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The American Brachytherapy Society consensus statement on intraoperative radiation therapy

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ABSTRACT

PURPOSE: Although radiation therapy has traditionally been delivered with external beam or brachytherapy, intraoperative radiation therapy (IORT) represents an alternative that may shorten the course of therapy, reduce toxicities, and improve patient satisfaction while potentially lowering the cost of care. At this time, there are limited evidence-based guidelines to assist clinicians with patient selection for IORT. As such, the American Brachytherapy Society presents a consensus statement on the use of IORT.

METHODS: Physicians and physicists with expertise in intraoperative radiation created a site-directed guideline for appropriate patient selection and utilization of IORT.

RESULTS: Several IORT techniques exist including radionuclide-based high-dose-rate, low-dose-rate, electron, and low-energy electronic. In breast cancer, IORT as monotherapy should only be used on prospective studies. IORT can be considered in the treatment of sarcomas with close/positive margins or recurrent sarcomas. IORT can be considered in conjunction with external beam radiotherapy for retroperitoneal sarcomas. IORT can be considered for colorectal malignancies with concern for positive margins and in the setting of recurrent gynecologic cancers. For thoracic, head and neck, and central nervous system malignancies, utilization of IORT should be evaluated on a case-by-case basis.

CONCLUSIONS: The present guidelines provide clinicians with a summary of current data regarding IORT by treatment site and guidelines for the appropriate patient selection and safe utilization of the technique. High-dose-rate, low-dose-rate brachytherapy methods are appropriate when IORT is to be delivered as are electron and low-energy based on the clinical scenario.

Keywords: Radiation therapy; Intraoperative radiation; IORT; Breast cancer; Head and neck; Sarcoma; Gynecologic; Colorectal

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Introduction

Radiation therapy can be delivered through multiple different methods including external beam radiation therapy (EBRT) with photons, electrons, and particle therapy as well as brachytherapy (sealed and unsealed sources). Intraoperative radiation therapy (IORT), traditionally a single-fraction treatment of a surgically exposed area, has been administered in conjunction with both EBRT and brachytherapy techniques and as monotherapy for multiple treatment sites. Although IORT has been incorporated into radiation therapy treatment paradigms for many years, it has more recently witnessed a resurgence in utilization, driven by new technology as well as a focus on value, quality of life, and reductions in treatment duration. However, at this time, there is a lack of guidelines available to assist clinicians with understanding different IORT techniques and appropriate patient selection by disease site based on currently available data. Therefore, we have provided the following consensus statement as a guide for the use of IORT.

Methods

The American Brachytherapy Society (ABS) Board of Directors appointed a group of physicians and physicists with expertise in IORT to provide a consensus statement. The goals of the project were to provide recommendations based on the data available for each treatment site. A review of the IORT literature with a focus on randomized trials, prospective studies, multiinstitutional series, and single-institution reports addressing clinical outcomes and toxicities was performed. After a discussion, the guidelines were created based on consensus among the authors. Before publication, the consensus statement was approved by the ABS Board of Directors.

Results

Review of IORT techniques

The choice of IORT modality impacts both the dose distribution and the method of treatment application. In many cases, the treatment unit will have to fit into an existing operating room suite, restricting the choice of modality according to available facilities and radiation shielding.

Electron beam IORT

Electron beam IORT (IOERT) has been in clinical use for many years, initially introduced using devices situated next to the operating room. Although such an approach is still in use today, the transfer of the patient from and to the operating room presents a logistical challenge for most hospitals. To solve this challenge, a dedicated IOERT unit was introduced (Mobetron, IntraOp Medical, Sunnyvale, CA). Although the unit is mobile and features a beam stopper, some shielding is still required. A special room may also be needed for storage and quality assurance (QA) of the unit before use.

