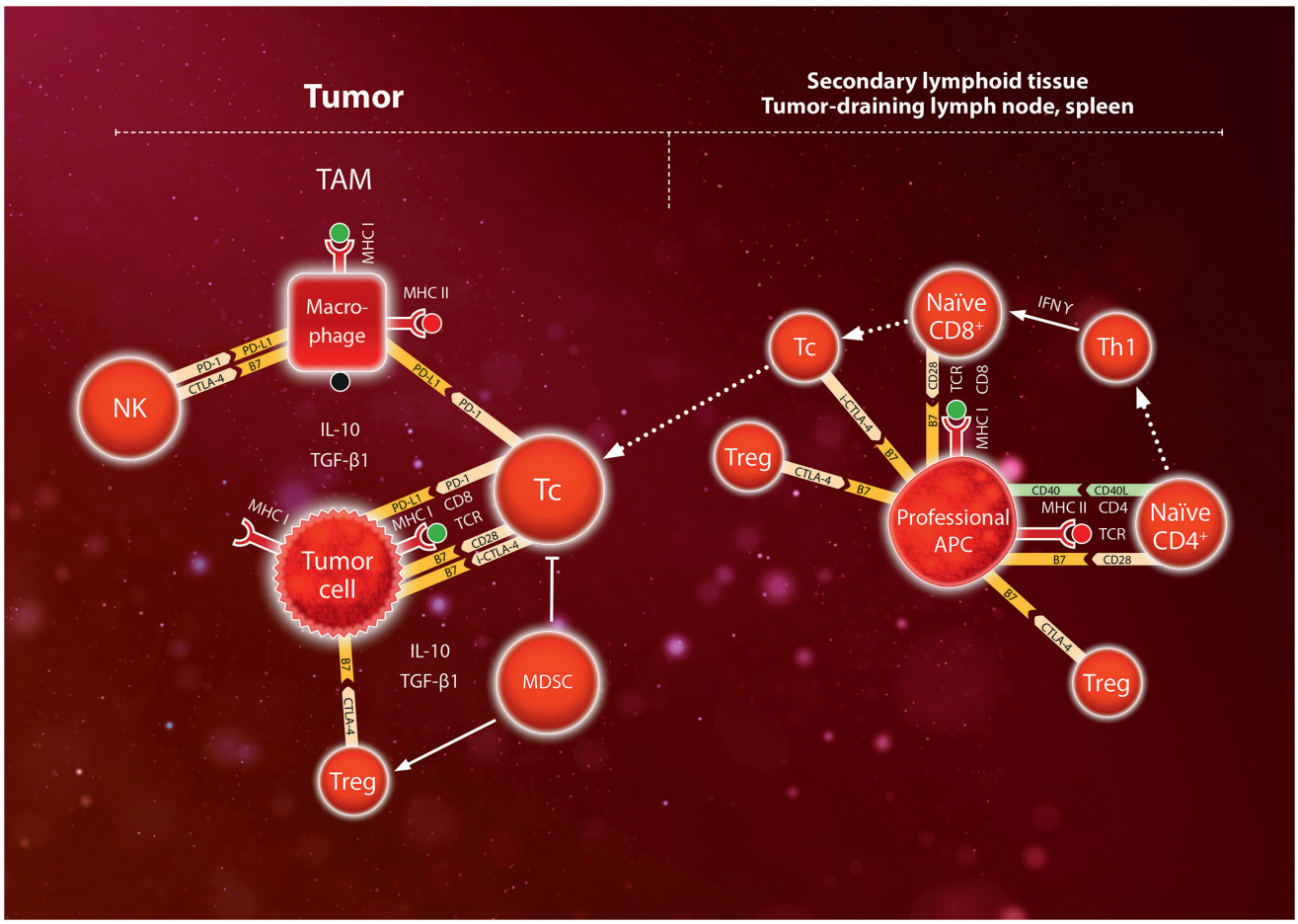

FIGURE 2 | Schematic model of immunosuppressive mechanisms during T-cell activation in the secondary lymphoid tissue (lymph nodes or spleen) and during the anti-tumor immune response in the tumor. Naïve $CD8^+$ lymphocytes express TCR which bind to a specific antigen presented by major histocompatibility complex (MHC) I on professional antigen-presenting cell (APC). Binding is reinforced by binding of CD8 to MHC, and secretion of IFNγ by Th1 cells leads to expression of the costimulatory molecules CD28 which binds to B7. Together, these signals activate the $CD8^+$ lymphocyte to become a cytotoxic Tc lymphocyte. However, CTLA-4 on regulatory T cells (Treg) competes for B7 in the APC thus dampening T-cell activation. Furthermore, induced CTLA-4 (i-CTLA-4) may contribute to inhibiting the activity of Tc. Cytotoxic Tc lymphocytes infiltrate the tumor and engage tumor cells by binding of TCR to the MHC I antigen complex, which is reinforced by binding of costimulatory molecules CD28 to B7. However, myeloid-derived suppressor cells (MDSC) and tumor-associated macrophages (TAM) secrete IL-10 and TGF-β1 which stimulate Treg to express CTLA-4 competing for B7, and also directly inhibit Tc cells. Furthermore, tumor cells may upregulate expression of the programmed death (PD) ligand (L)1 which binds PD-1 on Tc thus inhibiting the activity of Tc against the tumor cells. In addition, TAM express PD-L1 binding to PD-1 on Tc and natural killer (NK) cells, and also B7 binding to CTLA-4 on NK cells. Tumor cells can upregulate these immune checkpoints to escape attack by the immune system. Use of immune checkpoint blockade (ICB) antibodies directed against CTLA-4 in the secondary lymphoid tissue or PD-1/PD-L1 in tumors can help override these immune checkpoints thereby stimulating immune activation (anti-CTLA-4) or inhibition of cytotoxic T-cells (anti-PD-1, anti-PD-L1).

termed T-cell "exhaustion" (55). Thus, according to the current model of immune checkpoints, CTLA-4 exerts its action mainly during antigen presentation and Tc activation, i.e., in the afferent arm of the adaptive immune response (leading to the secondary lymphoid tissue). By contrast, PD-L1/PD-1 is considered to act mainly in the efferent arm (leading from the lymph nodes back to the affected tissue) by modulating the cytotoxic action of $CD8^+$ T cells in the tumor, although PD-1 is also expressed on Tregs, NK, and B cells, while PD-L1 is expressed on myeloid cells in tumors (56, 57). In addition to Tregs, myeloid-derived suppressor cells (MDSC; of monocytic and granulocytic lineages) contribute to immune suppression *via* secretion of immunosuppressive cytokines IL-10, and TGF-β1, and other mechanisms (58). The major immune checkpoints currently exploited in cancer therapy are shown schematically in **Figure 2**.

Because tumor cells arise from the body's own cells they might be expected to escape immune surveillance. In spite of this inherent tolerance, an immune response may be elicited by over-expressing naturally occurring "self" proteins (tumor-associated antigens), mutated "self" proteins, or foreign proteins such as viral proteins (tumor-specific antigens, TSA) (59). However, genetic and epigenetic changes during tumor progression may select for mechanisms that avoid detection or suppress the immune response. Thus, an inflammatory response in tumors may upregulate PD-L1 and cause tumor-associated macrophages and MDSC to express IL-10 and TGF-β1 (60, 61).

Targeting the immune checkpoints by antibodies against CTLA-4 and PD-1/PD-L1 has recently shown to result in clinically relevant responses in some cancer patients (62–66). Antibodies against CTLA-4 broadly stimulate the adaptive immune response but may be associated with severe side effects, while anti PD-1/PD-L1 therapy may be more specific toward tumors and appears to be better tolerated (51). However, ICB antibodies given alone are effective only if the tumor is immunogenic *per se*.

RADIATION-INDUCED ENHANCEMENT OF IMMUNE ACTIVITY

Although low doses of radiation are immunosuppressive, it has become clear in the last 10–15 years that higher doses may stimulate the antitumor immune response (45, 67, 68). Indeed, some evidence suggests that immunogenic cell death contributes to the efficacy of hypofractionated or single-dose radiotherapy (37, 69, 70). However, data regarding the influence of dose and fractionation are conflicting, thus warranting a critical review of the dose dependence of immune activation.

The first evidence that irradiation releases DAMP molecules was found in murine thymoma cells that released HMGB1 after a dose of 10 Gy in an apoptosis-dependent fashion since the release was suppressed by the caspase inhibitor Z-VAD-fmk (71). Golden et al. found that CRT translocation and the release of DAMP molecules ATP and HMGB1 in a murine breast adenocarcinoma cell line were increased by single doses in the range of 2–20 Gy (72). The data indicated a quasi-linear increase up to 10 Gy, whereas 20 Gy produced a moderate further increase for CRT and ATP but only little further increase of HMGB1. Radiation-induced release of DNA into the cytosol (e.g., from the mitochondria) activates the STING pathway leading to the induction of type I IFN, the first step in the inflammatory cytokine cascade (73). Thus, IFNβ was induced after a single dose of 20 Gy to B16 melanoma tumors (74). NK cells and lymphocytes are very radiosensitive and undergo apoptosis after doses <2Gy. Furthermore, translocation of nuclear HMGB1 into the cytosol was recently reported after irradiation of human skin fibroblasts with doses in the range 4–12 Gy (75). Therefore, it seems a distinct possibility that high-dose irradiation of the normal tissue in the tumor bed may contribute to producing an inflammatory microenvironment conducive of an antitumor immune reaction.

Irradiation induces cytokines in various cell types, most importantly *via* nuclear factor (NF)-κB [reviewed in Ref. (76)], which can be activated by DNA damage-induced kinases, ATM, and DNA-PKcs (77, 78). Furthermore, HMGB1 is a ligand for RAGE and TLR4 signaling to NFκB, which may contribute to cytokine induction after higher doses (79). NFκB regulates transcription of a large number of cytokine genes, including pro-inflammatory cytokines such as IL-1β, IL-6, IL-8, IL-33, and TNF-α. Thus, expression of IL-1β and TNF-α was induced within a few hours of irradiating macrophages with doses of 3–20 Gy *in vitro* (80–82). Early upregulation of IL-1β was also observed after *in vivo* irradiation with 18.5 Gy (83), whereas a lower dose of 3 Gy caused upregulation approximately 5–7 days later, during macrophage differentiation preceding regeneration of the spleen (80). Early transcriptional upregulation of a number of cytokines including IL-1β and TNF-α occurred in brain or lung tissue after irradiation with doses of 7–25 Gy (84, 85). Thus, robust expression seems to require high single doses although daily fractions of 4 Gy also produced sustained expression in lung macrophages (85). Strong, dose-dependent secretion of IL-6 regulated by NFκB and activator-protein-1 was found in HeLa cells 24 h after irradiation with 3–20 Gy, while no significant increase was observed after 1 Gy (86, 87). In another study, secretion of IL1-α, IL-6, and IL-8 over 24 h was induced 1.7-, 1.6-, and 2.1-fold, respectively, by a low dose of 1.5 Gy in a monocytic cell line but not in A549 adenocarcinoma cells (88). However, irradiation of murine lymphoma with a single high-dose of 30 Gy initially decreased IFNγ and TNF-α in splenocytes but expression recovered 7–10 days after irradiation (70). A comprehensive review of the inflammatory response to ionizing radiation was given recently by Di Maggio et al. (89).

While it is not surprising that leukocytes express cytokines, it may be important for other cell types that p53 and NF-κB show a reciprocal relationship (90, 91). Veldwijk et al. (22) tested the secretion of 36 cytokines by p53 wild-type MCF7 breast cancer cells over 24 h after irradiation with 15 Gy. Only six cytokines (CD40L, IFNγ, IL-6, IL-8, IL-23, and Serpine E1) were detectable, and none showed significant upregulation after irradiation. Thus, it is conceivable that radiation-induced p53 may limit induction of the ATM/DNA-PKcs/NFκB pathway in p53 wild-type normal and tumor cells (A549 and MCF7) and that stronger induction in HeLa cells is due to the suppression of p53 by expression of the HPV18 E6 protein. Whereas *in vitro* induction may require high doses, there is ample evidence for radiation-induced expression of pro-inflammatory cytokines after moderate doses given *in vivo* (76). For example, dose-dependent upregulation was demonstrated in peritoneal mouse macrophages isolated 16 h after whole-body irradiation with 0.075–6 Gy with maximum upregulation at 4 Gy showing twofold increase for IL-12 and fivefold increase for IL-18 (92). The apparently higher sensitivity *in vivo* may be explained by additional activation due to lymphocyte apoptosis that may release DAMP molecules *in situ* including HMGB1 which activates the NF-κB pathway (79, 93).

Tumor cells frequently downregulate MHC surface molecules, thus reducing the opportunity of antigen presentation. However, radiation doses of 10–20 Gy upregulated MHC class I expression by ≥10% in 8/23 human colon, lung, and prostate, tumor cell lines tested (94). In a human melanoma cell line, MHC class I was increased in a dose- and time-dependent fashion with maximum expression at 48–72 h yielding a twofold increase for 10–25 Gy compared to 1.3-fold after 4 Gy (95). This study also showed that intracellular peptides for antigen presentation were initially generated by the degradation of existing proteins, but at later time points, novel peptides from new protein synthesis were presented on MHC class I. In a similar system, upregulation of MHC class I appeared to depend partly on radiation-induced IFNγ (96). Further aspects of different radiotherapy schemes on immune stimulation *in vitro* and *in vivo* have been reviewed in Ref. (97, 98).

Experiments using a tumor antigen-specific adenoviral vaccine showed that a single, moderate dose of 8 Gy given before

vaccination produced a synergetic antitumor effect against a murine colorectal tumor, which was also observed when irradiation was given in three fractions of 3.5 Gy each (99). Since irradiation after vaccination had no effect, this seems to suggest a role of irradiation as an adjuvant creating a local microenvironment that supports immunization rather than a role in antigen presentation in this setting. Such a model is supported by the strong immunogenic effect of a TLR-7 agonist on a colorectal tumor, which was potentiated by fractionated radiotherapy with 5 × 2 Gy beginning simultaneously with the first application of the agonist but without any further immune therapy (100). However, the complexity and multiple components of the dynamic immune reaction may explain why combining radiotherapy with systemic type I or II IFNs was mostly unsuccessful, while the combination with IL-2 or IL-12 showed only limited effects in early clinical studies [reviewed in Ref. (101, 102)].

TUMOR-DIRECTED, RADIATION-INDUCED IMMUNE EFFECTS *IN VIVO*

Few studies have investigated antitumor immunogenic effects of radiation *in vivo* without applying immune stimulation or checkpoint inhibitors. Lugade et al. found that a single radiation dose of 15 Gy increased the number of APC capable of activating IFNγ-secreting cells in lymph nodes in an experimental mouse model B16 of melanoma genetically modified to express ovalbumin (OVA) as a non-self antigen (67). A fractionated schedule of 5 × 3 Gy showed smaller increases of such APC in the lymph nodes. A similar difference between single and fractionated irradiation was seen for infiltration of the tumor by $CD45^+$, $CD4^+$, $CD8^+$, CD11c, and CD11b immune cells 7 days after irradiation, indicating the recruitment of T cells, DC, macrophages, and possibly NK cells ($CD8^+$ but $CD3^-$). Interestingly, the difference between single and fractionated doses was observed for specific T cells, activated by tumor-derived peptide presentation on MHC I but not on MHC II in both lymph nodes and tumors. Infiltration into the tumors was due to lymphocyte trafficking and was dependent on the upregulation of vascular cell adhesion molecule-1 on endothelial cells (96). A study by Lee et al. using unmodified B16 melanoma confirmed a growth inhibitory effect after a single dose of 20 Gy when tumors were grown from 2×10^6 injected cells, and local control was observed after 15 Gy when the number of injected cells was reduced to 1×10^5 (69). In the same study, local tumor control was also observed when an MHC class I-binding peptide ("SIY") was introduced as antigen and tumors grown from 2×10^5 injected cells were irradiated with 25 Gy. Growth delay for 5×10^5 injected cells and irradiation with 20 Gy was dependent on $CD8^+$ and was not seen for fractionated irradiation with 4 × 5 Gy. The effect of dose and fraction size was studied by Schaue et al. who irradiated B16-OVA tumors with single doses of 5–15 and 15 Gy applied in 1, 2, 3, or 5, fractions (103). Inhibition of tumor growth was seen at 7.5–15 Gy, whereas no significant effect was seen after 5 Gy. Applying a dose of 15 Gy in 1, 2, 3, or 5, fractions reduced tumor size and increased antigen-specific IFNγ expressing cells in the spleen for all schedules with a trend for 2 × 7.5 Gy being more effective. Notably, doses of 1 × 7.5 Gy or 2 × 7.5 Gy, but not other doses, also seemed to reduce the number of Tregs in the spleen. Taken together, single doses of 15-25 Gy, or hypofractionated irradiation with large dose fractions (7.5 Gy), seem capable of eliciting an immunogenic antitumor response against the primary tumor in the B16 murine melanoma system even without including ICB in the treatment.

The combination of radiotherapy with ICB has shown considerable synergies on local tumor control in experimental systems. Demaria et al. found that a single dose of 12 Gy followed by CTLA-4 blockade showed a synergistic growth delay of mammary tumors and two fractions of 12 Gy separated by 48 h combined with CTLA-4 blockade produced local control in a small number of animals (104). In a study by Dewan et al., a single dose of 20 Gy, or daily fractionated irradiation with 3 × 8 Gy or 5 × 6 Gy, caused similar growth delay but adding anti-CTLA-4 antibody 2, 5, and 8 days after the first irradiation inhibited growth for all schemes with an apparent, small advantage of 3 × 8 Gy (105). Incidentally, 5 × 3 Gy fractionated irradiation of B16 melanoma produced slightly more tumor infiltration than a single dose of 15 Gy for $CD8^+$ T cells activated by tumor-derived peptide presented on MHC class II, whereas 1 × 15 Gy produced higher numbers of cells activated by peptide presentation on MHC class I (67). This would seem consistent with a model in which hypofractionated irradiation combined with CTLA-4 blockade increases MHC class II-mediated antigen presentation by APC, while high single doses may be more efficient in promoting antigen presentation *via* MHC class I. In a radioresistant triple-negative mammary tumor studied by Verbrugge et al., a single dose of 12 Gy combined with anti-CD137 and anti-PD-L1 antibody treatment produced regression with some control of subcutaneous tumors while 4 × 5 Gy daily fractionated irradiation in combination with the same antibodies was effective in orthotopic tumors (106). Sharabi et al. showed regression of murine melanoma and mammary tumors irradiated with a single dose of 12 Gy combined with anti-PD-1 treatment (107). Irradiation with five fractions of 2 Gy upregulated expression of PD-L1 in colorectal cancer cells isolated from murine tumors but did not control tumors in a study by Dovedi et al. (108). However, concomitant administration of anti-PD-1 or anti-PD-L1 during and after irradiation resulted in 66–80% local control, and significant effects were confirmed in two other tumor lines. Irradiation combined with both anti-PD-1 and anti-PD-L1 showed no further enhancement. While local control was influenced by NK cells, survival was dependent on $CD8^+$ T cells that also induced PD-L1 *via* IFNγ. Azad et al. irradiated syngenic pancreatic ductal adenocarcinoma (PDAC) tumors combined with anti-PD-L1 antibody therapy (109). In the KPC line, combined treatment produced non-significant growth delays after 1 × 6 Gy or 5 × 2 Gy, while a single dose of 20 Gy produced growth inhibition but excessive dermatitis required termination of the experiment. By contrast, combined treatment with a single dose of 12 Gy, or 5 × 3 Gy fractionated irradiation, caused significant growth delay in KPC and regression in the Pan02 line. This was associated with an increase in T-cell infiltration and a reduction in myeloid cell numbers and was only seen for simultaneous treatment and not when anti-PD-L1 was started 1 week after irradiation. In another study, Twyman-Saint Victor

TABLE 1 | Preclinical results on the effect of immune reactions on the growth of the irradiated tumor.