When comparing electron energies, lower energy electrons may offer shallower depth dose curves and the potential to spare underlying tissues but are characterized by lower surface dose compared with higher energy electron beams. Bolus material can be used to increase the surface dose and electron energies can be selected based on desired depth of coverage. Electron beam energies between 3 and 15 MeV have often been used. The application of IOERT uses dedicated cones that are placed in direct apposition to the targeted surface. The use of fixed cones may present a limitation in hard to access treatment sites where the beam angle with respect to the treated surface results in inhomogeneous dose distributions or when large areas need to be treated requiring multiple field treatments that may result in large dose variations at field junctions. Another source of dose uncertainty results from tissue inhomogeneities and the application of the beam to geometrically irregular surfaces.

Radionuclide-based IORT-HDR

High-dose-rate (HDR), high energy (>100 keV) brachytherapy-based IORT (IORT-HDR) offers a high degree of versatility in terms of the delivered dose distribution and having been applied to many clinical treatment geometries (1). IORT-HDR has been used in conjunction with balloon applicators, customized applicators for the treatment of irregular volumes and cavities, and surface applicators. Applicators such as the H.A.M. applicator (Mick Radio-Nuclear Instruments, an Eckert and Ziegler, BEBIG Company, Mt Vernon, NY) that are packed or sutured in place are also frequently used (1). As with other IORT techniques, sensitive tissues can be retracted and/or shielded. Such applicators overcome the restriction of fixed cone size, and applicator access limitations seen with other IORT techniques.

HDR treatment planning systems can be used to modulate the dose through the treatment area to enhance treatment of high-risk regions and further spare healthy tissue (2). In addition, these applicators are moderately flexible and can conform to the target surface area within limits, but extremely irregular, curved, or deep targets may present a challenge for applicator placement and positioning. Curvature of the applicator may also introduce some dose uncertainty as it may be difficult to estimate and model in the treatment planning system without proper imaging, which is typically not done when used in the operating room (1).

HDR afterloaders most commonly use an Ir-192 source, characterized by its relatively high photon energy (average photon energy of 380 keV) and long half-life (~74 days). For this reason, IORT-HDR requires a designated shielded OR equipped with safety interlocks, monitors, and remote patient monitoring (1). In addition, emergency procedures should reflect the need to move the afterloader (and exposed source) from the patient in the intraoperative setting when the patient may not be moved from the operating room. One solution incorporates a shielded vault into the operating room that houses the afterloader and serves as emergency containment in radiation emergency scenarios. The

application of HDR brachytherapy in IORT also introduces the challenge of potentially complex treatment planning in a high-pressure environment. Staff involved in these procedures should be properly credentialed, and procedures should be set to streamline the process from patient examination, through applicator placement, prescription, planning, and treatment while observing operating room sterile protocols (1). Introducing redundancy into communications between staff and into forms used is an effective strategy to help ensure treatment intent is correctly translated into treatment planning parameters. Standard brachytherapy procedures should be adhered to and include the completion of a written directive, review and approval of the treatment plan by the authorized user (AU), independent verification of the treatment plan before treatment, and the presence of the AU and qualified medical physicist during treatment (1).

Low-energy electronic-based IORT

Guidelines for the use of low-energy electronic IORT (eIORT) are outlined in The American Brachytherapy Society Consensus Statement for Electronic Brachytherapy (3). Briefly, due to the low-energy x-ray beam (50 kVp) of these devices (INTRABEAM, Carl Zeiss Surgical, Oberkochen, Germany; Axxent, Xoft, Inc., subsidiary of iCAD Inc., San Jose, CA; Esteya, Elekta. Stockholm, Sweden), increased rates of toxicity may occur for traditional prescription depths of 5 or 10 mm from the applicator surface due to the high dose gradient. Consequently, prescription depth for these devices is often limited to the surface (e.g., breast cancer) of the applicator or within a few mm (e.g., nonmelanomatous skin cancer, vaginal cuff up to 5 mm) (1, 4). It should be noted that these devices are also considered HDR radiation sources with a dose rate output of more than 12 Gy per hour (5).

In their current configurations, the placement of the x-ray source for these devices is limited to one applicator (or channel) at a time. This restricts their practical clinical application to single treatment cavities, small surface treatment areas, or single lumen applicators (3). By far the most common application of low energy eIORT is for the treatment of breast cancer using spherical or balloon type applicators. Applicators for brain resection cavities, the spine, and other sites are also available. The small footprint of these devices combined with the low energy profile makes them highly portable and usable in standard operating rooms with little if any shielding. These devices also offer limited access to imaging to evaluate applicator placement and treatment planning, which is a disadvantage compared with other radiation therapy modalities, although ultrasound can be considered and is available in most ORs (6, 7). Owing to its unique properties compared with other brachytherapy techniques, it is important not to extrapolate data from other brachytherapy or IORT techniques to justify the use for eIORT (3).

Intraoperative permanent low-dose-rate brachytherapy

In general, iodine-125 (I-125) seeds can be sutured into a mesh around the tumor bed at 1 cm intervals to form a planar implant (mesh) prescribed to deliver a dose of 85–150 Gy to the minimum peripheral dose (5). Standard dosimetry of LDR using the American Association of Physicists in Medicine (AAPM) Task Group (TG)-43 formulation is used for treatment planning (8). When using LDR mesh, source orientation and spacing can be challenging to maintain during mesh customization, leading to dose uncertainties, in particular if the implant is permanent (8). Recently, the CivaSheet (CivaTech Oncology Inc., Durham, NC), an implantable unidirectional palladium-103 (Pd-103) planar low-dose brachytherapy device, has been developed. The CivaSheet Pd-103 sources are encapsulated in an organic polymer and embedded within an 8 mm × 8 mm grid that consists of a flexible bioabsorbable substrate. The sources are unidirectional due to a shielded gold layer, attenuating the dose to less than 10%. This offers a new technique to reduce dose toward the adjacent critical organs using a low-dose-rate IORT (IORT-LDR) approach although clinical data are limited at this time (9–11).

Clinical sites

Breast cancer

The role of IORT in breast cancer has been previously reviewed in the ABS consensus statement on accelerated partial breast irradiation (12). Breast cancer represents a disease site where randomized trials have been conducted, evaluating the role of IORT as compared with more traditional radiotherapy

Table 1
Comparison of partial-breast techniques

Technique	Randomized trials	Number of patients	Followup (years)	Local recurrence
Interstitial brachytherapy	National Institute of Oncology (18)	258	10.2	5.9% APBI vs. 5.1% WBI
	GEC-ESTRO (19)	1,184	5	1.4% APBI vs. 0.9% WBI
	NSABP B-39	4,216	N/A	N/A
Applicator brachytherapy	NSABP B-39	4,216	N/A	N/A
3D-CRT	RAPID (20)	2,135	8.6	3.0% APBI vs. 2.8% WBI
	Barcelona (21)	102	5	0% Both arms
	NSABP B-39	4,216	N/A	N/A
IMRT	IMPORT LOW (22)	2,018	6.2	0.5% APBI vs. 1.1% WBI vs. 0.2% SIB
	University of Florence (23)	520	5.0	1.5% Both arms
IORT	TARGIT-A (13)	3,451	2.4	Increased rates of local recurrence (3.3% vs. 1.3%)
	ELIOT (15)	1,305	5.8	Increased rates of local recurrence (4.4% vs. 0.4%)

APBI = accelerated partial-breast irradiation; IMRT = intensity-modulated radiotherapy; IORT = intraoperative radiation therapy; SIB = simultaneous integrated boost; WBI = whole-breast irradiation.