Reference	Irrad. (RT)	Immunotherapy		Tumor model	Endpoint/effect/comments	
	no. fx, d/fx	Type	Start			
Lugade et al. (67)	1 × 15 Gy	None	n.a.	Melanoma (B16-OVA)	Activation of APC and specific immune cells, increased TIL trafficking	
	5 × 3 Gy	None	n.a.	Melanoma (B16-OVA)	Reduced growth delay, APC and MHC I-specific activation, TIL trafficking	
Lugade et al. (96)	1 × 15 Gy	None	n.a.	Melanoma (B16-OVA)	Radiation-induced IFNγ upregulates vascular cell adhesion molecule-1, MHC I	
Lee et al. (69)	1 × 20 Gy	None	n.a.	Melanoma (B16)	Growth delay	2×10^6 cells inj.; delay T-cell dependent
	1 × 15 Gy	None	n.a.	Melanoma (B16)	Survival	1×10^5 cells inj.; local control $CD8^+$ dependent
	1 × 25 Gy	None	n.a.	Melanoma (B16-SYI)	Survival	2×10^5 cells inj.
	1 × 20 Gy	None	n.a.	Melanoma (B16-SYI)	Growth delay	5×10^5 cells inj., $CD8^+$ dependent
	4 × 5 Gy	None	n.a.	Melanoma (B16-SYI)	No growth delay	5×10^5 cells inj.
Schaue et al. (103)	1 × 15 Gy	None	n.a.	Melanoma (B16-OVA)	Growth delay	Signif. delay, activ. specif. splenocytes; (Treg) increased?
	1 × 10 Gy	None	n.a.	Melanoma (B16-OVA)	Growth delay	Signif. delay, activ. specif. splenocytes; (Treg reduced?)
	1 × 7.5 Gy	None	n.a.	Melanoma (B16-OVA)	Growth delay	Signif. delay, activ. specif. splenocytes; Treg reduced
	1 × 5 Gy	None	n.a.	Melanoma (B16-OVA)	Growth delay	No signif. delay, little splenocyte activ.; Treg unchanged
	1 × 15 Gy	None	n.a.	Melanoma (B16-OVA)	Growth delay	Signif. delay, activ. specif. splenocytes; (Treg increased?)
	2 × 7.5 Gy	None	n.a.	Melanoma (B16-OVA)	Growth delay	Signif. delay, activ. specif. splenocytes; Treg unchanged
	3 × 5 Gy	none	n.a.	Melanoma (B16-OVA)	Growth delay	Signif. delay, activ. specif. splenocytes; (Treg increased?)
	5 × 3 Gy	None	n.a.	Melanoma (B16-OVA)	Growth delay	Signif. delay, activ. specif. splenocytes; Treg increased (?)
Demaria et al. (26)	1 × 6 Gy	Flt3-L	1 day after	Breast ca. (67NR)	No enhanced growth delay (similar to RT)	
	1 × 2 Gy	Flt3-L	1 day after	Breast ca. (67NR)	No enhanced growth delay (similar to RT)	
Demaria et al. (104)	1 × 12 Gy	α-CTLA-4	1 day after	Breast ca. (4T1)	Growth delay	
	2 × 12 Gy	α-CTLA-4	1 day after	Breast ca. (4T1)	Regression/local control; tumor-specific CTL in spleen	
Dewan et al. (105)	1 × 20 Gy	α-CTLA-4	0 days	Breast ca. (TSA)	Growth delay	No regression
	1 × 20 Gy	α-CTLA-4	2 days after	Breast ca. (TSA)	Growth delay	No Regression
	3 × 8 Gy	α-CTLA-4	0 days	Breast ca. (TSA)	Growth delay	Regression
	3 × 8 Gy	α-CTLA-4	2 days after	Breast ca. (TSA)	Growth delay	Regression
	3 × 8 Gy	α-CTLA-4	4 days after	Breast ca. (TSA)	Growth delay	No Regression
	5 × 6 Gy	α-CTLA-4	2 days after	Breast ca. (TSA)	Growth delay	No regression
	1 × 20 Gy	α-CTLA-4	2 days after	Colon ca. (MCA38)	Non-signif. growth delay	
	3 × 8 Gy	α-CTLA-4	2 days after	Colon ca. (MCA38)	Growth delay	
Yoshimoto et al. (70)	1 × 30 Gy	None	n.a.	Lymphoma (EL4)	Survival	T-cell dependent
	1 × 30 Gy	None	n.a.	Lewis lung carc.	Growth delay	$CD8^+$ dependent
	1 × 30 Gy	α-CTLA-4	1 day after	Lewis lung carc.	Growth delay	
Twyman-Saint Victor et al. (110)	1 × 20 Gy	α-CTLA-4	3 days before	Melanoma (B16-F10)	Growth delay	$CD8^+$ dependent
	1 × 20 Gy	α-CTLA-4	1 day after	Melanoma (B16-F10)	Growth delay	

(*Continued*)

TABLE 1 | Continued

Reference	Irrad. (RT)	Immunotherapy		Tumor model	Endpoint/effect/comments	
	no. fx, d/fx	Type	Start			
	1 × 20 Gy	α-CTLA-4, α-PD-L1	3 days before	Melanoma (B16-F10)	Survival	
	1 × 20 Gy	α-CTLA-4, α-PD-L1	3 days before	Breast ca. (TSA)	Survival	
	1 × 20 Gy	α-CTLA-4, α-PD-L1	3 days before	Pancreatic ca. (KPC)	Survival	
	1 × 20 Gy	α-CTLA-4, α-PD-1	3 days before	Melanoma (B16-F10)	Survival	
Verbrugge et al. (106)	1 × 12 Gy	α-CD40, α-CD137	0 days	Breast ca. (AT-3)	Growth delay	
	1 × 12 Gy	α-PD-L1	0 days	Breast ca. (AT-3)	Growth delay	
	1 × 12 Gy	α-CD137, α-PD-L1	0 days	Breast ca. (AT-3)	Growth delay	$CD8^+$ depend., regression/control
	1 × 12 Gy	α-CD137, α-PD-L1	0 days	Orthopic AT-3	Survival	
	4 × 5 Gy	α-CD137, α-PD-L1	0 days	Breast ca. (AT-3)	Survival	
	4 × 4 Gy	α-CD137, α-PD-L1	0 days	Breast ca. (AT-3)	Regression	
Azad et al. (109)	1 × 20 Gy	α-PD-L1	0 days	Pancreatic ca. (KPC)	Growth delay	Termination due to dermatitis
	1 × 12 Gy	α-PD-L1	0 days	Pancreatic ca. (KPC)	Growth delay	$CD8^+$ dependent
	1 × 12 Gy	α-PD-L1	6 days after	Pancreatic ca. (KPC)	No growth delay	
	1 × 6 Gy	α-PD-L1	0 days	Pancreatic ca. (KPC)	Growth delay	Non-significant, no regression
	5 × 3 Gy	α-PD-L1	0 days	Pancreatic ca. (KPC)	Growth delay	$CD8^+$ dependent
	5 × 2 Gy	α-PD-L1	0 days	Pancreatic ca. (KPC)	Growth delay	Non-significant, no regression
	1 × 12 Gy	α-PD-L1	0 days	Pancreatic ca. (Pan02)	Regression	
	5 × 3 Gy	α-PD-L1	0 days	Pancreatic ca. (Pan02)	Regression	
Deng et al. (111)	1 × 20 Gy	α-PD-L1	1 day before	Colon ca. (MC38)	Regression	Delayed regrowth
	1 × 12 Gy	α-PD-L1	1 day before	Breast ca. (TUBO)	Regression	$CD8^+$ dependent
Dovedi et al. (108)	5 × 2 Gy	α-PD-L1	1 day after	Colorectal ca. (CT26)	Survival	$CD8^+$ dependent, $CD4^+$ inhibits
	5 × 2 Gy	α-PD-1	1 day after	Colorectal ca. (CT26)	Survival	
	5 × 4 Gy	α-PD-L1	1 day after	Breast ca. (4T1)	Growth delay	
	5 × 2 Gy	α-PD-L1	1 day after	Myeloma (4434)	Growth delay	Delayed regrowth after regression
Sharabi et al. (107)	1 × 12 Gy	α-PD-1	1 day before	Melanoma (B16-OVA)	Regression	Treg in tumor increased by RT, but reduced by α-PD-1
	1 × 12 Gy	α-PD-1	1 day before	Breast ca. (4T1-HA)	Regression	Treg in tumor increased by RT, but reduced by α-PD-1
Park et al. (118)	1 × 15 Gy	α-PD-1	1 day before	Melanoma (B16-OVA)	Growth delay	
	1 × 15 Gy	α-PD-1	1 day before	Renal cell ca. (RENCA)	No enhanced growth delay (similar to RT)	

α, anti; APC, antigen-presenting cells; TIL, tumor-infiltrating lymphocytes; MHC, major histocompatibility complex; Treg, regulatory T cells; VCAM-1, vascular cell adhesion molecule-1; PD-1, programmed death-1; PD-L1, PD-ligand 1.

et al. showed that resistance in patients against hypofractionated SBRT combined with anti-CTLA4 was caused by the upregulation of PD-L1. Mimicking this in a mouse model, the resistance could be overcome by combining CTLA-4 and PD-L1 blockade with radiation, thus confirming and exploiting that the two immune checkpoints are non-redundant (110).

An overview of preclinical studies on immune effects in irradiated tumors is given in **Table 1**. Overall, dose fractions larger than 7–8 Gy seem to be more efficient in eliciting an inflammatory response and immune effects in irradiated tumors (67, 69, 103, 109). In many systems, tumor-infiltrating lymphocytes are increased after irradiation and an increase in the $CD8^+$/Treg ratio seems to be associated with a successful immune reaction in some systems (103, 109, 110), although this is not universally found and MDSC reduction in tumors also seems to play a role (57, 110, 111).

The question whether high single doses or hypofractionated irradiation with large fraction sizes is more efficient may depend on the tumor system, the role of antigen presentation by MHC class II, and the immune checkpoint being targeted.

RADIATION-INDUCED ABSCOPAL EFFECTS

Sporadic cases of abscopal effects of radiotherapy were first described in clinical case reports (112–114), but meanwhile, this rare phenomenon is well documented although in some cases it may be associated (or to some extent overlap) with spontaneous regression [reviewed in Ref. (115)]. Experimentally, a non-specific abscopal effect on unirradiated distant tumors (Lewis

lung carcinoma or T241 fibrosarcoma) was found by irradiating a non-tumor-bearing leg of mice with five fractions of 10 Gy each, whereas a lower dose of 12 × 2 Gy normo-fractionated irradiation was less effective (116). Interestingly, this effect was dependent on wild-type p53 function in the host animal cells. Irradiation and a special form of immunotherapy prevented distant metastases in the lung when primary tumors of a melanoma B16 line over-expressing CC chemokine receptor-7, or the breast cancer cell line 4T1, were irradiated with 2 × 12 Gy followed by adenoviral transduction with LIGHT, a TNF superfamily member, which enhances host immune responses (69). However, the systemic potential of radiation was much clearer when DC were stimulated by a growth factor or an ICB antibody was added (26, 105, 117). An early study achieved 60% long-term survival in a metastatic Lewis lung tumor model by irradiating the primary tumor with a single, very high dose of 60 Gy combined with the DC growth factor Flt-3 ligand (Ftl3-L) given for 10 days beginning 1 day after irradiation (117). Significant growth retardation was also obtained in a mammary tumor model after irradiation of one of the two tumors with a moderate dose of only 2 Gy combined with Flt3-L (26). In metastatic mammary tumors, the number of lung metastases was reduced in a $CD8^+$-dependent fashion after 12 Gy followed by CTLA-4 blockade (104). Another study compared different fractionation schemes in combination with CTLA-4 blockade in irradiated primary and unirradiated secondary tumors (105). The growth delay in secondary tumors was larger for 3 × 8 Gy, intermediate for 5 × 6 Gy, and smallest for 1 × 20 Gy. For 3 × 8 Gy, delaying the CTLA-4 antibody until 4 days after the first fraction (2 days after the last fraction) reduced the abscopal effect. The alternative approach of combining radiation with a PD-L1 checkpoint inhibitor was tested using two mouse mammary tumors irradiated with single doses of 12 or 20 Gy combined with anti-PD-L1 every third day on days 0–9 (57). After regression of the primary tumor, rechallenge did not result in tumor growth, and furthermore, an abscopal effect on growth delay was seen in unirradiated secondary tumors. Similarly, blocking PD-1 at the time of irradiation showed abscopal effects on the growth of unirradiated secondary tumors (melanoma and renal cell carcinoma) when the primary tumors were irradiated with single fractions of 15 Gy (118). A recent study reported an anti-metastatic effect of radiation and anti-PD-L1 after *ex vivo* irradiation of tumor cells with 12 Gy but because no primary tumor was irradiated,

TABLE 2 | Preclinical results on abscopal immune effects (growth of non-irradiated secondary tumors) induced by irradiation elsewhere.

Reference	Irradiation	Immunotherapy		Irrad. tumor/abscopal	Abscopal endpoint/effect/comment	
	No. fx, d/fx	Type	Start	(Irrad. prim./unirrad. second.)	Non-irradiated tumor	
Camphausen et al. (116)	5 × 10 Gy	None	n.a.	Normal tissue/Lewis lung carc.	Growth delay	p53 dependent (host)
Lee et al. (69)	2 × 12 Gy	ad-LIGHT (transduct.)	0 days	Melanoma (B16-CC chemokine receptor-7)/n.a.	Metastases	1×10^5 cells inj.
	2 × 12 Gy	ad-LIGHT (transduct.)	0 days	Breast ca. (4T1)/n.a.	Metastases	1×10^5 cells inj.
Chakravarty et al. (117)	1 × 60 Gy	Flt3-L	1 day after	Lewis lung carc./metastases	Survival due to Tc dependent effect on metastases	
Demaria et al. (26)	1 × 6 Gy	Flt3-L	1 day after	Breast ca. (67NR/67NR)	Growth delay	
	1 × 2 Gy	Flt3-L	1 day after	Breast ca. (67NR/67NR)	Growth delay	T-cell dependent, tumor-specific
Demaria et al. (104)	1 × 12 Gy	α-CTLA-4	1 day after	Breast ca. (4T1/4T1)	Lung metastases reduced, $CD8^+$ dependent	
Dewan et al. (105)	1 × 20 Gy	α-CTLA-4	0 days	Breast ca. (TSA/TSA)	No/insignif. growth delay	
	1 × 20 Gy	α-CTLA-4	2 days after	Breast ca. (TSA/TSA)	No/insignif. growth delay	
	3 × 8 Gy	α-CTLA-4	0 days	Breast ca. (TSA/TSA)	Reduced growth delay	
	3 × 8 Gy	α-CTLA-4	2 days after	Breast ca. (TSA/TSA)	Growth delay	
	3 × 8 Gy	α-CTLA-4	4 days after	Breast ca. (TSA/TSA)	More reduced growth delay	
	5 × 6 Gy	α-CTLA-4	2 days after	Breast ca. (TSA/TSA)	Intermediate growth delay	
	1 × 20 Gy	α-CTLA-4	2 days after	Colon ca. (MCA38/MCA38)	Non-signif. growth delay	
	3 × 8 Gy	α-CTLA-4	2 days after	Colon ca. (MCA38/MCA38)	Growth delay	
Yoshimoto et al. (70)	1 × 30 Gy	None	n.a.	Lymphoma (EL4/EL4)	No growth of second inoculation	
	1 × 30 Gy	None	n.a.	Lymphoma (EL4/EL4)	Growth delay of secondary tumor	
Twyman-Saint Victor et al. (110)	1 × 20 Gy	α-CTLA-4	3 days before	Melanoma (B16-F10/B16-F10)	Local control	
Deng et al. (111)	1 × 20 Gy	α-PD-L1	1 day before	Breast ca. (TUBO/TUBO)	Tumor rechallenge	
	1 × 12 Gy	α-PD-L1	1 day before	Breast ca. (TUBO/TUBO)	Growth delay of secondary tumor	
Park et al. (118)	1 × 15 Gy	None	1 day before	Melanoma (B16-OVA/B16-OVA)	Growth delay of secondary tumor; $CD8^+$ dependent	
	1 × 15 Gy	α-PD-1	1 day before	Melanoma (B16-OVA/B16-OVA)	Growth delay of secondary tumor	
	1 × 15 Gy	α-PD-1	1 day before	Renal cell ca. (RENCA/RENCA)	Local control of secondary tumor, tumor specific	

α, *anti; PD-1, programmed death-1; PD-L1, PD-ligand 1*

this experimental design detected tumor take and not an abscopal effect (109). An overview of preclinical studies on abscopal effects of irradiation is given in **Table 2**.

Most studies found that immune effects of RT alone or in combination with ICB were dependent on $CD8^+$ T cells (57, 69, 70, 94, 104, 106, 108). However, there is also evidence on an influence of NK cell (106, 108), though this has been less often tested and was not found in an earlier study (69). The role of $CD4^+$ T cells is more ambiguous with little or even a negative influence in most studies (104, 106, 108), while an important role was reported in a glioma model (119). This variation may be explained by the fact that $CD4^+$ represents not only tumor-reactive Th cells but also Treg cells. Since the latter constitutes a significant but variable fraction, the stimulating effect of Th and the inhibitory effect of Treg may frequently cancel each other. Although PD-L1 may enhance Treg, their number was not affected in the mammary tumors (57). Instead irradiation combined with anti-PD-L1 treatment was found to confer a delayed decrease in immunosuppressive MDSC mediated by TNF secreted by infiltrating Tc cells (57). Similarly, no change in the $CD8^+$/Treg ratio but a late decrease in myeloid cell numbers was observed in PDAC tumors after irradiation with a single dose of 12 Gy combined with PD-L1 blockade (109).

In accordance with the stimulating effect of Flt3-L on antigen presentation and the effect of CTLA-4 inhibition on Tc activation and Treg downregulation, these agents were effective when applied concurrently with and immediately after irradiation though full abscopal effects were only manifested several weeks later. Since blocking the PD-1/PD-L1 checkpoint is considered to prevent the exhaustion of cytotoxic Tc lymphocytes infiltrating the tumor in the efferent phase, one might expect a synergistic effect by applying radiation and anti-PD-1/PD-L1 antibody sequentially. However, delaying the beginning of PD-L1 blockade until 6 days after irradiation abrogated the synergistic immune effect on irradiated tumors (109). Since four anti-PD-L1 treatments were given in 10 days, this seems to imply that irradiation acts on the tumor microenvironment *before* modulation by ICB, while ICB acts on the inflammatory microenvironment *induced* by irradiation. This suggests that although the PD-L1/PD-1 checkpoint is considered to be effective mainly in the efferent pathway of the adaptive immune response (120), it may be more important in the afferent pathway (activation and antigen presentation) after irradiation than previously thought. If this finding is confirmed in other systems, it would provide a strong argument for starting ICB immediately after irradiation (which is supported by initial clinical data, see below).

The success of ICB antibodies in preclinical and early clinical trials has prompted a large number of clinical trials applying different ICB antibodies with radiotherapy in different schedules and tumor sites [reviewed in Ref. (121)].

TABLE 3 | Outcomes of combined application of stereotactic radiosurgery (SRS), and ipilimumab (IPI) in melanoma brain metastases (BM), whole-brain radiotherapy (WBRT).

Reference	Number of patients	Median OS	*P*
Knisely et al. (30)	50 (controls: SRS)	4.9 months	0.044
	27 (+IPI)	21.3 months	
	11 IPI before SRS	19.8 months	0.58
	16 IPI after SRS	21.3 months	
Silk et al. (31)	37 (controls: WBRT or SRS)	5.3 months	0.005
	33 (+IPI)	18.3 months	
	IPI before WBRT or SRS	8.1 months	n.a.
	IPI after WBRT or SRS	18.4 months	
Mathew et al. (129)	33 (controls: SRS)	45% 6-month OS	0.18
	25 (+IPI) before, concurrent, or after SRS	56% 6-month OS	
Shoukat et al. (130)	179 (controls: SRS)	6.8 months	<0.001
	38 (+IPI)	28.3 months	
Patel et al. (33)	34 (controls: SRS)	39% 1-year OS	0.84
	20 (+IPI)	37% 1-year OS	
	7 (+IPI) ≤ 15 days after SRS	43% 1-year OS	0.64
	13 (+IPI) > 15 days after SRS	34% 1-year OS	
	No IPI (SRS only)	39% 1-year OS	
Tazi et al. (32)	21 (no BM) IPI only (no SRS)	33.1 months	0.90
	10 (BM, SRS) +IPI concurrent or after SRS	29.3 months	
Kiess et al. (131)	IPI ≥ 9 weeks		
	15 IPI peri-/concurr. w. SRS (SRS during IPI)	65% 1-year OS	0.008
	12 IPI compl. before SRS (SRS > 1 month after IPI)	40% 1-year OS	
	19 IPI ≥ 1 day after SRS (SRS before IPI)	56% 1-year OS	

COMBINING SRS WITH IMMUNE THERAPY FOR BM

With the discovery of a lymphatic vessel system in the CNS (122), and the knowledge that antigen presentation to T cells occurs in the (deep) cervical lymph nodes (123), it is becoming clear that the immune system of the brain communicates with its systemic counterpart (124). In fact the traditional concept of CNS immune privilege no longer seems appropriate (124, 125). Microglial cells representing CNS innate immune cells perform many functions similar to macrophages, including recognition of DAMP, while DC appear to be important for antigen presentation in the cervical lymph nodes (125). Thus, the general model of immune response and immunosuppression also applies to tumors located in the brain (126).

A series of articles by Lim and colleagues examined the interaction between stereotactic irradiation with a single dose of 10 Gy and different ICB antibodies in an intracranial glioma model using a small-animal irradiator. Anti-PD-1 antibody given three times in 4 days beginning the day of irradiation produced significant survival at 3 months in approximately 28% of the animals (127). Challenging the survivors with glioma cells in the flank demonstrated adaptive immune memory. Triple treatment with a CD137 agonist, an anti-CTLA-4 antibody, and radiation resulted in 50% long-term survival (119). Omitting the CD137 agonist yielded approximately 20% survival for concurrent treatment starting before or on the day of irradiation but only 10% when CTLA-4 inhibition was started 2 days after irradiation. Survivors after triple treatment also produced

a memory response. A different triple treatment combining anti-TIM-3 and anti-PD-1 ICB antibodies with irradiation achieved 60% survival (128).

These preclinical data are in line with a number of clinical studies that suggested considerably improved overall survival rates by adding the antibody ipilimumab (IPI, anti-CTLA-4) to SRS (30–33, 129–131) (**Table 3**). In two of the studies, a median number of two BM was present (32, 131), but generally the number and size of metastases varied over a wide range. In some of the studies, information on prescription dose and fractionation was missing or incomplete but the treatment of individual BM with a single fraction of 20–21 Gy (median dose) appeared to be common (129, 131). However, doses and the number of fractions to individual BM varied: 14–24 Gy and 1–5 fractions (31), 15–20 Gy (129), 15–24 Gy in a single fraction (131), or 15–21 Gy with 16/20 patients receiving a single fraction and 3–5 fractions given to the last four (33). These early studies used retrospective or prospective series of patients, the sequence of IPI and SRS varied greatly, which may have contribute to the variable outcome, and frequently little detail was given regarding timing. Thus, clearly prospective studies with defined protocols are needed. Nevertheless, some of the studies seem to support the preclinical results that this ICB antibody shows better efficacy when given concurrently or immediately after SRS compared to delayed treatment although differences may exist between the irradiated metastases and abscopal effects on out-of-field disease (31, 33, 129, 131). However, although one trial included four patients who underwent prior resection of metastases before SRS to the cavity plus IPI (131), none have *a priori* addressed therapy of a purely resected population. Combining SRS with an anti-PD-1 antibody (nivolumab) has only been described in a single study on 73 lesions in 26 patients with median 9.4 months follow-up (132), including patients with resected lesions. Overall, local control (82% at 12 months) was comparable to conventional treatments, while distant control (53%) was higher than for other treatments. Interestingly, seven patients with resected BM appeared to have superior overall survival with five patients surviving after 24 months.

BIOLOGICAL EFFECTS OF IORT

Although the application of radiotherapy during surgery to inactivate any malignant cells remaining after tumor excision is not a new concept, IORT has only become a practical option during the last decade owing to the development of novel, dedicated machines. Thus, mobile linear accelerators producing high-energy electrons, or miniature X-ray machines emitting LEX allow irradiation of the tumor bed in the operating room with minimal radiation protection issues directly after the tumor has been removed (133–135). Different dose distributions can be achieved using special applicators in combination with the type and energy of the beam (136–138). However, IORT differs from conventional adjuvant RT in several aspects that may potentially influence the biological effect [reviewed in Ref. (20, 21)].

Intraoperative radiotherapy is given as a single fraction during surgery, whereas fractionated RT has been the established procedure for decades, applying daily fractions of typically 1.8–2.0 Gy. Thus, IORT eliminates the time of some weeks required for wound healing between surgery and the beginning of RT during which residual cancer stem cells may proliferate and increase the number of recurrence-forming cells that need to be inactivated, or possibly spread by migration out of the tumor bed and thus escape focused SRS (139). SRS represents an intermediate between the two since it is usually applied as a single, large-dose fraction a few weeks after surgery. When comparing the biological effects of IORT and conventionally fractionated RT, the radiation quality, distribution of dose, and dose rate must be considered. High-energy electrons show a relative biologic effectiveness (RBE) similar to that of high-energy X-rays (20) and produce a relatively uniform dose distribution at dose rates of 1–5 Gy/min. IORT with LEX involves increased RBE values, a non-uniform dose distribution with a steep radial dose gradient, and protracted irradiation with reduced dose rates allowing the repair of sublethal damage during irradiation. The biological implications of these characteristics have been studied by radiobiological modeling and experimental measurements (140–142). Adverse reactions of the normal, healthy tissue are limited to a small volume around the applicator, while the risk of recurrence is predicted to be similar to that of conventional external beam radiotherapy within a spherical shell, the "sphere of equivalence," thus defining a new target volume for tumor bed irradiation with LEX (140–145).

POTENTIAL OF COMBINING IORT WITH IMMUNE THERAPY FOR BM

The treatment of solitary BM by excision and IORT in 23 patients using 50 kV X-rays at a dose of 14 Gy in 2 mm depth yielded a disease-specific outcome at 5-year follow-up that was comparable to other modalities (18). In a large retrospective study from the same institution, localized RT versus WBRT alone or in combination was compared in 212 patients including 37 patients treated with SRS only and 19 patients treated with IORT only (146). The results indicated a slightly higher local recurrence rate for SRS/IORT, though this was not significant ($P = 0.27$). Rates of distant intracranial recurrences were higher than for local recurrences in both groups (WBRT and SRS/IORT) and were significantly higher after SRS/IORT compared with WBRT ($P < 0.001$). In spite of this, overall survival was comparable in the two groups and perhaps even marginally higher for SRS/IORT ($P = 0.27$). These results emphasize that distant recurrence is an issue when treating single lesions, especially with adjuvant localized RT although it may not directly affect overall survival.

At present, no studies combining IORT with ICB have been published. However, IORT differs from single fraction SRS by eliminating the delay between tumor excision and postoperative SRS. Thus, residual tumor cells are irradiated before they can be stimulated by factors released during the wound-healing process. Another important aspect is that the primary tumor is not irradiated but only the tumor bed, consisting mainly of normal brain tissue with an unknown, presumably low number of residual tumor cells. This poses the question whether the radiation-induced immune activity will suffice to elicit a tumor-directed immune response on which an interaction with ICB may

be based. In the following, key points relevant to the potential use of ICB in combination with IORT for BM are discussed.

(1) *Safety and efficacy of IORT in BM*: a variety of reports have demonstrated that IORT is safe and efficient in primary [reviewed in Ref. (17)] and secondary brain tumors (18, 147, 148). The study from the Cleveland Clinic mentioned earlier yielded local control rates after surgery plus IORT similar to other modalities, despite including heavily pre-treated (SRS) recurrent BM (18). Of note, almost 60% of the patients died from extracranial progression. IORT as primary treatment after surgery would have the biological advantage of eliminating repopulation by remaining tumor cells during the delay between surgery and irradiation required for wound healing before SRS can be given. Based on the study on SRS plus nivolumab, in which neurotoxicity was mostly limited and could be relieved by treatment with steroids (132), combining IORT with anti-PD-1 is expected to be well tolerated.

(2) *Immunogenicity after resection of the tumor*: in contrast with most of the previous studies combining ICB with tumor irradiation, IORT is applied after the bulk of the tumor mass has been removed surgically. Therefore, only few tumor cells are expected to remain in the tumor bed after excision of the brain metastasis, raising the question whether the tumor load is sufficient to induce a tumor-directed immune response after irradiation. Since at least half of the patients will suffer local recurrence after surgery without adjuvant radiotherapy (1), tumor cells will be present in sufficient numbers to give rise to recurrence in these patients. Furthermore, antigens from the metastasis may already be presented to T cells by DC in the lymph nodes at the time of surgery. In addition, micrometastases elsewhere in the brain may contribute to an underlying endogenous immune response. The study on SRS plus nivolumab mentioned earlier showed an extended survival of 5/7 patients with resected metastases, whereas only 3/19 patients without resection were alive at 24 months

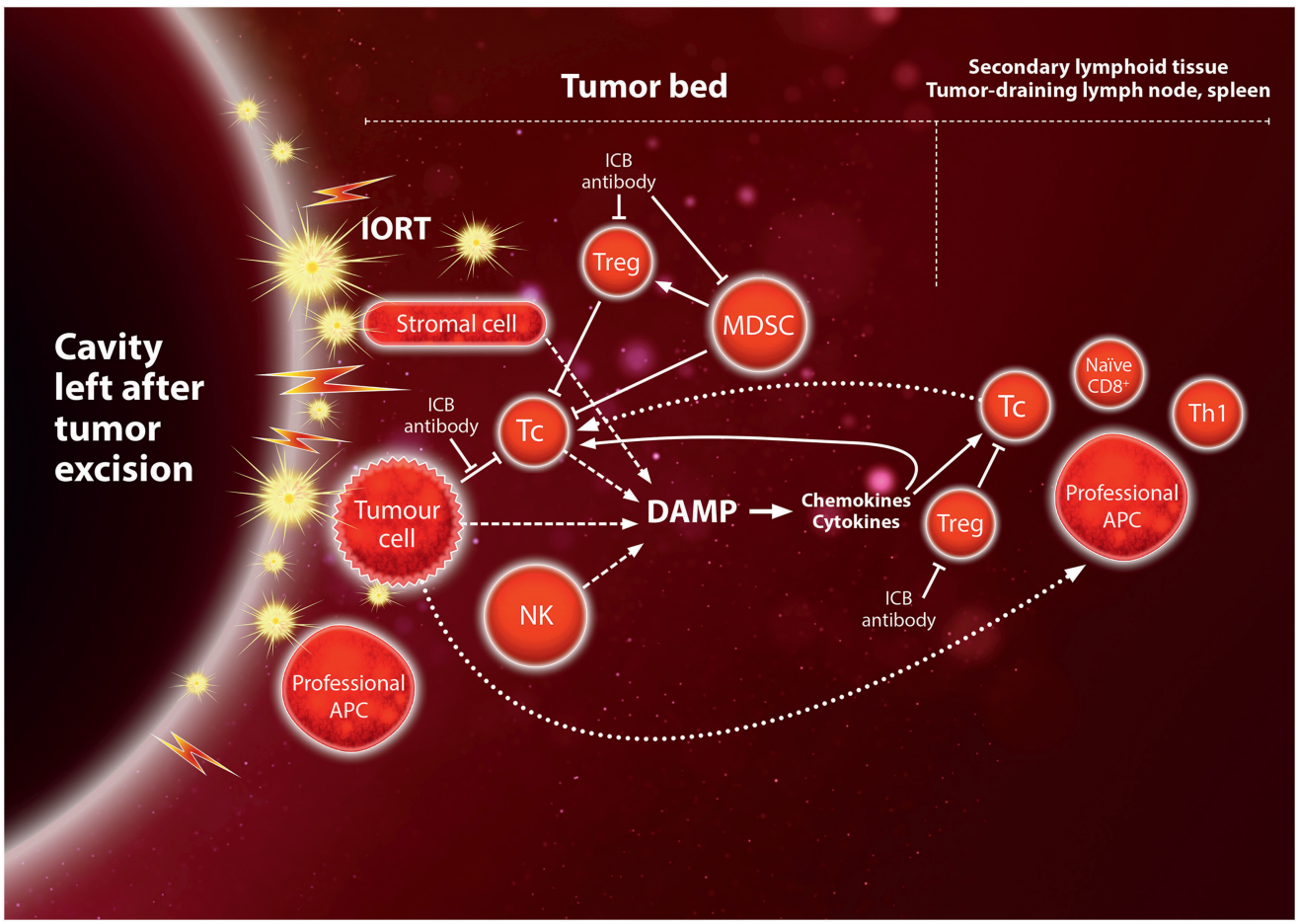

FIGURE 3 | Hypothetical immune activation by IORT to the tumor bed after tumor excision of the metastasis. Irradiation of the normal tissue induces inflammatory "danger" signals, damage-associated molecular pattern (DAMP), leading to expression of chemokines and cytokines which recruit immune cells to the tumor bed (see also **Figure 1**), and may thus act as an adjuvant for the tumor-directed immune response. Cytotoxic Tc cells may target tumor cells as a result of being activated by antigen-presenting cell (APC) presenting tumor-specific or tumor-associated antigens before surgical excision. Immunogenic cell death of residual tumor cells in the tumor bed may contribute to antigen presentation and further inflammatory signals, creating a positive feedback loop. This would provide opportunities for synergy with immune checkpoint blockade (ICB) in the tumor bed or the secondary lymphoid tissue (see also **Figure 2**).

(132). This strongly supports that irradiation of the resected cavity is indeed capable of eliciting an antitumor immune response and furthermore suggests that the tumor cell load may be an important factor in controlling residual disease. Further support that irradiation of normal tissue may play a role as an adjuvant in this response comes from the abscopal anti-tumor effect seen after irradiation of an unaffected leg with large fraction sizes (116). As discussed in the previous sections, preclinical studies indicate that the inflammatory microenvironment induced by high-dose irradiation may play an important role in enabling a tumor-directed immune response. Thus, while most irradiated lymphocytes in the tumor bed will undergo apoptosis after IORT, DAMP signals produced by irradiated immune cells and stromal cells, and cells damaged by the surgical procedure, may start a cascade of chemokines and cytokines that will attract and activate cells of the innate and adaptive immune systems. This will renew the lost lymphocyte population, which in turn may attack remaining tumor cells, thereby releasing more antigens and DAMP molecules.

(3) *Synergy between IORT and immunotherapy*: ICB antibodies in lymph nodes and the tumor bed – and to some extent irradiation itself – reduce the number and activity of immunosuppressive cells such as Treg and MDSC, thereby allowing a pre-existing antitumor immune response to become active. Thus, combining ICB antibodies with IORT is likely to enhance such a response. In this case, it is important to avoid irradiating (or exposing) the tumor-draining, deep cervical nodes, where antigen presentation to T cells may occur at the time of surgery since T cells are prone to undergo apoptosis even at moderate doses in the range 1–2 Gy. If breaking the immunosuppression is successful, an enhanced immune response to residual tumor cells may release more tumor antigens creating a positive feedback to reinforce the response (**Figure 3**). With development of a memory response, there may be a real chance for ICB in combination with IORT to establish a manifest abscopal immune response against microscopic disease elsewhere in the brain. Based on the majority of preclinical and clinical studies, it is likely that a single dose of at least 8 Gy high-energy photons (equivalent to approximately 6 Gy of LEX) will produce an immunogenic response and that ICB should be started simultaneously with irradiation. With 50 kV X-rays, such doses are feasible up to 8–10 mm from the surface of a spherical applicator. In the study on SRS plus nivolumab, the majority of patients received a single dose of 21–24 Gy SRS, although doses for patients with resected tumors were not specified. For IORT with 50 kV X-rays, doses in the range 14–20 Gy of 50 kV X-rays are achieved at 0–2 mm depth, corresponding to 18–27 Gy of high-energy X-rays when the higher RBE of 50 kV X-rays is taken into account [assuming RBE ~1.35 (142)].

(4) *Sequence of IORT and immunotherapy*: although to date, no systematic assessment on the sequence of application was performed, initial data point toward better outcome after concurrent application of SRS and immunotherapy. An analysis of 46 patients that received different schedules detected a trend toward better local control in patients receiving IPI during SRS (0% 1-year local recurrence) than in those receiving SRS before (13%) or after (11%) the administration of IPI (131). Similar data were shown in a retrospective analysis of 75 patients receiving SRS and anti-CTLA-4 or anti-PD-therapy: the study found that lesion responses were greater and more rapid with concurrent administration of immunotherapy and SRS (149). Translated into the setting of IORT, this would require administration of immunotherapy at the same day of surgery, provided that surgery is not complicated by the administration of the substances.

(5) *Safety of concurrent immunotherapy and surgery*: as concurrent application of immunotherapy and surgery appears to be required to achieve maximum therapeutic efficacy, safety is a major concern. Although not prospectively assessed, we believe that at least for the anti-CTLA4 antibody IPI and the anti-PD-1 antibody nivolumab, these concerns can be dispelled. Gyorki et al. analyzed 34 operations on 23 patients treated with IPI (150). Beside some grade 1 or 2 wound complications (22%), no grade 3–5 complications were seen. In line with this, a systematic review from Baker et al. also detected no IPI-related surgical complications so far (151). Similarly, neoadjuvant administration of nivolumab 2 or 4 weeks prior to surgery was seen to be safe and feasible in operable NSCLC (Forde et al. ESMO 2016, NCT02259621).

CONCLUSION

Brain metastases have a high likelihood of local recurrence after resection, but at present, there is no standard radiotherapy technique to boost the surgical cavity. Thus, SRS to a narrow high-dose volume (e.g., by focusing different beam angles and/or by modulating the beam intensities) with Gammaknife or Cyberknife, or a linear accelerator are being used. An intraoperative boost of IORT appears a promising alternative, which does not require irradiating large volumes of healthy tissues or organs and which would eliminate the time required for wound healing (typically 2–4 weeks) before SRS is initiated. For both modalities, high single doses may elicit immunological effects that can reach beyond the tumor bed. A review of the mechanisms of radiation-induced immune reactions supports a model in which doses >~8 Gy may act as an adjuvant for antitumor immune reactions present before irradiation or enhanced by the release of tumor antigens from irradiated residual cancer cells in the tumor bed and possibly by immunogenic cancer cell death elsewhere. The efficacy of an immune response is supported by retrospective studies on SRS for (mainly) unresected BM combined with ICB antibodies (mostly IPI), suggesting that the antibody must be present at the time of and immediately after irradiation. Recent data on a small number of patients with resected BM indicate that SRS in combination with ICB antibodies, and in particular anti-PD-1, might increase overall survival in these patients, thus supporting the rationale for combining IORT with ICB for resected BM. Since IORT limits the dose to a small volume of normal brain tissue, one might even hypothesize that this approach would not preclude adding SRS in the case of oligometastases. Although these effects need to be more comprehensively

understood, a combination therapy of very large dose fractions with ICB antibodies appears to be specifically synergistic, warranting further prospective clinical evaluation.

AUTHOR CONTRIBUTIONS

CH performed the literature search, wrote the manuscript, and drafted the figures. FW included clinical aspects and suggested literature. FG performed the clinical literature search and wrote the manuscript. All authors conceived of the aim of the review and read the final manuscript.

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REFERENCES

1. Kocher M, Soffietti R, Abacioglu U, Villa S, Fauchon F, Baumert BG, et al. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. *J Clin Oncol* (2011) 29(2):134–41. doi:10.1200/JCO.2010.30.1655
2. Brown PD, Jaeckle K, Ballman KV, Farace E, Cerhan JH, Anderson SK, et al. Effect of radiosurgery alone vs radiosurgery with whole brain radiation therapy on cognitive function in patients with 1 to 3 brain metastases: a randomized clinical trial. *JAMA* (2016) 316(4):401–9. doi:10.1001/jama.2016.9839
3. Sahgal A, Aoyama H, Kocher M, Neupane B, Collette S, Tago M, et al. Phase 3 trials of stereotactic radiosurgery with or without whole-brain radiation therapy for 1 to 4 brain metastases: individual patient data meta-analysis. *Int J Radiat Oncol Biol Phys* (2015) 91(4):710–7. doi:10.1016/j.ijrobp.2014.10.024
4. Karlovits BJ, Quigley MR, Karlovits SM, Miller L, Johnson M, Gayou O, et al. Stereotactic radiosurgery boost to the resection bed for oligometastatic brain disease: challenging the tradition of adjuvant whole-brain radiotherapy. *Neurosurg Focus* (2009) 27(6):E7. doi:10.3171/2009.9.FOCUS09191
5. Roberge D, Souhami L. Tumor bed radiosurgery following resection of brain metastases: a review. *Technol Cancer Res Treat* (2010) 9(6):597–602. doi:10.1177/153303461000900608
6. Tsao MN, Rades D, Wirth A, Lo SS, Danielson BL, Gaspar LE, et al. Radiotherapeutic and surgical management for newly diagnosed brain metastasis(es): an American Society for Radiation Oncology evidence-based guideline. *Pract Radiat Oncol* (2012) 2(3):210–25. doi:10.1016/j.prro.2011.12.004
7. Mathieu D, Kondziolka D, Flickinger JC, Fortin D, Kenny B, Michaud K, et al. Tumor bed radiosurgery after resection of cerebral metastases. *Neurosurgery* (2008) 62(4):817–23. doi:10.1227/01.neu.0000316899.55501.8b
8. Brennan C, Yang TJ, Hilden P, Zhang Z, Chan K, Yamada Y, et al. A phase 2 trial of stereotactic radiosurgery boost after surgical resection for brain metastases. *Int J Radiat Oncol Biol Phys* (2014) 88(1):130–6. doi:10.1016/j.ijrobp.2013.09.051
9. Fujiwara T, Honma Y, Ogawa T, Irie K, Kuyama H, Nagao S, et al. Intraoperative radiotherapy for gliomas. *J Neurooncol* (1995) 23(1):81–6. doi:10.1007/BF01058463
10. Matsutani M, Nakamura O, Nagashima T, Asai A, Fujimaki T, Tanaka H, et al. Intra-operative radiation therapy for malignant brain tumors: rationale, method, and treatment results of cerebral glioblastomas. *Acta Neurochir (Wien)* (1994) 131(1–2):80–90. doi:10.1007/BF01401457
11. Nemoto K, Ogawa Y, Matsushita H, Takeda K, Takai Y, Yamada S, et al. Intraoperative radiation therapy (IORT) for previously untreated malignant gliomas. *BMC Cancer* (2002) 2:1. doi:10.1186/1471-2407-2-1
12. Sakai N, Yamada H, Andoh T, Hirata T, Nishimura Y, Miwa Y, et al. Intraoperative radiation therapy for malignant glioma. *Neurol Med Chir (Tokyo)* (1991) 31(11):702–7. doi:10.2176/nmc.31.702
13. Schueller P, Micke O, Palkovic S, Schroeder J, Moustakis C, Bruns F, et al. 12 years' experience with intraoperative radiotherapy (IORT) of malignant gliomas. *Strahlenther Onkol* (2005) 181(8):500–6. doi:10.1007/s00066-005-1354-2
14. Schueller P, Palkovic S, Moustakis C, Kónemann S, Wassmann H, Willich N. Clinical results and isodose planning of neuronavigation-guided intraoperative radiotherapy (IORT) in 77 brain tumor patients: adequate target volume coverage improve results. *Rev Cancer (Madrid)* (2008) 22(extra):1–58.
15. Schueller P, Schroeder J, Micke O, Moustakis C, Willich N. 9 years tumor free survival after resection, intraoperative radiotherapy (IORT) and whole brain radiotherapy of a solitary brain metastasis of non-small cell lung cancer. *Acta Oncol* (2006) 45(2):224–5. doi:10.1080/02841860500374505
16. Giordano FA, Brehmer S, Mürle B, Welzel G, Sperk E, Keller A, et al. RTHP-05. Intraoperative radiotherapy (IORT) using low-energy X-rays in a cohort of predominantly incompletely resected newly diagnosed glioblastoma multiforme (intrago trial). *Neuro Oncol* (2016) 18(Suppl_6):vi 174–5. doi:10.1093/neuonc/now212.731
17. Giordano FA, Wenz F, Petrecca K. Rationale for intraoperative radiotherapy in glioblastoma. *J Neurosurg Sci* (2016) 60(3):350–6.
18. Weil RJ, Mavinkurve GG, Chao ST, Vogelbaum MA, Suh JH, Kolar M, et al. Intraoperative radiotherapy to treat newly diagnosed solitary brain metastasis: initial experience and long-term outcomes. *J Neurosurg* (2015) 122(4):825–32. doi:10.3171/2014.11.JNS1449
19. Brown JM, Koong AC. High-dose single-fraction radiotherapy: exploiting a new biology? *Int J Radiat Oncol Biol Phys* (2008) 71(2):324–5. doi:10.1016/j.ijrobp.2008.02.003
20. Herskind C, Ma L, Liu Q, Zhang B, Schneider F, Veldwijk MR, et al. Biology of high single doses of IORT: RBE, 5 R's, and other biological aspects. *Radiat Oncol* (2017) 12(1):24. doi:10.1186/s13014-016-0750-3
21. Herskind C, Wenz F. Radiobiological aspects of intraoperative tumour-bed irradiation with low-energy X-rays (LEX-IORT). *Transl Cancer Res* (2014) 3(1):3–17. doi:10.3978/j.issn.2218-676X.2014.01.06
22. Veldwijk MR, Zhang B, Wenz F, Herskind C. The biological effect of large single doses: a possible role for non-targeted effects in cell inactivation. *PLoS One* (2014) 9(1):e84991. doi:10.1371/journal.pone.0084991
23. Brown JM, Carlson DJ, Brenner DJ. The tumor radiobiology of SRS and SBRT: are more than the 5 Rs involved? *Int J Radiat Oncol Biol Phys* (2014) 88(2):254–62. doi:10.1016/j.ijrobp.2013.07.022
24. Demaria S, Formenti SC. Radiation as an immunological adjuvant: current evidence on dose and fractionation. *Front Oncol* (2012) 2:153. doi:10.3389/fonc.2012.00153
25. Margolin K, Ernstoff MS, Hamid O, Lawrence D, McDermott D, Puzanov I, et al. Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial. *Lancet Oncol* (2012) 13(5):459–65. doi:10.1016/S1470-2045(12)70090-6
26. Demaria S, Ng B, Devitt ML, Babb JS, Kawashima N, Liebes L, et al. Ionizing radiation inhibition of distant untreated tumors (abscopal effect) is immune mediated. *Int J Radiat Oncol Biol Phys* (2004) 58(3):862–70. doi:10.1016/j.ijrobp.2003.09.012
27. Prins RM, Vo DD, Khan-Farooqi H, Yang MY, Soto H, Economou JS, et al. NK and CD4 cells collaborate to protect against melanoma tumor formation in the brain. *J Immunol* (2006) 177(12):8448–55. doi:10.4049/jimmunol.177.12.8448
28. Cao Y, Tsien CI, Shen Z, Tatro DS, Ten Haken R, Kessler ML, et al. Use of magnetic resonance imaging to assess blood-brain/blood-glioma barrier opening during conformal radiotherapy. *J Clin Oncol* (2005) 23(18):4127–36. doi:10.1200/JCO.2005.07.144
29. Nakata H, Yoshimine T, Murasawa A, Kumura E, Harada K, Ushio Y, et al. Early blood-brain barrier disruption after high-dose single-fraction irradiation in rats. *Acta Neurochir (Wien)* (1995) 136(1–2):82–6. doi:10.1007/BF01411440

30. Knisely JP, Yu JB, Flanigan J, Sznol M, Kluger HM, Chiang VL. Radiosurgery for melanoma brain metastases in the ipilimumab era and the possibility of longer survival. *J Neurosurg* (2012) 117(2):227–33. doi:10.3171/2012.5.JNS111929
31. Silk AW, Bassetti MF, West BT, Tsien CI, Lao CD. Ipilimumab and radiation therapy for melanoma brain metastases. *Cancer Med* (2013) 2(6):899–906. doi:10.1002/cam4.140
32. Tazi K, Hathaway A, Chiuzan C, Shirai K. Survival of melanoma patients with brain metastases treated with ipilimumab and stereotactic radiosurgery. *Cancer Med* (2015) 4(1):1–6. doi:10.1002/cam4.315
33. Patel KR, Shoukat S, Oliver DE, Chowdhary M, Rizzo M, Lawson DH, et al. Ipilimumab and stereotactic radiosurgery versus stereotactic radiosurgery alone for newly diagnosed melanoma brain metastases. *Am J Clin Oncol* (2015). doi:10.1097/COC.0000000000000199
34. Gerber NK, Young RJ, Barker CA, Wolchok JD, Chan TA, Yamada Y, et al. Ipilimumab and whole brain radiation therapy for melanoma brain metastases. *J Neurooncol* (2015) 121(1):159–65. doi:10.1007/s11060-014-1617-9
35. Brandau S. The dichotomy of neutrophil granulocytes in cancer. *Semin Cancer Biol* (2013) 23(3):139–40. doi:10.1016/j.semcancer.2013.02.008
36. Farkas AM, Kilgore TM, Lotze MT. Detecting DNA: getting and begetting cancer. *Curr Opin Investig Drugs* (2007) 8(12):981–6.
37. Kroemer G, Galluzzi L, Kepp O, Zitvogel L. Immunogenic cell death in cancer therapy. *Annu Rev Immunol* (2013) 31:51–72. doi:10.1146/annurev-immunol-032712-100008
38. Raghavan M, Wijeyesakere SJ, Peters LR, Del Cid N. Calreticulin in the immune system: ins and outs. *Trends Immunol* (2013) 34(1):13–21. doi:10.1016/j.it.2012.08.002
39. Tecchio C, Micheletti A, Cassatella MA. Neutrophil-derived cytokines: facts beyond expression. *Front Immunol* (2014) 5:508. doi:10.3389/fimmu.2014.00508
40. Liu S, Feng M, Guan W. Mitochondrial DNA sensing by STING signaling participates in inflammation, cancer and beyond. *Int J Cancer* (2016) 139(4):736–41. doi:10.1002/ijc.30074
41. Fauriat C, Long EO, Ljunggren HG, Bryceson YT. Regulation of human NK-cell cytokine and chemokine production by target cell recognition. *Blood* (2010) 115(11):2167–76. doi:10.1182/blood-2009-08-238469
42. Neefjes J, Ovaa H. A peptide's perspective on antigen presentation to the immune system. *Nat Chem Biol* (2013) 9(12):769–75. doi:10.1038/nchembio.1391
43. Chao MP, Jaiswal S, Weissman-Tsukamoto R, Alizadeh AA, Gentles AJ, Volkmer J, et al. Calreticulin is the dominant pro-phagocytic signal on multiple human cancers and is counterbalanced by CD47. *Sci Transl Med* (2010) 2(63):63ra94. doi:10.1126/scitranslmed.3001375
44. Peters LR, Raghavan M. Endoplasmic reticulum calcium depletion impacts chaperone secretion, innate immunity, and phagocytic uptake of cells. *J Immunol* (2011) 187(2):919–31. doi:10.4049/jimmunol.1100690
45. Demaria S, Bhardwaj N, McBride WH, Formenti SC. Combining radiotherapy and immunotherapy: a revived partnership. *Int J Radiat Oncol Biol Phys* (2005) 63(3):655–66. doi:10.1016/j.ijrobp.2005.06.032
46. Yuseff MI, Pierobon P, Reversat A, Lennon-Dumenil AM. How B cells capture, process and present antigens: a crucial role for cell polarity. *Nat Rev Immunol* (2013) 13(7):475–86. doi:10.1038/nri3469
47. Crotty S. Follicular helper CD4 T cells (TFH). *Annu Rev Immunol* (2011) 29:621–63. doi:10.1146/annurev-immunol-031210-101400
48. Murphy K, Weaver C. *Janeway's Immunobiology*. 9th ed. New York and London: Garland Science (2017).
49. Weinberg RA. *The Biology of Cancer*. 2nd ed. New York and London: Garland Science (2014).
50. Schmidt A, Oberle N, Krammer PH. Molecular mechanisms of Treg-mediated T cell suppression. *Front Immunol* (2012) 3:51. doi:10.3389/fimmu.2012.00051
51. Baumeister SH, Freeman GJ, Dranoff G, Sharpe AH. Coinhibitory pathways in immunotherapy for cancer. *Annu Rev Immunol* (2016) 34:539–73. doi:10.1146/annurev-immunol-032414-112049
52. Takahashi T, Tagami T, Yamazaki S, Uede T, Shimizu J, Sakaguchi N, et al. Immunologic self-tolerance maintained by CD25(+)CD4(+) regulatory T cells constitutively expressing cytotoxic T lymphocyte-associated antigen 4. *J Exp Med* (2000) 192(2):303–10. doi:10.1084/jem.192.2.303
53. Alegre ML, Noel PJ, Eisfelder BJ, Chuang E, Clark MR, Reiner SL, et al. Regulation of surface and intracellular expression of CTLA4 on mouse T cells. *J Immunol* (1996) 157(11):4762–70.
54. Chen L, Han X. Anti-PD-1/PD-L1 therapy of human cancer: past, present, and future. *J Clin Invest* (2015) 125(9):3384–91. doi:10.1172/JCI80011
55. Wherry EJ. T cell exhaustion. *Nat Immunol* (2011) 12(6):492–9. doi:10.1038/ni.2035
56. Pardoll D. Cancer and the immune system: basic concepts and targets for intervention. *Semin Oncol* (2015) 42(4):523–38. doi:10.1053/j.seminoncol.2015.05.003
57. Deng L, Liang H, Burnette B, Beckett M, Darga T, Weichselbaum RR, et al. Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice. *J Clin Invest* (2014) 124(2):687–95. doi:10.1172/JCI67313
58. Srivastava MK, Zhu L, Harris-White M, Huang M, St John M, Lee JM, et al. Targeting myeloid-derived suppressor cells augments antitumor activity against lung cancer. *Immunotargets Ther* (2012) 2012(1):7–12. doi:10.2147/ITT.S32617
59. Platten M, Bunse L, Wick W, Bunse T. Concepts in glioma immunotherapy. *Cancer Immunol Immunother* (2016) 65(10):1269–75. doi:10.1007/s00262-016-1874-x
60. Noy R, Pollard JW. Tumor-associated macrophages: from mechanisms to therapy. *Immunity* (2014) 41(1):49–61. doi:10.1016/j.immuni.2014.06.010
61. Vatner RE, Formenti SC. Myeloid-derived cells in tumors: effects of radiation. *Semin Radiat Oncol* (2015) 25(1):18–27. doi:10.1016/j.semradonc.2014.07.008
62. Eggermont AM, Chiarion-Sileni V, Grob JJ, Dummer R, Wolchok JD, Schmidt H, et al. Prolonged survival in stage III melanoma with ipilimumab adjuvant therapy. *N Engl J Med* (2016) 375(19):1845–55. doi:10.1056/NEJMoa1611299
63. Ferris RL, Blumenschein G Jr, Fayette J, Guigay J, Colevas AD, Licitra L, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. *N Engl J Med* (2016) 375(19):1856–67. doi:10.1056/NEJMoa1602252
64. Nghiem PT, Bhatia S, Lipson EJ, Kudchadkar RR, Miller NJ, Annamalai L, et al. PD-1 blockade with pembrolizumab in advanced Merkel-cell carcinoma. *N Engl J Med* (2016) 374(26):2542–52. doi:10.1056/NEJMoa1603702
65. Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med* (2016) 375(19):1823–33. doi:10.1056/NEJMoa1606774
66. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med* (2012) 366(26):2443–54. doi:10.1056/NEJMoa1200690
67. Lugade AA, Moran JP, Gerber SA, Rose RC, Frelinger JG, Lord EM. Local radiation therapy of B16 melanoma tumors increases the generation of tumor antigen-specific effector cells that traffic to the tumor. *J Immunol* (2005) 174(12):7516–23. doi:10.4049/jimmunol.174.12.7516
68. Demaria S, Coleman CN, Formenti SC. Radiotherapy: changing the game in immunotherapy. *Trends Cancer* (2016) 2(6):286–94. doi:10.1016/j.trecan.2016.05.002
69. Lee Y, Auh SL, Wang Y, Burnette B, Meng Y, Beckett M, et al. Therapeutic effects of ablative radiation on local tumor require CD8+ T cells: changing strategies for cancer treatment. *Blood* (2009) 114(3):589–95. doi:10.1182/blood-2009-02-206870
70. Yoshimoto Y, Suzuki Y, Mimura K, Ando K, Oike T, Sato H, et al. Radiotherapy-induced anti-tumor immunity contributes to the therapeutic efficacy of irradiation and can be augmented by CTLA-4 blockade in a mouse model. *PLoS One* (2014) 9(3):e92572. doi:10.1371/journal.pone.0092572
71. Apetoh L, Ghiringhelli F, Tesniere A, Obeid M, Ortiz C, Criollo A, et al. Toll-like receptor 4-dependent contribution of the immune system to anticancer chemotherapy and radiotherapy. *Nat Med* (2007) 13(9):1050–9. doi:10.1038/nm1622
72. Golden EB, Frances D, Pellicciotta I, Demaria S, Helen Barcellos-Hoff M, Formenti SC. Radiation fosters dose-dependent and chemotherapy-induced immunogenic cell death. *Oncoimmunology* (2014) 3:e28518. doi:10.4161/onci.28518
73. Deng L, Liang H, Fu S, Weichselbaum RR, Fu YX. From DNA damage to nucleic acid sensing: a strategy to enhance radiation therapy. *Clin Cancer Res* (2016) 22(1):20–5. doi:10.1158/1078-0432.CCR-14-3110

74. Burnette BC, Liang H, Lee Y, Chlewicki L, Khodarev NN, Weichselbaum RR, et al. The efficacy of radiotherapy relies upon induction of type I interferon-dependent innate and adaptive immunity. *Cancer Res* (2011) 71(7):2488–96. doi:10.1158/0008-5472.CAN-10-2820
75. Wang L, He L, Bao G, He X, Fan S, Wang H. Ionizing radiation induces HMGB1 cytoplasmic translocation and extracellular release. *Guo Ji Fang She Yi Xue He Yi Xue Za Zhi* (2016) 40(2):91–9.
76. Hellweg CE. The nuclear factor kappaB pathway: a link to the immune system in the radiation response. *Cancer Lett* (2015) 368(2):275–89. doi:10.1016/j.canlet.2015.02.019
77. Panta GR, Kaur S, Cavin LG, Cortes ML, Mercurio F, Lothstein L, et al. ATM and the catalytic subunit of DNA-dependent protein kinase activate NF-kappaB through a common MEK/extracellular signal-regulated kinase/p90(rsk) signaling pathway in response to distinct forms of DNA damage. *Mol Cell Biol* (2004) 24(5):1823–35. doi:10.1128/MCB.24.5.1823-1835.2004
78. Wu ZH, Shi Y, Tibbetts RS, Miyamoto S. Molecular linkage between the kinase ATM and NF-kappaB signaling in response to genotoxic stimuli. *Science* (2006) 311(5764):1141–6. doi:10.1126/science.1121513
79. van Beijnum JR, Buurman WA, Griffioen AW. Convergence and amplification of toll-like receptor (TLR) and receptor for advanced glycation end products (RAGE) signaling pathways via high mobility group B1 (HMGB1). *Angiogenesis* (2008) 11(1):91–9. doi:10.1007/s10456-008-9093-5
80. Ishihara H, Tanaka I, Nemoto K, Tsuneoka K, Cheeramakara C, Yoshida K, et al. Immediate-early, transient induction of the interleukin-1 beta gene in mouse spleen macrophages by ionizing radiation. *J Radiat Res* (1995) 36(2):112–24. doi:10.1269/jrr.36.112
81. Ishihara H, Tsuneoka K, Dimchev AB, Shikita M. Induction of the expression of the interleukin-1 beta gene in mouse spleen by ionizing radiation. *Radiat Res* (1993) 133(3):321–6. doi:10.2307/3578216
82. O'Brien-Ladner A, Nelson ME, Kimler BF, Wesselius LJ. Release of interleukin-1 by human alveolar macrophages after in vitro irradiation. *Radiat Res* (1993) 136(1):37–41. doi:10.2307/3578637
83. Nemoto K, Ishihara H, Tanaka I, Suzuki G, Tsuneoka K, Yoshida K, et al. Expression of IL-1 beta mRNA in mice after whole body X-irradiation. *J Radiat Res* (1995) 36(2):125–33. doi:10.1269/jrr.36.125
84. Hong JH, Chiang CS, Campbell IL, Sun JR, Withers HR, McBride WH. Induction of acute phase gene expression by brain irradiation. *Int J Radiat Oncol Biol Phys* (1995) 33(3):619–26. doi:10.1016/0360-3016(95)00279-8
85. Hong JH, Chiang CS, Tsao CY, Lin PY, McBride WH, Wu CJ. Rapid induction of cytokine gene expression in the lung after single and fractionated doses of radiation. *Int J Radiat Biol* (1999) 75(11):1421–7. doi:10.1080/095530099139287
86. Beetz A, Messer G, Oppel T, van Beuningen D, Peter RU, Kind P. Induction of interleukin 6 by ionizing radiation in a human epithelial cell line: control by corticosteroids. *Int J Radiat Biol* (1997) 72(1):33–43. doi:10.1080/095530097143518
87. Beetz A, Peter RU, Oppel T, Kaffenberger W, Rupec RA, Meyer M, et al. NF-kappaB and AP-1 are responsible for inducibility of the IL-6 promoter by ionizing radiation in HeLa cells. *Int J Radiat Biol* (2000) 76(11):1443–53. doi:10.1080/09553000050176207
88. Chauhan V, Howland M, Wilkins R. A comparative assessment of cytokine expression in human-derived cell lines exposed to alpha particles and X-rays. *ScientificWorldJournal* (2012) 2012:609295. doi:10.1100/2012/609295
89. Di Maggio FM, Minafra L, Forte GI, Cammarata FP, Lio D, Messa C, et al. Portrait of inflammatory response to ionizing radiation treatment. *J Inflamm (Lond)* (2015) 12:14. doi:10.1186/s12950-015-0058-3
90. Cooks T, Harris CC, Oren M. Caught in the cross fire: p53 in inflammation. *Carcinogenesis* (2014) 35(8):1680–90. doi:10.1093/carcin/bgu134
91. Gudkov AV, Gurova KV, Komarova EA. Inflammation and p53: a tale of two stresses. *Genes Cancer* (2011) 2(4):503–16. doi:10.1177/1947601911409747
92. Shan YX, Jin SZ, Liu XD, Liu Y, Liu SZ. Ionizing radiation stimulates secretion of pro-inflammatory cytokines: dose-response relationship, mechanisms and implications. *Radiat Environ Biophys* (2007) 46(1):21–9. doi:10.1007/s00411-006-0076-x
93. Venereau E, Schiraldi M, Uguccioni M, Bianchi ME. HMGB1 and leukocyte migration during trauma and sterile inflammation. *Mol Immunol* (2013) 55(1):76–82. doi:10.1016/j.molimm.2012.10.037
94. Garnett CT, Palena C, Chakraborty M, Tsang KY, Schlom J, Hodge JW. Sublethal irradiation of human tumor cells modulates phenotype resulting in enhanced killing by cytotoxic T lymphocytes. *Cancer Res* (2004) 64(21):7985–94. doi:10.1158/0008-5472.CAN-04-1525
95. Reits EA, Hodge JW, Herberts CA, Groothuis TA, Chakraborty M, Wansley EK, et al. Radiation modulates the peptide repertoire, enhances MHC class I expression, and induces successful antitumor immunotherapy. *J Exp Med* (2006) 203(5):1259–71. doi:10.1084/jem.20052494
96. Lugade AA, Sorensen EW, Gerber SA, Moran JP, Frelinger JG, Lord EM. Radiation-induced IFN-gamma production within the tumor microenvironment influences antitumor immunity. *J Immunol* (2008) 180(5):3132–9. doi:10.4049/jimmunol.180.5.3132
97. Deloch L, Derer A, Hartmann J, Frey B, Fietkau R, Gaipl US. Modern radiotherapy concepts and the impact of radiation on immune activation. *Front Oncol* (2016) 6:141. doi:10.3389/fonc.2016.00141
98. Popp I, Grosu AL, Niedermann G, Duda DG. Immune modulation by hypofractionated stereotactic radiation therapy: therapeutic implications. *Radiother Oncol* (2016) 120(2):185–94. doi:10.1016/j.radonc.2016.07.013
99. Witek M, Blomain ES, Magee MS, Xiang B, Waldman SA, Snook AE. Tumor radiation therapy creates therapeutic vaccine responses to the colorectal cancer antigen GUCY2C. *Int J Radiat Oncol Biol Phys* (2014) 88(5):1188–95. doi:10.1016/j.ijrobp.2013.12.043
100. Dovedi SJ, Adlard AL, Ota Y, Murata M, Sugaru E, Koga-Yamakawa E, et al. Intravenous administration of the selective toll-like receptor 7 agonist DSR-29133 leads to anti-tumor efficacy in murine solid tumor models which can be potentiated by combination with fractionated radiotherapy. *Oncotarget* (2016) 7(13):17035–46. doi:10.18632/oncotarget.7928
101. Herskind C, Fleckenstein K, Lohr J, Li CY, Wenz F, Lohr F. [Antitumoral action of interferons and interleukins in combination with radiotherapy. Part I: immunologic basis]. *Strahlenther Onkol* (2004) 180(4):187–93. doi:10.1007/s00066-004-9119-x
102. Lohr F, Herskind C, Lohr J, Wenz F, Li C-Y. Enhancement of the radiation response with interleukins and interferons. In: Nieder C, Milas L, Ang KK, editors. *Modification of Radiation Response Cytokines, Growth Factors, and Other Biological Signals. Medical Radiology. Diagnostic Imaging and Radiation Oncology*. Berlin, Heidelberg, New York: Springer-Verlag (2003). p. 205–26.
103. Schaue D, Ratikan JA, Iwamoto KS, McBride WH. Maximizing tumor immunity with fractionated radiation. *Int J Radiat Oncol Biol Phys* (2012) 83(4):1306–10. doi:10.1016/j.ijrobp.2011.09.049
104. Demaria S, Kawashima N, Yang AM, Devitt ML, Babb JS, Allison JP, et al. Immune-mediated inhibition of metastases after treatment with local radiation and CTLA-4 blockade in a mouse model of breast cancer. *Clin Cancer Res* (2005) 11(2):728–34.
105. Dewan MZ, Galloway AE, Kawashima N, Dewyngaert JK, Babb JS, Formenti SC, et al. Fractionated but not single-dose radiotherapy induces an immune-mediated abscopal effect when combined with anti-CTLA-4 antibody. *Clin Cancer Res* (2009) 15(17):5379–88. doi:10.1158/1078-0432.CCR-09-0265
106. Verbrugge I, Hagekyriakou J, Sharp LL, Galli M, West A, McLaughlin NM, et al. Radiotherapy increases the permissiveness of established mammary tumors to rejection by immunomodulatory antibodies. *Cancer Res* (2012) 72(13):3163–74. doi:10.1158/0008-5472.CAN-12-0210
107. Sharabi AB, Nirschl CJ, Kochel CM, Nirschl TR, Francica BJ, Velarde E, et al. Stereotactic radiation therapy augments antigen-specific PD-1-mediated antitumor immune responses via cross-presentation of tumor antigen. *Cancer Immunol Res* (2015) 3(4):345–55. doi:10.1158/2326-6066.CIR-14-0196
108. Dovedi SJ, Adlard AL, Lipowska-Bhalla G, McKenna C, Jones S, Cheadle EJ, et al. Acquired resistance to fractionated radiotherapy can be overcome by concurrent PD-L1 blockade. *Cancer Res* (2014) 74(19):5458–68. doi:10.1158/0008-5472.CAN-14-1258
109. Azad A, Yin Lim S, D'Costa Z, Jones K, Diana A, Sansom OJ, et al. PD-L1 blockade enhances response of pancreatic ductal adenocarcinoma to

radiotherapy. *EMBO Mol Med* (2017) 9(2):167–80. doi:10.15252/emmm.201606674
110. Twyman-Saint Victor C, Rech AJ, Maity A, Rengan R, Pauken KE, Stelekati E, et al. Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer. *Nature* (2015) 520(7547):373–7. doi:10.1038/nature14292
111. Deng L, Liang H, Burnette B, Weichselbaum RR, Fu YX. Radiation and anti-PD-L1 antibody combinatorial therapy induces T cell-mediated depletion of myeloid-derived suppressor cells and tumor regression. *Oncoimmunology* (2014) 3:e28499. doi:10.4161/onci.28499
112. Ehlers G, Fridman M. Abscopal effect of radiation in papillary adenocarcinoma. *Br J Radiol* (1973) 46(543):220–2. doi:10.1259/0007-1285-46-543-220
113. Ohba K, Omagari K, Nakamura T, Ikuno N, Saeki S, Matsuo I, et al. Abscopal regression of hepatocellular carcinoma after radiotherapy for bone metastasis. *Gut* (1998) 43(4):575–7. doi:10.1136/gut.43.4.575
114. Robin HI, AuBuchon J, Varanasi VR, Weinstein AB. The abscopal effect: demonstration in lymphomatous involvement of kidneys. *Med Pediatr Oncol* (1981) 9(5):473–6. doi:10.1002/mpo.2950090510
115. Reynders K, Illidge T, Siva S, Chang JY, De Ruysscher D. The abscopal effect of local radiotherapy: using immunotherapy to make a rare event clinically relevant. *Cancer Treat Rev* (2015) 41(6):503–10. doi:10.1016/j.ctrv.2015.03.011
116. Camphausen K, Moses MA, Menard C, Sproull M, Beecken WD, Folkman J, et al. Radiation abscopal antitumor effect is mediated through p53. *Cancer Res* (2003) 63(8):1990–3.
117. Chakravarty PK, Alfieri A, Thomas EK, Beri V, Tanaka KE, Vikram B, et al. Flt3-ligand administration after radiation therapy prolongs survival in a murine model of metastatic lung cancer. *Cancer Res* (1999) 59(24):6028–32.
118. Park SS, Dong H, Liu X, Harrington SM, Krco CJ, Grams MP, et al. PD-1 restrains radiotherapy-induced abscopal effect. *Cancer Immunol Res* (2015) 3(6):610–9. doi:10.1158/2326-6066.CIR-14-0138
119. Belcaid Z, Phallen JA, Zeng J, See AP, Mathios D, Gottschalk C, et al. Focal radiation therapy combined with 4-1BB activation and CTLA-4 blockade yields long-term survival and a protective antigen-specific memory response in a murine glioma model. *PLoS One* (2014) 9(7):e101764. doi:10.1371/journal.pone.0101764
120. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer* (2012) 12(4):252–64. doi:10.1038/nrc3239
121. Kang J, Demaria S, Formenti S. Current clinical trials testing the combination of immunotherapy with radiotherapy. *J Immunother Cancer* (2016) 4:51. doi:10.1186/s40425-016-0156-7
122. Louveau A, Smirnov I, Keyes TJ, Eccles JD, Rouhani SJ, Peske JD, et al. Structural and functional features of central nervous system lymphatic vessels. *Nature* (2015) 523(7560):337–41. doi:10.1038/nature14432
123. Ransohoff RM, Engelhardt B. The anatomical and cellular basis of immune surveillance in the central nervous system. *Nat Rev Immunol* (2012) 12(9):623–35. doi:10.1038/nri3265
124. Louveau A, Harris TH, Kipnis J. Revisiting the mechanisms of CNS immune privilege. *Trends Immunol* (2015) 36(10):569–77. doi:10.1016/j.it.2015.08.006
125. Dunn GP, Okada H. Principles of immunology and its nuances in the central nervous system. *Neuro Oncol* (2015) 17(Suppl 7):vii 3–8. doi:10.1093/neuonc/nov175
126. Dutoit V, Migliorini D, Walker PR, Dietrich PY. Immunotherapy of brain tumors. *Prog Tumor Res* (2015) 42:11–21. doi:10.1159/000436986
127. Zeng J, See AP, Phallen J, Jackson CM, Belcaid Z, Ruzevick J, et al. Anti-PD-1 blockade and stereotactic radiation produce long-term survival in mice with intracranial gliomas. *Int J Radiat Oncol Biol Phys* (2013) 86(2):343–9. doi:10.1016/j.ijrobp.2012.12.025
128. Kim JE, Patel MA, Mangraviti A, Kim ES, Theodros D, Velarde E, et al. Combination therapy with anti-PD-1, anti-TIM-3, and focal radiation results in regression of murine gliomas. *Clin Cancer Res* (2017) 23(1):124–36. doi:10.1158/1078-0432.CCR-15-1535
129. Mathew M, Tam M, Ott PA, Pavlick AC, Rush SC, Donahue BR, et al. Ipilimumab in melanoma with limited brain metastases treated with stereotactic radiosurgery. *Melanoma Res* (2013) 23(3):191–5. doi:10.1097/CMR.0b013e32835f3d90
130. Shoukat S, Marcus DM, Rizzo M, Lawson DH, Khosa F, Liu Y, et al. Outcome with stereotactic radiosurgery (SRS) and ipilimumab (Ipi) for malignant melanoma brain metastases (mets). *J Clin Oncol* (2014) 32(15_suppl):9076. doi:10.1200/jco.2014.32.15_suppl.9076
131. Kiess AP, Wolchok JD, Barker CA, Postow MA, Tabar V, Huse JT, et al. Stereotactic radiosurgery for melanoma brain metastases in patients receiving ipilimumab: safety profile and efficacy of combined treatment. *Int J Radiat Oncol Biol Phys* (2015) 92(2):368–75. doi:10.1016/j.ijrobp.2015.01.004
132. Ahmed KA, Abuodeh YA, Echevarria MI, Arrington JA, Stallworth DG, Hogue C, et al. Clinical outcomes of melanoma brain metastases treated with stereotactic radiosurgery and anti-PD-1 therapy, anti-CTLA-4 therapy, BRAF/MEK inhibitors, BRAF inhibitor, or conventional chemotherapy. *Ann Oncol* (2016) 27(12):2288–94. doi:10.1093/annonc/mdw417
133. Calvo FA, Sole CV, Gonzalez ME, Tangco ED, Lopez-Tarjuelo J, Koubychine I, et al. Research opportunities in intraoperative radiation therapy: the next decade 2013-2023. *Clin Transl Oncol* (2013) 15(9):683–90. doi:10.1007/s12094-013-1019-z
134. Debenham BJ, Hu KS, Harrison LB. Present status and future directions of intraoperative radiotherapy. *Lancet Oncol* (2013) 14(11):e457–64. doi:10.1016/S1470-2045(13)70270-5
135. Kraus-Tiefenbacher U, Steil V, Bauer L, Melchert F, Wenz F. A novel mobile device for intraoperative radiotherapy (IORT). *Onkologie* (2003) 26(6):596–8. doi:10.1159/000074158
136. Goubert M, Parent L. Dosimetric characterization of INTRABEAM(R) miniature accelerator flat and surface applicators for dermatologic applications. *Phys Med* (2015) 31(3):224–32. doi:10.1016/j.ejmp.2015.01.009
137. Nairz O, Deutschmann H, Kopp M, Wurstbauer K, Kametriser G, Fastner G, et al. A dosimetric comparison of IORT techniques in limited-stage breast cancer. *Strahlenther Onkol* (2006) 182(6):342–8. doi:10.1007/s00066-006-1580-2
138. Schneider F, Clausen S, Tholking J, Wenz F, Abo-Madyan Y. A novel approach for superficial intraoperative radiotherapy (IORT) using a 50 kV X-ray source: a technical and case report. *J Appl Clin Med Phys* (2014) 15(1):4502. doi:10.1120/jacmp.v15i1.4502
139. Weidle UH, Birzele F, Kollmorgen G, Ruger R. Dissection of the process of brain metastasis reveals targets and mechanisms for molecular-based intervention. *Cancer Genomics Proteomics* (2016) 13(4):245–58.
140. Herskind C, Griebel J, Kraus-Tiefenbacher U, Wenz F. Sphere of equivalence – a novel target volume concept for intraoperative radiotherapy using low-energy X rays. *Int J Radiat Oncol Biol Phys* (2008) 72(5):1575–81. doi:10.1016/j.ijrobp.2008.08.009
141. Herskind C, Steil V, Kraus-Tiefenbacher U, Wenz F. Radiobiological aspects of intraoperative radiotherapy (IORT) with isotropic low-energy X rays for early-stage breast cancer. *Radiat Res* (2005) 163(2):208–15.
142. Liu Q, Schneider F, Ma L, Wenz F, Herskind C. Relative biologic effectiveness (RBE) of 50 kV X-rays measured in a phantom for intraoperative tumor-bed irradiation. *Int J Radiat Oncol Biol Phys* (2013) 85(4):1127–33. doi:10.1016/j.ijrobp.2012.08.005
143. Herskind C, Ma L, Liu Q, Wenz F. Biological effect of single, very large dose fractions as used in intraoperative radiotherapy (IORT). *WC2009 Medical Physics and Biomedical Engineering*; IFMBE Proceedings 25/3; Munich: Springer (2009). p.18–21. doi:10.1007/978-3-642-03902-7
144. Herskind C, Wenz F. Is there more to intraoperative radiotherapy (IORT) than physical dose? *Int J Radiat Oncol Biol Phys* (2009) 74(3):976–7. doi:10.1016/j.ijrobp.2009.02.042
145. Herskind C, Wenz F. Radiobiological comparison of hypofractionated accelerated partial-breast irradiation (APBI) and single-dose intraoperative radiotherapy (IORT) with 50-kV X-rays. *Strahlenther Onkol* (2010) 186(8):444–51. doi:10.1007/s00066-010-2147-9
146. Hsieh J, Elson P, Otvos B, Rose J, Loftus C, Rahmathulla G, et al. Tumor progression in patients receiving adjuvant whole-brain radiotherapy vs localized radiotherapy after surgical resection of brain metastases. *Neurosurgery* (2015) 76(4):411–20. doi:10.1227/NEU.0000000000000626
147. Kubo O, Muragaki Y, Iseki H, Takakura K. [Clinical evaluation of intraoperative radiotherapy using photon radiosurgery system for brain tumors]. *Gan To Kagaku Ryoho* (1998) 25(9):1348–51.
148. Colombo F, Francescon P, Cavedon C. [Intraoperative radiotherapy by means of a photon radiosurgical system (PRS400) after removal of

recurring glioblastoma]. *Zh Vopr Neirokhir Im N N Burdenko* (2007) (3):39–40.
149. Qian JM, Yu JB, Kluger HM, Chiang VL. Timing and type of immune checkpoint therapy affect the early radiographic response of melanoma brain metastases to stereotactic radiosurgery. *Cancer* (2016) 122(19):3051–8. doi:10.1002/cncr.30138
150. Gyorki DE, Yuan J, Mu Z, Zaidi B, Pulitzer M, Busam K, et al. Immunological insights from patients undergoing surgery on ipilimumab for metastatic melanoma. *Ann Surg Oncol* (2013) 20(9):3106–11. doi:10.1245/s10434-013-2999-1
151. Baker JJ, Stitzenberg KB, Collichio FA, Meyers MO, Ollila DW. Systematic review: surgery for patients with metastatic melanoma during active treatment with ipilimumab. *Am Surg* (2014) 80(8):805–10.

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REVIEW
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Intraoperative Radiation Therapy: A Promising Treatment Modality in Head and Neck Cancer

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Every year, almost 62,000 are diagnosed with a head and neck cancer (HNC) and 13,000 will succumb to their disease. In the primary setting, intraoperative radiation therapy (IORT) can be used as a boost in select patients in order to optimize local control. Addition of external beam radiation to limited volumes results in improved disease control over surgery and IORT alone. In the recurrent setting, IORT can improve outcomes from salvage surgery especially in patients previously treated with external beam radiation. The use of IORT remains limited to select institutions with various modalities being currently employed including orthovoltage, electrons, and high-dose rate brachytherapy. Practically, execution of IORT requires a coordinated effort and careful planning by a multidisciplinary team involving the head and neck surgeon, radiation oncologist, and physicist. The current review summarizes common uses, outcomes, toxicities, and technical aspects of IORT in HNC patients.

Keywords: recurrent cancer, locally advanced, head and neck tumors, salivary gland tumors, intraoperative radiation therapy

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INTRODUCTION

Head and neck cancers (HNCs) continue to take a high toll with an estimated incidence of around 62,000 new cases in the United States in 2016 (1). Radiation therapy (RT) is commonly used as adjuvant treatment or, as definitive modality when surgical resection is not possible. Delivering radiation at the time of resection of HNCs is particularly helpful in cases at high risk for recurrence, particularly where there is gross or microscopic residual disease or for recurrent disease (2). The safety and effectiveness of intraoperative radiation therapy (IORT) for HNCs have been established in studies from several institutions (3–5). Although IORT is mainly used in recurrent patients, few studies reported on its use in the primary setting. Two forms of IORT have been studied for HNCs: high-dose rate (HDR) brachytherapy (6) and external beam that includes electrons and orthovoltage photons IORT (3, 4). The purpose of this manuscript is to review experience over the past four decades with the use of IORT in patients with primary or recurrent cancer of head and neck.

ROLE OF IORT IN HEAD AND NECK TUMORS

Recurrent HNC

The treatment of recurrent HNC is challenging, especially in the setting of previous irradiation. As per the NCCN 2017 guidelines, surgery is the mainstay of treatment for resectable locoregional recurrences with or without the addition of postoperative reirradiation (7). However, the NCCN

adds a word of caution that reirradiation should be limited to a highly selected group of patients (8). The main challenge in reirradiation is the dose limiting tolerance of surrounding normal tissue. Hence, many studies have reported on the use of IORT since it provides the advantage of decreasing the treatment volume to the site that is directly observed in the operating room (OR), in addition to the possibility of operative mobilization of organs at risk, and normal tissue shielding. Encouraging results have been observed with the use of IORT for recurrent head and neck tumors at the primary site, neck, or salivary glands (**Table 1**).

Neck Recurrences

Intraoperative radiation therapy for neck recurrences is one of the most common IORT uses in head and neck tumors probably due to the difficulty of completely resecting recurrent tumors close to critical structures such as the carotid artery or due to fixation to deep tissues especially after fibrosis induced by previous irradiation. We previously reported one of the largest retrospective series on neck IORT (12); it included 231 patients with advanced cervical metastasis, 88% (198 patients) had recurrent tumors. All included patients had either microscopic or gross residual disease. Intraoperative electron radiation therapy (IOERT) with a median dose of 15–20 Gy was used. Postoperative EBRT was offered to 50 patients (21.6%). With a median follow-up of around a year, 5-year recurrence-free survival (RFS) and overall survival (OS) were 49 and 26%, respectively, for all included patients (12). Another study on neck IORT included 52 patients with recurrent tumors who received a median dose of 20 Gy of IOERT. With a median follow up of 2 years, 2-year local control (LC) and OS were 68 and 45%, respectively, for all 75 patients (18). Most of the other series on IORT for neck recurrences, listed in **Table 1**, included between 17 and 84 patients (10, 14, 15, 19). The majority used IOERT while two of the studies used high dose radiation brachytherapy known as HDR IORT. The median dose ranged from 12 to 20 Gy. Most used adjuvant EBRT in addition to IORT with a median dose range of 41–50 Gy. The 2-year in-field LC reached up to 62%. LC was higher in patients with gross total resection (GTR), where 2-year LC was 50–100% after GTR vs. 0–24% with gross residual disease. It was also higher for primary recurrences as compared to neck recurrences (LC: 100 vs. 75%, respectively). As for survival outcomes, in a study, by Teckie et al, on 57 patients who received 15 Gy of HDR IORT, 3-year OS reached 50% in patients who had in-field control vs. 32% in those not achieving in-field control (10). Survival was also superior for patients with clear margins; where 2-year OS reached 70% in patients with clear margins in a study by Toita et al. which included 17 patients with 22 treated sites (19). In summary, IORT, with a median dose of 15–20 Gy, results in very good LC in patients with neck recurrences and can improve survival outcomes, especially in those who attain negative surgical margins.

Primary Site Recurrences

Good outcomes have been also reported for recurrences at the primary site treated with IORT. Perry et al. presented a study on 34 patients that included salivary gland tumor (SGT) recurrences (21%) in addition to tumor recurrence at other head and neck the primary sites. Most of the patients had a history of irradiation with EBRT to a median dose of 63 Gy. Adjuvant EBRT at recurrence was given to 15% of the patients with a median dose of 50 Gy. With 10–20 Gy of HDR IORT, 2-year LC and 2-year OS were 56 and 55%, respectively (6). An earlier series by Nag et al. reported less favorable outcomes as compared to other listed studies. It included 38 patients, 29% of which were treated with IOERT for primary site recurrence. The dose was 15 Gy for close or microscopically positive margins and 20 Gy for gross disease. It is worth noting however that patients did not receive adjuvant EBRT in addition to IORT resulting in a 2-year LC and OS of 13 and 21%, respectively (15).

SGT Recurrences

Recurrent SGTs were addressed in two main studies, which included patients, treated with IOERT, with the parotid gland being the most common site. Patients in both studies had a history of irradiation (EBRT) with a median dose of 60 Gy. We reported on 46 patients with recurrent parotid tumors treated by 15–20 Gy IOERT in addition to EBRT in 54% (dose of 45 Gy) and chemotherapy in 19%. Favorable outcomes were observed with a relatively long follow-up of 5.6 years. For those with recurrent tumors, 5-year RFS and 5-year OS were both 48% (11). The second study included 37 patients with recurrent SGT who received a median dose of 15 Gy IOERT in addition to EBRT (54 Gy) in 15%. LC at 5 years was better with IORT compared to no IORT (82 vs. 60%) and 5-year OS was 34% for the entire sample (2).

Prognostic Factors

Most of the studies on IORT in the recurrent setting showed a significant correlation between in field control and margin status. Scala et al. reported that 1-year in-field control for patients with negative margins was 82% compared to 56% in those with a positive margin (9). At least five other studies also showed that positive margins (more so for gross residual than microscopic residual) at the time of IORT significantly predicted for in-field failure when compared to close or clear margins (2, 11, 13, 18, 19). In addition, doses of IORT of more than 15 Gy were shown to be associated with better LC (10, 12). Other prognostic factors for LC and RFS include pre-reirradiation recurrence-free interval of more than 12 months (10), use of adjuvant EBRT (9), absence of nodal extra-capsular extension (10), and tumor size (11). Furthermore, patients with neck metastasis who had no PNI, no LVSI, and no involvement of the carotid artery were reported to have better OS after IORT (12). Taken together, these results underscore the prognostic importance of surgical pathology details in addition to treatment dose in this patient cohort.

Locally Advanced (LA) Primary HNC

One of the potential benefits of intraoperative RT in LA HNC is minimization of the time interval between surgery and RT as studies have shown that delayed radiotherapy compromises LC outcomes (20, 21). The importance of IORT in LA HNC is in boosting microscopic or gross residual disease in close proximity to or extending to critical structures, in a setting where negative surgical margins cannot be achieved without significant morbidity. A larger volume is usually irradiated postoperatively using external beam radiation therapy (EBRT). IORT has the advantage

TABLE 1 | Summary of retrospective studies on IORT use in recurrent head and neck cancer.

Reference	*N*[a]	Primary location (most common)	Median tumor size[e]	IORT location	IORT modality	Dose range	Median dose	Adjuvant therapy at rec.	Hx of RT	Duration to reirradiation	Median *F/U*	LC	Survival	Toxicity
Scala et al. (9)	*n* = 76 (87 sites)	Oral cavity (29%), SGT (18%), OP (16%)	Median field size: 5 = 6 cm	Neck (46%); face (13%)	HDR IORT	12–17.5 Gy[b]	12 Gy	24% EBRT (45 Gy) 41% (chemo)	EBRT: (59.8–63.9 Gy)	2 years	11 months	2 year IFLC: 62%	MS: 33 months (in field control) and 17 months (no control)	Flap revision: 4%, carotid hemorrhage: 1%, vagal neuropathy: 1%
Teckie et al. (10)	*n* = 57 (59 sites)	OP, hypopharynx, SGT	≤2 cm: 42% 2.1–4 cm: 32% >4 cm: 25%	Neck (71%); parotid (12%)	HDR IORT	12–20 Gy	15 Gy	21% EBRT: (50 Gy) 27% (chemo) 11% (both)	EBRT: median dose: 66 Gy	Median: 15 months	16 months	3-year IFPFS: 57%	3 year OS: 50% (in field control) vs. 32% (no control)	Fibrosis: 29%, trismus: 24%, cellulitis: 10%, CN injury: 26%, dysphagia: 39%, fistula: 15%
Zeidan et al. (11)	*n* = 46 (out of 96 total)	Parotid gland	≤2 cm: 47% 2.1–4 cm: 39% >4 cm: 14%	Parotid (100%)	IOERT (Mobetron)	15 Gy or 20 Gy	15–20 Gy	57% EBRT (45 Gy), 19% chemo	EBRT: median dose: 60 Gy	8.7 months	5.6 years	5 year RFS: 48.1% (recurrent)	3 year OS: 59%, 5 year OS: 48% (recurrent)[c]	Comp.: 27% vascular: 7%, trismus: 6%, ORN: 4%, fistulas: 4%, flap necrosis: 2%, wound dehiscence: 2%, neuropathy 1%
Zeidan et al. (12)	*n* = 198 (out of 231 total)	UAD tract	4.3 cm	Neck (100%)	IOERT	10–25 Gy	15–20 Gy	22% EBRT (45 Gy), 43% chemo	EBRT: dose not reported	NR	1.03 years	3 year RFS: 55%, 5 year RFS: 49% (for all)	3 year OS: 34%, 5 year OS: 26% (for all)	Vascular: 11.3%, fistula: 9.8%, wound dehiscence: 9.8%, neuropathy: 3%ORN: 4%
Perry et al. (6)	*n* = 34	Salivary g land (21%) and OP (21%)	≤2 cm: 53% 2.1–4 cm: 26% >4 cm: 21%	Salivary gland (21%) and OP (21%)	HDR-IORT	10–20 Gy	15 Gy	15% EBRT: (50 Gy) 21% chemo	EBRT: median dose: 63 Gy	median: 16 months	23 months	2 year LC = 56%	2 year OS = 55%, MS = 24 months	Fibrosis: 38, trismus: 23%, cellulitis: 14%, fistula or wound: 9%, ORN 3%, trigeminal neuralgia: 3%, 2nd tumor: 3%
Chen et al. (2)	*n* = 37 (out of 99)	SGT (100%)	≤2 cm: 28% 2.1–4 cm: 41% >4 cm: 30%	SGT (100%) parotid most common (34%)	IOERT	12–18 Gy	15 Gy	15% EBRT (54 Gy) 9% chemo	EBRT: median dose 60 Gy	3.1 years	3.7 years	5 year LC: 82% (with IORT) and 60% (without IORT)	3 year OS: 54%, 5 year OS: 34% (all). MS: 12 mo. (neck rec) vs. 20 months (primary site rec)	Superficial wound infection: 5%, trismus: 3%, Facial neuropathy: 3%

(*Continued*)

TABLE 1 | Continued

Reference	*N*[a]	Primary location (most common)	Median tumor size[e]	IORT location	IORT modality	Dose range	Median dose	Adjuvant therapy at rec.	Hx of RT	Duration to reirradiation	Median *F/U*	LC	Survival	Toxicity
Chen et al. (4)	*n* = 137 d	OP, oral cavity, paranasal sinus, parotid.	≤2 cm: 45% 2.1–4 cm: 33% >4 cm: 22%	Local (64%); neck (28%); both (8%)	IOERT	NR	15 Gy	26% EBRT (54 Gy) 72% chemo	EBRT median dose: 64 Gy	13 months	18 months	3 year in field control: 62% 3 year LRC 51%	3 year OS: 36% (3-year OS: 44% primary rec compared with 19% neck rec)	Superficial wound infection: 3%, fistula: 1.5%, wound dehiscence: 0.7%, trismus: 0.7%, neuropathy: 0.7%
Pinheiro et al. (13)	*n* = 44 (34 SCC and 10 non-SCC[d])	OP, oral cavity	NR	Skull base (56%) and neck (44%)	IOERT	12.5–22.5 Gy	NR	NR	NR	NR	6.3 years	2 year LF: 54% (SCC) and 48% (non-SCC)	2 year OS: 50% (non-SCC) and 32% (SCC)	Soft tissue: 11.3%, fistula: 6.8%, neuropathy: 11.3%, fatal hemorrhage: 2.2%, wound: 4.5%
Schleicher et al. (14)	*n* = 84 (113 sites)	Hypopharynx, larynx and OP	Median field size: 34 cm^2	Jugular chain (80%)	IOERT	10–20 Gy	20 Gy	9.5%: chemo	EBRT: median dose: 56 Gy	median: 38.3 weeks	NR	LC: 24% R2, 41.7% R1, 50% R0	MS = 6.8 months	Wound healing: 9%, 4%, salivary fistula: 3.5%, necrosis: 2%
Nag et al. (15)	*n* = 38	Larynx and oral cavity	NR	Primary H&N site (29%), neck only (37%)	IOERT	15 Gy: close or microscopically + margins, 20 for gross	15 or 20 Gy	0% EBRT	EBRT: median dose 65.1 Gy	NR	30 months	2 year LC = 13%, 2 year LRC: 4%	2 year OS: 21%, 3 year OS: 8%	Comp.: 16%, orocutaneous fistula: 5%, fatal fistula, wound or tracheal dehiscence and carotid occlusion: 2.6% each
Martinez-Monge et al. (16)	*n* = 23 (31 total)	NR	NR	NR	IOERT	10–15 Gy	NR	NR	EBRT: median dose 50 Gy	NR	NR	2 year LRC: 26%: recurrent	2 year OS: 31% (recurrent)	Comp.: 10%
Ling et al. (17)	*n* = 25 (out of 30 total)	NR	NR	NR	IOERT	15 Gy	15 Gy	NR	NR	NR	30 months	3 year LRC: 60% (for all)	3 year OS: 70% (for all)	Comp.: 16%
Freeman et al. (18)	*n* = 52 (out of 75 total)	NR	>3 cm	Neck (100%)	IOERT	10–25 Gy	20 Gy	33% EBRT (Dose NR)	EBRT: dose NR	NR	2 years	2 year LC: 68%: all patients	2 year OS: 45% (all patients)	Comp.: 25% including carotid blowout, sepsis, ORN, PE, flap necrosis, MI and hypocalcemia
Toita et al. (19)	*n* = 17 (22 sites out of 24 total)	Oral cavity (46%)	NR	Neck (86%); primary (14%)	IOERT	10–30 Gy	20 Gy	67% EBRT (41.2 Gy)	EBRT: 26–70 Gy range	NR	19 months	2 year LC: 54% all[f] GR: 0% MR: 55%, CM: 82%	2 year OS: 45%; 0% GR, 33% MR, 70% CM (all)	Comp: 22%, carotid blowout: 3 patients, osteoradionecrosis (all more than or = 20 Gy): 4 sites

(*Continued*)

TABLE 1 | Continued

Reference	N[a]	Primary location (most common)	Median tumor size[e]	IORT location	IORT modality	Dose range	Median dose	Adjuvant therapy at rec.	Hx of RT	Duration to reirradiation	Median F/U	LC	Survival	Toxicity
Freeman et al. (3)	$n = 64$ (out of 104 total)	Mucosa of UAD tract (71%), SGT (23%)	NR	Neck (35%), skull base (19%), parotid (17%)	IOERT	15–20 Gy	20 Gy: neck, 15 Gy: skull base, oral cavity and SG	NR	NR	NR	2 years	2 year LC: 40% (all)	NR	ORN: 6%, fistulas: 6%, carotid blowout: 3%, MI and PE: 3%

IORT, intraoperative radiation therapy; IOERT, intraoperative electron radiation therapy; HDR IORT, high-dose brachytherapy; F/U, follow-up; LC, local control; IFLC, in-field local control; IFPFS, in-field progression-free survival; RFS, recurrence-free survival; OS, overall survival; SGT, salivary gland tumor; OP, oropharynx; SCC, squamous cell carcinoma; Comp., complications; ORN, osteoradionecrosis; EBRT, external beam radiation therapy; RT, radiation therapy; LRC, locoregional control.

[a]*N: patients with recurrent tumors who received IORT.*

[b]*12 Gy: negative margins, 15–17.5 Gy for microscopically positive margins.*

[c]*1% LR in the IORT field, 20% regional, 13% distant in all.*

[d]*It included primary and recurrent tumors.*

[e]*Median field size, when available, is given when median tumor size is not reported.*

[f]*LC: 78% primary and 43% for neck.*

of reducing the volume of the radiation boost field, allowing dose escalation to target tissue with selective shielding of sensitive structures.

IORT As a Boost to Primary HNC

The Methodist Hospital of Indiana introduced IORT for HNC in 1982 to improve on LC rates and select patients' survival outcomes (3, 22). Few studies have examined the role of IORT in the primary HN setting exclusively. Most studies included patients with recurrent HNC, and most included a heterogeneous patient population with a wide variety of HNC disease sites. One of the first published studies by Garrett et al. reported on 28 patients with LA or recurrent HNC treated with surgery followed by IORT with 1-year OS rates of 67%. Indications for IORT in this study were as follows: (1) gross residual disease, (2) microscopic residual disease, or (3) close margins. In this series, all patients with residual gross disease recurred locally, whereas LC rates were 87 and 75% for close surgical margins and microscopic residual disease, respectively. The 43% of the patients received EBRT, in addition to IORT, with a median dose of 50 Gy. Carotid blowout was found to be a major treatment complication (in two patients). Results were not stratified by primary versus recurrent treatment (22). The same group at the Methodist Hospital of Indiana also reported on their experience with IORT in 104 patients with LA and recurrent HNCs (40 patients previously untreated, and the rest with recurrent disease). Patients were treated with surgery followed by IORT at a dose of 15–20 Gy. Some of the indications for IORT use were close surgical margins, fixation to the carotid sheath, deep muscles of the tongue, pre-vertebral fascia, extension to skull base or dura, or preservation of critical structures function, such as facial nerve. The percentage of patients who also received EBRT in addition to IORT was not reported. Results were promising, with 2-year LC rates of 54%, with better LC rates for parotid cancers ($n = 19$, 2-year LC = 69%) and tongue cancers ($n = 16$, 2-year LC = 57%) (3). Another small study by Freeman et al. included 25 patients with primary ($n = 11$) or recurrent ($n = 14$) tumors close to the skull base, who were treated with IORT for close surgical margins, or residual gross or microscopic disease, with LC rates of 64% at 1 year. The 36% of those patients also received postoperative EBRT (23). A third paper by Freeman et al., mentioned in the above section on neck recurrences, that studied 75 patients with advanced cervical lymph node metastases with 2-year LC and OS of 68 and 45%, respectively, included 22 patients with primary advanced untreated disease. This study did not report on the percent of patients also receiving adjuvant EBRT (18). These three studies with promising results paved the way for more single-institution studies.

In a study by Pinheiro et al., 44 patients with recurrent ($n = 31$) and LA ($n = 13$) HNCs (56% with skull base cancers) were treated with IORT at doses between 12.5 and 22.5 Gy, with around 50% tumor control rates overall. All patients with primary LA tumors received adjuvant EBRT (dose not reported) after IORT (13). Similar control rates were also documented in another study including 25 patients with mainly primary ($n = 17$) LA HNC treated with surgery and 12 Gy of IORT, with 2-year locoregional recurrence-free survival and disease-free survival rates of 58.5 and 50.6%, respectively (21). Nag et al. also studied

53 patients with primary HNC (out of 65 included patients) who were treated with 7.5–20 Gy intraoperative HDR brachytherapy to sites inaccessible to intraoperative electron beam radiotherapy, with 5-year LC rates of 59% and 5-year OS rates of 42%, and no major intraoperative or postoperative complications (24). Although the abovementioned studies have limitations inherent to their retrospective design, they all report LC rates of 50–68% at 2–5 years. It is worth noting that the majority of those studies do not report on adjuvant EBRT use.

Primary SGTs

Locally advanced SGT may involve or be in close contact with vital nerves or blood vessels within the head and neck. Adequate surgical margins might be difficult to attain in such a context. IORT might therefore be a good option in patients with salivary gland cancers at high risk of recurrence. The largest report of IORT in the multimodal management of patients with parotid cancers is a single-practice experience, which included 96 patients with primary (50 patients) or recurrent (46 patients) parotid cancers treated between 1982 and 2007 (11). In this study, 5-year recurrence-free survival (RFS) rates were 77.8% and OS rates were 65.7% for patients treated in the primary setting with IORT boost dose of 15–20 Gy using 4–6 MeV electrons. Larger tumor size was predictive of recurrence after IORT, and patient age was predictive of survival on multivariate analysis. These results have to be put into perspective, as other RT modalities were tried in the management of LA parotid cancers with promising results. The use of fast neutron RT yielded 5-year locoregional control (LRC) rates of 92 and 63% in patients treated with RT alone (without surgery), and with postoperative RT for gross residual disease, respectively (25). Garden et al. also reported LRC of 85% with the use of postoperative EBRT in patients with malignant tumors of the parotid gland (26). Taken together, these studies demonstrate that IORT could be considered as an option in multimodal management of patients with primary HNC, to address gross or microscopic residual disease in a setting where complete resection would be too morbid due to proximity to a major vessel or critical nerve, or as a boost for traditionally radioresistant tumors, such as SGT.

TOXICITY OF IORT

Intraoperative radiation therapy-related complications rate reported in the literature (**Table 1**) ranges between 22 and 52% in both the primary and recurrent setting (11–13, 18, 19, 27). Early studies by Toita et al. reported a significant increase in the rate of toxicities with doses exceeding 20 Gy (19), whereas other studies failed to show significant changes in toxicity rates with different doses (10, 12). Of the several reported complications, carotid artery rupture incidence ranged between 2 and 5% (3, 13, 18) and up to 10% in older series (19). Carotid blow out is a treatment complication associated with the highest mortality rates. Fistula/abscess rate ranged between 4 and 15% (3, 4, 10–12, 14, 18, 27). Wound related toxicity from cellulitis to flap necrosis ranged from 0 to 12% (2–4, 6, 10–12, 14, 27). Osteoradionecrosis rates are reported to range from 0 to 13% (3, 4, 6, 11, 12, 14, 19). Furthermore, some studies report on treatment related neuropathy ranging from 1 to 3% and mostly treated by symptomatic pain management (2, 4, 6, 11–13). Of note, higher neuropathy rates were noted in a study from MSKCC reporting the outcomes of 57 patients with recurrent tumors, where neuropathy rates reached 26%, trismus rate of 24%, and fibrosis rate of 29% (10). Similar rates of trismus and fibrosis, 28 and 23% respectively, were reported from MSKCC in another retrospective study of 34 patients with recurrent disease (6). It is worth mentioning, however, that the above studies used different toxicity scales and had variable median follow up. Taken together, IORT in experienced centers has reasonable toxicity profile, and does not increase perioperative mortality (2, 4, 5, 11, 12) or hospital length-of-stay (5).

RADIOBIOLOGY OF IORT

Using IORT in different clinical settings, including HNCs, is well grounded in several well-known radio-biologic principles. IORT provides a significant dose–response relationship advantage with the high dose given in a single IORT fraction having 1.5–2.5 times the biological effectiveness of the same dose given at standard fractionation (28). While it is debatable to rely solely on the linear quadratic model at very high doses, there is little doubt that tumor cell survival is significantly reduced when using a higher dose per fraction as compared to conventional fractionation. Moreover, there remains a need to better evaluate the effects radio-sensitizing compounds may have on normal tissue tolerances as well as tumor cell survival in the IORT setting (29).

Despite the efforts made intraoperatively to decrease the treatment volume, provide adequate retraction, and adequate shielding, the high fraction dose that is used during IORT does not give ample time for normal tissue repair. This may contribute to vessel injury, neuropathies, fibrosis, and other late effects in surrounding healthy tissues (30, 31). However, the quick drop off in dose with IORT HDR may help prevent treating critical structures surrounding the post-op bed to high dose. Regardless of treatment modality (photons/electrons or brachytherapy), treating residual tumor cells with radiation during surgery as opposed to days or weeks postoperatively reduces the disadvantageous role of tumor cell re-population. Also, it is well established that ischemic tumor areas may be more resistant to radiation treatment due to the paucity of oxygen fixing DNA damage caused by free radicals, and thus, a single high IORT dose does not provide ample time for tumor re-oxygenation. However, it is quite likely that the effect of this unfavorable ischemic milieu is counterbalanced by the single high IORT dose, when compared to standard external beam fractionation (12, 31). Moreover, there is evidence to suggest that high dosage of radiation in a single fraction can eradicate cancer stem cells that would have been radioresistant at standard fractionation and has even been theorized to have implications in unleashing favorable immune responses such as the abscopal effect (32, 33). Therefore, IORT has a promising role from a radiobiology perspective, in improving LC after resection of primary or recurrent HNCs.

MODALITIES FOR IORT

Intraoperative radiation therapy can be delivered using several techniques and modalities that optimize target dose while

minimizing it to the surrounding tissues. HDR brachytherapy, and electron and photon IORT are methods for this localized delivery of dosage. While harboring several similarities, the physics and radiobiology involved generally display a broad variance among the modalities and allow for suitable selections tailored for different HNC patients. Employing these tools correctly plays a particularly critical role in HNCs where surgical management of certain territories may be constrained by essential tissues or adjacent vascular components.

High-dose rate IORT allows the administration of focused radiation in regions where an EBRT cone is not appropriate (34). Application consists of placing a high activity source in close physical proximity to the post-surgical tumor bed while retracting or shielding adjacent structures. Treatment times typically elapse 15–60 min, allowing for treatment during a surgical procedure in a shielded room (35). HDR IORT offers strict spatial restriction of the administered dose, owing to the sharp fall in the inverse square function at short distances from the HDR source, resulting in relatively very little dose delivered beyond the prescribed 100% isodose line (36).

Although HDR IORT offers several advantages in tumor bed management, electron (IOERT) or photon IORT on the other hand provide optimal flexibility for a wide range of treatment sites. These forms of IORT may be delivered using radiation at different energies (37). At the present time, external beam IORT is administered by a dedicated linear accelerator with parallel electron beams of 3–12 MeV kinetic energy or isotropic photon fields with energies between contact and superficial therapy of 50 kV X-rays (38). Such low photon energy beams (e.g., Intrabeam® by Carl Zeiss AG, Germany) have demonstrated favorable outcomes in some sites but with many questions remaining unanswered (39, 40).

CHALLENGES AND FUTURE DIRECTIONS IN IORT FOR HNC

Although IORT has emerged as a feasible modality in management of HNC, several challenges warrant further investigation. First, the efficacy of IORT needs to be further evaluated in randomized phase III trials. Due to paucity of radiotherapy centers with IORT equipment, this is best conducted *via* multicenter cooperative groups such as International Society of Intraoperative Radiation Therapy. Second, there needs to be professional guidelines describing IORT workflow and coordination between surgical and radiation specialties. Third, the therapeutic window for IORT in HNC patients needs to be further improved by using small molecule adjuncts that radiosensitize tumor cells and/or further protect normal tissues. Recent research efforts cast a promising future for HNC IORT (**Figure 1**) (28). For instance, the introduction of IOERT treatment planning system (41) affords accurate documentation of target and normal tissues dose distribution. This is anticipated to yield improved target coverage and better documentation of normal tissue doses.

Finally, assuring radiation safety when using IORT in the OR is a major concern. Typical stray doses from IORT at a 1 m distance from the patient are around 6 μSv per Gy of patient dose (42). Radiation safety regulations usually require shielding which reduces dose below the permitted constraints at any position around the OR under the assumption that the highest dose of stray radiation occurs in the direction of the beam during the complete workload. This need for structural shielding could be reduced by the possible use of mobile shielding walls (43). For example, in a study from Poland by Rabin et al., they calculated that it is sufficient to have mobile lead shield parameters of 1 cm × 140 cm × 150 cm between the accelerator in the OR and the control room to have the dose distribution in the patient plane meet radiation protection requirements (44). However, some authorities might object to mobile shielding due to the lack of control of correct placement by the personnel. A possible future solution might be the development of interlocked systems, which permit irradiation only if the crucial directions around the accelerator are adequately protected by correctly positioning the mobile shields (43).

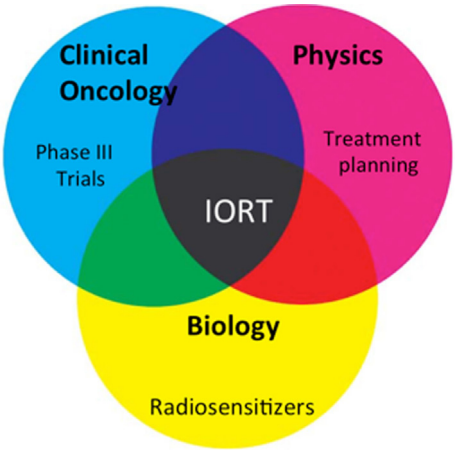

FIGURE 1 | Summary of future directions. Phase III trials (clinical), treatment planning (physics), and radiosensitizers (biology) are at the forefront of current intraoperative radiation therapy research efforts.

CONCLUSION

Intraoperative radiation therapy has emerged as an effective modality for HNC patients at high risk for local failure. To date, most of the scientific literature on head and neck IORT remains by and large limited to single institutional experiences. Recent technological advances and the advent of new IORT platforms predict an expansion of radiotherapy centers offering IORT. This is anticipated to accelerate opening of multi-institutional clinical trials in order to refine indications for IORT in HNC patients.

AUTHOR CONTRIBUTIONS

LH and YZ outlined the manuscript. LH added **Table 1**. LH, KF, IG, PR, J-PO, and YZ wrote the sections of the manuscript. FG, BY, and WJ reviewed and edited the manuscript.

REFERENCES

1. American Cancer Society. *Cancer Facts & Figures 2016*. Atlanta, GA: American Cancer Society (2016).
2. Chen AM, Garcia J, Bucci MK, Chan AS, Kaplan MJ, Singer MI, et al. Recurrent salivary gland carcinomas treated by surgery with or without intraoperative radiation therapy. *Head Neck* (2008) 30(1):2–9. doi:10.1002/hed.20651
3. Freeman SB, Hamaker RC, Singer MI, Pugh N, Garrett P, Ross D. Intraoperative radiotherapy of head and neck cancer. *Arch Otolaryngol Head Neck Surg* (1990) 116:165–8. doi:10.1001/archotol.1990.01870020041011
4. Chen AM, Bucci MK, Singer MI, Garcia J, Kaplan MJ, Chan AS, et al. Intraoperative radiation therapy for recurrent head-and-neck cancer: the UCSF experience. *Int J Radiat Oncol Biol Phys* (2007) 67:122–9. doi:10.1016/j.ijrobp.2006.08.038
5. Haller JR, Mountain RE, Schuller DE, Nag S. Mortality and morbidity with intraoperative radiotherapy for head and neck cancer. *Am J Otolaryngol* (1996) 17:308–10. doi:10.1016/S0196-0709(96)90016-2
6. Perry DJ, Chan K, Wolden S, Zelefsky MJ, Chiu J, Cohen G, et al. High-dose-rate intraoperative radiation therapy for recurrent head-and-neck cancer. *Int J Radiat Oncol Biol Phys* (2010) 76(4):1140–6. doi:10.1016/j.ijrobp.2009.03.025
7. NCCN. *Head and Neck Cancer*. (2017). Available at: https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf
8. Janot F, de Raucourt D, Benhamou E, Ferron C, Dolivet G, Bensadoun R-J, et al. Randomized trial of postoperative reirradiation combined with chemotherapy after salvage surgery compared with salvage surgery alone in head and neck carcinoma. *J Clin Oncol* (2008) 26:5518–23. doi:10.1200/JCO.2007.15.0102
9. Scala LM, Hu K, Urken ML, Jacobson AS, Persky MS, Tran TN, et al. Intraoperative high-dose-rate radiotherapy in the management of locoregionally recurrent head and neck cancer. *Head Neck* (2013) 35:485–92. doi:10.1002/hed.23007
10. Teckie S, Scala LM, Ho F, Wolden S, Chiu J, Cohen GN, et al. High-dose-rate intraoperative brachytherapy and radical surgical resection in the management of recurrent head-and-neck cancer. *Brachytherapy* (2013) 12:228–34. doi:10.1016/j.brachy.2013.01.165
11. Zeidan YH, Shiue K, Weed D, Johnstone PA, Terry C, Freeman S, et al. Intraoperative radiotherapy for parotid cancer: a single-institution experience. *Int J Radiat Oncol Biol Phys* (2012) 82:1831–6. doi:10.1016/j.ijrobp.2011.02.033
12. Zeidan YH, Yeh A, Weed D, Terry C, Freeman S, Krowiak E, et al. Intraoperative radiation therapy for advanced cervical metastasis: a single institution experience. *Radiat Oncol* (2011) 6:72. doi:10.1186/1748-717X-6-72
13. Pinheiro AD, Foote RL, McCaffrey TV, Kasperbauer JL, Bonner JA, Olsen KD, et al. Intraoperative radiotherapy for head and neck and skull base cancer. *Head Neck* (2003) 25:217–25; discussion 225–6. doi:10.1002/hed.10203
14. Schleicher UM, Phonias C, Spaeth J, Schlöndorff G, Ammon J, Andreopoulos D. Intraoperative radiotherapy for pre-irradiated head and neck cancer. *Radiother Oncol* (2001) 58(1):77–81. doi:10.1016/S0167-8140(00)00297-8
15. Nag S, Schuller DE, Martinez-Monge R, Rodriguez-Villalba S, Grecula J, Bauer C. Intraoperative electron beam radiotherapy for previously irradiated advanced head and neck malignancies. *Int J Radiat Oncol Biol Phys* (1998) 42:1085–9. doi:10.1016/S0360-3016(98)00289-2
16. Martinez-Monge R, Azinovic I, Alcalde J, Aristu J, Paloma V, Garcia-Tapia R, et al. IORT in the management of locally advanced or recurrent head and neck cancer. *Front Radiat Ther Oncol* (1997) 31:122–5. doi:10.1159/000061179
17. Ling SM, Roach M III, Fu KK, Coleman C, Chan A, Singer M. Local control after the use of adjuvant electron beam intraoperative radiotherapy in patients with high-risk head and neck cancer: the UCSF experience. *Cancer J Sci Am* (1996) 2:321–9.
18. Freeman SB, Hamaker RC, Rate WR, Garrett PG, Pugh N, Huntley TC, et al. Management of advanced cervical metastasis using intraoperative radiotherapy. *Laryngoscope* (1995) 105:575–8. doi:10.1288/00005537-199506000-00003
19. Toita T, Nakano M, Takizawa Y, Sueyama H, Kakihana Y, Kushi A, et al. Intraoperative radiation therapy (IORT) for head and neck cancer. *Int J Radiat Oncol Biol Phys* (1994) 30:1219–24. doi:10.1016/0360-3016(94)90332-8
20. Ang KK, Trotti A, Brown BW, Garden AS, Foote RL, Morrison WH, et al. Randomized trial addressing risk features and time factors of surgery plus radiotherapy in advanced head-and-neck cancer. *Int J Radiat Oncol Biol Phys* (2001) 51:571–8. doi:10.1016/S0360-3016(01)01690-X
21. Rosenthal DI, Liu L, Lee JH, Vapiwala N, Chalian AA, Weinstein GS, et al. Importance of the treatment package time in surgery and postoperative radiation therapy for squamous carcinoma of the head and neck. *Head Neck* (2002) 24:115–26. doi:10.1002/hed.10038
22. Garrett P, Pugh N, Ross D, Hamaker R, Singer M. Intraoperative radiation therapy for advanced or recurrent head and neck cancer. *Int J Radiat Oncol Biol Phys* (1987) 13:785–8. doi:10.1016/0360-3016(87)90300-2
23. Freeman SB, Hamaker RC, Singer MI, Pugh N, Garrett P, Ross D. Intraoperative radiotherapy of skull base cancer. *Laryngoscope* (1991) 101:507–9. doi:10.1288/00005537-199105000-00011
24. Nag S, Koc M, Schuller DE, Tippin D, Grecula JC. Intraoperative single fraction high-dose-rate brachytherapy for head and neck cancers. *Brachytherapy* (2005) 4:217–23. doi:10.1016/j.brachy.2005.06.002
25. Buchholz TA, Laramore GE, Griffin TW. Fast neutron radiation for recurrent pleomorphic adenomas of the parotid gland. *Am J Clin Oncol* (1992) 15:441–5. doi:10.1097/00000421-199210000-00009
26. Garden AS, el-Naggar AK, Morrison WH, Callender DL, Ang KK, Peters LJ. Postoperative radiotherapy for malignant tumors of the parotid gland. *Int J Radiat Oncol Biol Phys* (1997) 37:79–85. doi:10.1016/S0360-3016(96)00464-6
27. Marucci L, Pichi B, Iaccarino G, Ruscito P, Spriano G, Arcangeli G. Intraoperative radiation therapy as an "early boost" in locally advanced head and neck cancer: preliminary results of a feasibility study. *Head Neck* (2008) 30:701–8. doi:10.1002/hed.20777
28. Calvo FA, Meirino RM, Gunderson LL, Willet CG. Intraoperative radiation therapy. In: Perez CA, Brady LW, Halperin EC, Schmidt-Ullrich RK editors. *Principles and Practice of Radiation Oncology*. Philadelphia, Baltimore, New York, London, Buenos Aires, Hong Kong, Sydney, Tokio: Lippincott Williams & Wilkins (2003).
29. Calvo FA, Sole CV, Gonzalez ME, Tangco ED, Lopez-Tarjuelo J, Koubychine I, et al. Research opportunities in intraoperative radiation therapy: the next decade 2013–2023. *Clin Transl Oncol* (2013) 15:683–90. doi:10.1007/s12094-013-1019-z
30. Calvo FA, Meirino RM, Orecchia R. Intraoperative radiation therapy first part: rationale and techniques. *Crit Rev Oncol Hematol* (2006) 59:106–15. doi:10.1016/j.critrevonc.2005.11.004
31. Czito BG, Calvo FA, Haddock MG, Palta M, Willett CG. Intraoperative irradiation. In: Gunderson L, Tepper J, editors. *Clinical Radiation Oncology*. 4th ed. Philadelphia, PA: Elseiver (2016). p. 325–40.e3.
32. Kirkpatrick JP, Meyer JJ, Marks LB. The linear-quadratic model is inappropriate to model high dose per fraction effects in radiosurgery. *Semin Radiat Oncol* (2008) 18:240–3. doi:10.1016/j.semradonc.2008.04.005
33. Sologuren I, Rodríguez-gallego C, Lara PC. Immune effects of high dose radiation treatment: implications of ionizing radiation on the development of bystander and abscopal effects. *Transl Cancer Res* (2014) 3:18–31. doi:10.3978/j.issn.2218-676X.2014.02.05
34. Moningi S, Armour EP, Terezakis SA, Efron JE, Gearhart SL, Bivalacqua TJ, et al. High-dose-rate intraoperative radiation therapy: the nuts and bolts of starting a program. *J Contemp Brachytherapy* (2014) 6:99–105. doi:10.5114/jcb.2014.42027
35. Furhang EE, Sillanpaa JK, Hu KS, Harrison LB. HDR-IORT: physics and techniques. In: Gunderson LL, Willett CG, Calvo FA, Harrison LB, editors. *Intraoperative Irradiation: Techniques and Results*. Totowa, NJ: Humana Press (2011). p. 73–84.
36. Crownover RL, Wilkinson DA, Weinhous MS. The radiobiology and physics of brachytherapy. *Hematol Oncol Clin North Am* (1999) 13:477–87. doi:10.1016/S0889-8588(05)70069-1
37. Herskind C, Ma L, Liu Q, Zhang B, Schneider F, Veldwijk MR, et al. Biology of high single doses of IORT: RBE, 5 R's, and other biological aspects. *Radiat Oncol* (2017) 12:24. doi:10.1186/s13014-016-0750-3
38. Kalakota K, Small WJ. Intraoperative radiation therapy techniques and options for breast cancer. *Expert Rev Med Devices* (2014) 11:265–73. doi:10.1586/17434440.2014.882653
39. Deneve JL, Hoefer RAJ, Harris EER, Laronga C. Accelerated partial breast irradiation: a review and description of an early North American surgical

experience with the intrabeam delivery system. *Cancer Control* (2012) 19:295–308.
40. Strnad V. Intraoperative radiotherapy (IORT) with 50-kV X-ray machines as boost in breast cancer – more questions than answers. *Onkologie* (2006) 29:73–5. doi:10.1159/000091475
41. Pascau J, Santos Miranda JA, Calvo FA, Bouche A, Morillo V, Gonzalez-San Segundo C, et al. An innovative tool for intraoperative electron beam radiotherapy simulation and planning: description and initial evaluation by radiation oncologists. *Int J Radiat Oncol Biol Phys* (2012) 83:e287–95. doi:10.1016/j.ijrobp.2011.12.063
42. Soriani A, Felici G, Fantini M, Paolucci M, Borla O, Evangelisti G, et al. Radiation protection measurements around a 12 MeV mobile dedicated IORT accelerator. *Med Phys* (2010) 37:995–1003. doi:10.1118/1.3298012
43. Hensley FW. Present state and issues in IORT physics. *Radiat Oncol* (2017) 12:37. doi:10.1186/s13014-016-0754-z
44. Wysocka-Rabin A, Adrich P, Wasilewski A. Radiation protection studies for a new mobile electron accelerator for intraoperative radiation therapy (IORT). *Prog Nucl Sci Technol* (2014) 4:298–302. doi:10.15669/pnst.4.298

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REVIEW
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Future Directions of Intraoperative Radiation Therapy: A Brief Review

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The use of intraoperative radiation therapy (IORT) is increasing with the development of new devices for patient treatment that allow irradiation without the need to move the patient from the surgical table. At the moment, ionizing radiation in the course of IORT is supported most often by the use of mobile devices that produce electrons, kilo voltage X-rays, and electronic brachytherapy and the development of applicators suitable for delivery of radionuclides for short-term brachytherapy. The establishment of new treatment devices and protocols that can be foreseen in the future, e.g., the development of proton or heavy ion sources suitable for IORT or the establishment of new treatment protocols such as the use of IORT in combination with immune system modulators or radiosensitizing nanoparticles, could lead to a significant increase in the use of IORT in the future. This review discusses the still limited use of IORT at this point in time and hypothesizes about possible future approaches to radiotherapy.

Keywords: intraoperative radiation therapy, immunotherapy, nanotechnology, radiosensitizers, normal tissue injury

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INTRAOPERATIVE RADIATION THERAPY (IORT) TODAY

By definition, IORT is delivered to the tumor and tumor bed (preferably to tissues at the 10 mm depth) as they are exposed during surgery to the patient; often, this also includes surgical distancing of normal tissues that could be injured by radiation (e.g., retraction of skin away from the IORT source). Regardless of the dose of radiation delivered, the critical feature of IORT is its precision and minimal exposure to the surrounding healthy tissues. In this manner, IORT fulfills one of the key promises of targeted radiation therapy—it accomplishes minimization of systemic side effects by limiting the irradiated normal tissue volume and increasing the therapeutic index. Thus, IORT has found its use in those situations where surgical intervention provides an opportunity to increase radiation dose to the tumor (dose escalation) and/or decrease total dose to normal tissues (dose de-escalation).

The use of radiation in combination with surgery has a long history. Before the 1960s, the preferred approach to combine these treatment modalities was to do a presurgical radiation treatment. For example, the delivery of 35–40 Gy to the chest wall followed at 6 weeks by mastectomy was a frequent approach for breast cancer patient care at MD Anderson before 1960s (1). Technical difficulties of delivering radiation at the time of surgery were probably the primary reasons why such treatment was attempted for the first time only after 1960. The first IORT work similar to current practice was done in Japan at Kyoto University (2–4); it was soon followed by similar work around the world (5). The successful results of this early work generated much excitement; the first group of IORT gastric cancer patients included two examples of posttreatment 5-year survival of patients with only partially resected gastric cancer who received a 40 Gy intraoperative dose (4). Further developments in the field followed, rapidly at first, with surgical suites built in radiation

rooms in some cases (5), and much instrument manipulation done collaboratively between hospitals and manufacturers of IR devices (6). IORT quickly became adopted worldwide despite the technical challenges (2, 7–10) but became less used once IR equipment manufacturers ceased engaging in customized instrument changes. A recent resurgence of this treatment modality can probably be credited to the development of new types of IORT dedicated radiation devices such as mobile linear accelerators (11) and specially designed applicators for positioning of high activity radioactive sources (12). Thus, although current medical device regulations prevent in-house development of IORT accelerators—a problem that slowed this field until recently, the availability of commercial devices obviated this necessity.

Early translational studies, conducted by Abe before the first patient IORT and subsequently by many who worked in this field, found a relatively high resilience of different tissues to IORT treatment. For example, experimental studies in a canine model established IORT doses for abdominal surgeries incompatible with different types of postsurgical healing (13). In a study that included nearly 70 animals, it was determined that the intact large blood vessels tolerate doses up to 50 Gy, the urethra up to 30 Gy, and bile ducts up to 20 Gy. Postsurgery the same tissues became less able to cope with radiation injury. Intestinal sutures and arterial anastomoses were found to heal after doses of 45 Gy although not without occasional fibrotic complications. These and subsequent studies in animal models and data from human patients led to the general conclusion that IORT doses as high as 25 Gy could be tolerated by the majority of normal (not surgically treated) tissues without significant toxicity (14, 15). Among the late effects of IORT, delayed progressive ischemia was found to be the complication of most concern. Most of these radiobiological studies were followed-up with patient work that helped drive the IORT field in general.

While some of the illustrative examples of IORT are discussed here, this document is not intended to provide a thorough overview of IORT in current practice. Several exhaustive reviews of IORT were published in recent years demonstrating obstacles and successes of this field (5, 12, 16, 17), and the diverse group of treatment approaches and cancer types treated by IORT in the past few decades. Conclusions from those studies were positive in all cases—if used in appropriate patient groups and controlled correctly, IORT is a life saving procedure. Patient selection criteria, according to these sources, include the following:

- Low local control rate achievable with surgery alone;
- No medical contraindications for gross tumor resection;
- "Standard" radiotherapy doses required for adequate local control exceeding normal tissue tolerance;
- No evidence of distant metastases.

The last of these criteria (no evidence of distant metastases) is the basis for most successful IORT treatments. Immediate, single dose irradiation after surgery, in low-risk patients who are most likely to be free of metastasis further assures long-term disease free survival of such patients. For example, an IORT study with women stratified into low-risk and high-risk cohorts as defined by the ELIOT trial, found a greater survival and greatest benefits from IORT in the low-risk group (18). While it may be disappointing that IORT is not of greater benefit for high-risk patients (in whom it does not seem to be of much effect), the fact that this treatment improves disease free survival in low-risk patients is one of the most significant arguments in favor of this therapy.

Nevertheless, it should also be recognized that IORT has found its place in other cancer related scenarios. These include supplemental treatment to recurrent cancers (not eligible for external beam radiotherapy), as well as in palliative care. For example, IORT may be used in combination with kyphoplasty in patients with vertebral metastases; few studies using IORT for metastatic disease documented good pain control (16).

A recent review by Pilar and others (12) provides an excellent resource for review of surgical situations known to employ IORT and lists the possible outcomes achieved by IORT under these different circumstances. In this, most recent review of IORT literature, cancer types treated by IORT include following: primary and recurrent head and neck cancers (IORT doses between 10 and 22 Gy, 2-year overall survival 20–60%), breast cancers (wide spectra of cancer types and outcomes), locally advanced colorectal cancers (IORT doses between 10 and 20 Gy, 5-year overall survival up to 75%), soft tissue sarcomas (IORT doses between 7.5 and 30 Gy, 5-year overall survival up to 7–40%), pediatric tumors (mostly neuroblastoma) (IORT doses between 7.5 and 20 Gy, 10-year overall survival up to 74%), gynecological tumors (IORT doses between 8 and 30 Gy, 5-year overall survival up to 47%), bladder and renal cancers (IORT doses between 9 and 20 Gy, 5-year overall survival up to 73%), prostate cancers (IORT doses between 10 and 30 Gy, 5-year overall survival up to 100%), gastric cancers (IORT doses between 12 and 35 Gy, 2-year overall survival up to 47%), and pancreatic cancers (IORT doses between 10 and 33 Gy, 5-year overall survival up to 35%).

FUTURE DIRECTIONS IN IORT

First, it should be mentioned that the potential combined use of IORT and immunotherapy was recognized in a recent review by Herskind and others (19). Increasing evidence suggests that high single doses of ionizing radiation may result in tumor-directed immune reactions, locally and systemically (20). While no conclusive data about immune reactions and IORT are available, high single doses delivered during IORT may be expected to cause immunogenic cell death (21) of tumor cells remaining *in situ* after surgery. The greatest concern lies with the fact that the numbers of tumor cells remaining after surgery may be too low to trigger a favorable immune system reaction. (In the same vein—it could perhaps be interesting to investigate the data from IORT cases with incomplete surgical resection, such as, for example, unexpected survivors from Abe's initial studies.) The possibility that IORT may lead to immunogenic cell death of tumor cells may provide an additional reason to investigate IORT anew, perhaps in combination with immune checkpoint blockade treatments (19).

Next, we would like to consider the fact that IORT could easily be combined with other therapies that are also more potent with local delivery and could, in turn, increase radiation sensitivity.

IORT is inherently a treatment approach designated for local cancer control. Local delivery is achieved "mechanically"—by placing the source of radiation close to tumor or tumor bed. New therapeutic modalities, still at preclinical testing such as nanoparticle therapies, could also benefit from using a postsurgery scenario to secure targeted local delivery. IORT would then be complemented with localized delivery of nanoparticles that could be designed, e.g., for a controlled release of cargo. Many nanomaterials have the capacity to respond differentially to different temperatures, pH conditions and more; for an extensive review of porous nanomaterials fine tuned for "gated" cargo delivery see, for example Ref. (22). While it may be difficult to guarantee that a given nanoparticle type may not encounter a "cargo-release signal" if delivered systemically, it is much easier to be sure that cargo delivery will be controlled if nanomaterial is to be delivered locally, to tumor or tumor bed physically revealed by the surgery.

It is also not a difficult next step to imagine a potential synergy between radiosensitizing nanoparticles and IORT. In its simplest form—one can envision combined use of IORT with nanoparticles with radiosensitizing small molecule cargo, increasing the efficiency of radiation therapy additively or synergistically. A more complex, and possibly more exciting situation could be accomplished by using nanoparticles with inherent and novel radiosensitizing capacity such as ability to intensify radiation effects by localized release of electrons or reactive oxygen species (23). An overview of different possible radiosensitizing nanoparticle materials (24) details how many Auger electrons, Compton electrons, and photoelectrons are expected for nanoparticles made of elements of different Z and lists the anticipated total energy absorbed and released by each material upon exposure to keV and MV ionizing radiation. Relative biological effectiveness calculated based on these data suggests that keV radiation may be more effective than MV radiation in the presence of nanomaterials rich in Auger electrons. Similarly, several predictions about radiosensitization that can be expected by combining gold nanoparticles with brachytherapy radionuclides (I-125, Pd-103, and Yb-169) and low-energy (50 keV) X-rays were also recently published (25, 26); as well as investigation of potential effects of combination of high Z nanomaterials and proton therapy (27). To all these considerations, one may also add that nanoparticle uptake by cells leads to radiosensitization by biological, cellular, and molecular mechanisms as well (23).

A significant concern in IORT is the dosimetry, and a 10 mm depth margin surrounding the tumor cavity is considered as tissue that must be treated. The current "standard" in IORT linacs that produce MeV electrons are devices called the Mobetron, the Liac, and the Novac; while IORT low-energy X-ray irradiators most frequently used at present are the Intrabeam System and the Papillon System (6). The linacs used for IORT produce electron beams with energies between 4 and 12 MeV with 2–3 MeV steps increase and corresponding penetration increase of 7–10 mm per step; use of higher energies is avoided to prevent neutron contamination that would require additional shielding (6). IORT low-energy X-ray irradiators produce 30 and/or 50 keV X-ray photons and the dose delivered with these devices decreases rapidly with distance; and a prescription at 10 mm depth is considered as best to ensure that desired dose arrives at this tissue depth for all applicator sizes (28). Based on discussion about high Z nanoparticles above, it is clear that they could significantly increase effect of IORT exposures and do so locally—which is the exact prerequisite for IORT.

Finally, it should be mentioned that it might be possible that IORT devices that produce protons or even heavy ions may become possible in the future. These radiation modalities could extend the postsurgical radiation treatment deeper and further than 10 mm from resection margin. While treatment distances further than 10 mm were not considered in IORT practice so far, it is possible that such devices would find their use in clinical practice as well.

CONCLUDING THOUGHTS

Intraoperative radiation therapy was originally an innovative and clever approach for delivery of radiation during the course of surgery to reduce normal tissue toxicity and at the same time improve tumor treatment. When the modality was first established, limitations revolved predominantly around the availability of instrumentation, the design of facilities and other physical concerns. Radiobiology done to understand constraints of the technology was limited and focused on available systems. With the deeper understanding of the importance of tumor immunology and the development of new tools in nanotechnology, it is hopeful that IORT will be rediscovered. Additional radiobiology experiments designed to probe possible new uses of IORT are essential to understand potential benefits and limitations of these treatments.

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TP and GW selected the references and cowrote the text.

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REFERENCES

1. Fletcher GH. Problems in clinical evaluation of radiotherapeutic methods. *JAMA* (1962) 179:871–7. doi:10.1001/jama.1962.03050110039008
2. Abe M. Intraoperative radiotherapy – past, present and future. *Int J Radiat Oncol Biol Phys* (1984) 10:1987–90. doi:10.1016/0360-3016(84)90282-7
3. Abe M, Takahashi M, Yabumoto E, Onoyama Y, Torizuka K. Techniques, indications and results of intraoperative radiotherapy of advanced cancers. *Radiology* (1975) 116:693–702. doi:10.1148/116.3.693
4. Abe M, Yabumoto E, Takahashi M, Tobe T, Mori K. Intraoperative radiotherapy of gastric cancer. *Cancer* (1974) 34:2034–41. doi:10.1002/1097-0142(197412)34:6<2034::AID-CNCR2820340623>3.0.CO;2-F

5. Valentini V, Balducci M, Tortoreto F, Morganti AG, De Giorgi U, Fiorentini G. Intraoperative radiotherapy: current thinking. *Eur J Surg Oncol* (2002) 28: 180–5. doi:10.1053/ejso.2001.1161
6. Hensley FW. Present state and issues in IORT physics. *Radiat Oncol* (2017) 12:37. doi:10.1186/s13014-016-0754-z
7. Goldson AL. Past, present, and prospects of intraoperative radiotherapy (IOR). *Semin Oncol* (1981) 8:59–64.
8. Gunderson LL, Tepper JE, Biggs PJ, Goldson A, Martin JK, McCullough EC, et al. Intraoperative ± external beam irradiation. *Curr Probl Cancer* (1983) 7:1–69. doi:10.1016/S0147-0272(83)80021-X
9. Kinsella TJ, Sindelar WF. Normal tissue tolerance to intraoperative radiation therapy. Experimental and clinical studies. *Front Radiat Ther Oncol* (1989) 23:202–14. doi:10.1159/000416584
10. Rich TA. Intraoperative radiotherapy. *Radiother Oncol* (1986) 6:207–21. doi:10.1016/S0167-8140(86)80155-4
11. Beddar AS, Domanovic MA, Kubu ML, Ellis RJ, Sibata CH, Kinsella TJ. Mobile linear accelerators for intraoperative radiation therapy. *AORN J* (2001) 74:700–5. doi:10.1016/S0001-2092(06)61769-9
12. Pilar A, Gupta M, Laskar SG, Laskar S. Intraoperative radiotherapy: review of techniques and results. *Ecancermedicalscience* (2017) 11:750. doi:10.3332/ecancer.2017.750
13. Sindelar WF, Kinsella T, Tepper J, Travis EL, Rosenberg SA, Glatstein E. Experimental and clinical studies with intraoperative radiotherapy. *Surg Gynecol Obstet* (1983) 157:205–19.
14. Emami B, Lyman J, Brown A, Coia L, Goitein M, Munzenrider JE, et al. Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol Phys* (1991) 21:109–22. doi:10.1016/0360-3016(91)90171-Y
15. Sindelar WF, Kinsella TJ. Normal tissue tolerance to intraoperative radiotherapy. *Surg Oncol Clin N Am* (2003) 12:925–42. doi:10.1016/S1055-3207(03)00087-5
16. Debenham BJ, Hu KS, Harrison LB. Present status and future directions of intraoperative radiotherapy. *Lancet Oncol* (2013) 14:e457–64. doi:10.1016/S1470-2045(13)70270-5
17. Willett CG, Czito BG, Tyler DS. Intraoperative radiation therapy. *J Clin Oncol* (2007) 25:971–7. doi:10.1200/JCO.2006.10.0255
18. Maluta S, Dall'Oglio S, Goer DA, Marciai N. Intraoperative electron radiotherapy (IOERT) as an alternative to standard whole breast irradiation: only for low-risk subgroups? *Breast Care (Basel)* (2014) 9:102–6. doi:10.1159/000362392
19. Herskind C, Wenz F, Giordano FA. Immunotherapy combined with large fractions of radiotherapy: stereotactic radiosurgery for brain metastases-implications for intraoperative radiotherapy after resection. *Front Oncol* (2017) 7:147. doi:10.3389/fonc.2017.00147
20. Demaria S, Ng B, Devitt ML, Babb JS, Kawashima N, Liebes L, et al. Ionizing radiation inhibition of distant untreated tumors (abscopal effect) is immune mediated. *Int J Radiat Oncol Biol Phys* (2004) 58:862–70. doi:10.1016/j.ijrobp.2003.09.012
21. Kepp O, Senovilla L, Vitale I, Vacchelli E, Adjemian S, Agostinis P, et al. Consensus guidelines for the detection of immunogenic cell death. *Oncoimmunology* (2014) 3:e955691. doi:10.4161/21624011.2014.955691
22. Wen J, Yang K, Liu F, Li H, Xu Y, Sun S. Diverse gatekeepers for mesoporous silica nanoparticle based drug delivery systems. *Chem Soc Rev* (2017) 46:6024–45. doi:10.1039/c7cs00219j
23. Paunesku T, Gutiontov S, Brown K, Woloschak GE. Radiosensitization and nanoparticles. *Cancer Treat Res* (2015) 166:151–71. doi:10.1007/978-3-319-16555-4_7
24. McMahon SJ, Paganetti H, Prise KM. Optimising element choice for nanoparticle radiosensitisers. *Nanoscale* (2016) 8:581–9. doi:10.1039/c5nr07089a
25. Cho SH, Jones BL, Krishnan S. The dosimetric feasibility of gold nanoparticle-aided radiation therapy (GNRT) via brachytherapy using low-energy gamma-/X-ray sources. *Phys Med Biol* (2009) 54:4889–905. doi:10.1088/0031-9155/54/16/004
26. Ngwa W, Makrigiorgos GM, Berbeco RI. Gold nanoparticle-aided brachytherapy with vascular dose painting: estimation of dose enhancement to the tumor endothelial cell nucleus. *Med Phys* (2012) 39:392–8. doi:10.1118/1.3671905
27. Ahmad R, Royle G, Lourenco A, Schwarz M, Fracchiolla F, Ricketts K. Investigation into the effects of high-Z nano materials in proton therapy. *Phys Med Biol* (2016) 61:4537–50. doi:10.1088/0031-9155/61/12/4537
28. Ebert MA, Carruthers B. Dosimetric characteristics of a low-kV intraoperative X-ray source: implications for use in a clinical trial for treatment of low-risk breast cancer. *Med Phys* (2003) 30:2424–31. doi:10.1118/1.1595611

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