Table 2
Summary of IORT doses by treatment site

Breast cancer			
Partial breast	(13) Vaidya 2014	eIORT	20 Gy to the surface
	(15) Veronesi 2013	IOERT	21 Gy, 6–9 MeV, 90% IDL
Cavity boost	(29) Kaiser 2018	IOERT	10 Gy (5–12 Gy), 6 MeV (4–18 MeV), to 2 cm depth from the cavity, 90% IDL
	(30) Vaidya 2011	eIORT	18 Gy–20 Gy to the surface
	(31) Blank 2010	eIORT	20 Gy to the surface
Sarcoma			
Sarcoma	(36) Roeder 2016	IOERT	15 Gy (8–20 Gy), 6–20 MeV, 90% IDL
	(37) Stucky 2014	IOERT	12.5 Gy (12.5–17.5 Gy), 9 MeV (9–12 MeV)
	(38) Cambeiro 2015	IOERT	12.5 Gy (10–20 Gy), 6–9 MeV
Retroperitoneal sarcoma	(39) Sindelar 1993	IOERT	20 Gy, 11–15 MeV, 90% IDL
	(44) Yoon 2010	IOERT	10 Gy for complete resection, 12.5–15 Gy for microscopic disease, 20 Gy for macroscopic disease, 6–15 MeV, 90% IDL
	(45) Roeder 2014	IOERT	12 Gy (10–20 Gy), 8 MeV (6–12 MeV)
	(47) Alektiar 2000	IORT-HDR	12–15 Gy to 1 cm depth from the source
Thorax			
Advanced NSCLC	(52) Calvo 1990	IOERT	10–15 Gy, 6–20 MeV, 90% IDL
	(53) Smolle-Juettner 1994	IOERT	10–20 Gy, 7–20 MeV
	(54) Aristu 1997	IOERT	10–15 Gy
	(55) Martinez-Monge 1994	IOERT	10–15 Gy, 6–20 MeV, 90% IDL
Early NSCLC	(63) Fernando 2014	IORT-LDR	100 Gy to 5 to 7 mm along the central axis of the sublobar resection margin
Head and neck			
Advanced head and neck cancer	(72) Schuller 2007	IOERT	7.5 Gy (10 Gy for positive margins), 6 MeV, 90% IDL
	(73) Nag 2005	IORT-HDR	10 Gy (7.5–20 Gy) to 0.5 cm depth from the applicator surface
Cervical nodal metastases	(77) Zeidan 2011	IOERT	10–25 Gy, 4–6 MeV, Dmax
Pancreas			
Pancreas	(83) Willet 2005	IOERT	15–20 Gy, 9–29 MeV, 90% IDL
	(85) Keane 2018	IOERT	10 Gy (8–13 Gy) for resectable, 15 Gy (15–17 Gy) for unresectable, 9 MeV (6–18 MeV), 80% IDL (80–90% IDL)
	(86) Chen 2016	IOERT	14 Gy (10–20 Gy), 12 MeV
	(87) Calvo 2013	IOERT	15 Gy (10–15 Gy), 10 MeV (9–18 MeV)
Colorectal			
Colorectal	(96) Gunderson 1997	IOERT	7.5–25 Gy, 6–18 MeV, 90% IDL
	(97) Terezakis 2015	IORT-HDR	15 Gy (10–20 Gy), to 0.5 cm depth from the applicator surface
	(98) Dubois 2011	IOERT	18 Gy, 6–21 MeV, 90% IDL
	(99) Masaki 2008	IOERT	18–20 Gy, 6–12 MeV
	(100) Nakfoor 1998	IOERT	10–20 Gy, 9–15 MeV
Central nervous system			
High-grade glioma	(109) Fujiwara 1995	IOERT	20–25 Gy, 6–10 MeV, 80% IDL
	(112) Nemoto 2002	IOERT	15 (12–15 Gy), 4–15 MeV
	(113) Schueller 2005	IOERT	20 Gy (15–25 Gy), 9–18 MeV, 90% IDL
	(114) Giordano 2018	eIORT	20, 30, or 40 Gy to the surface, *30 Gy chosen for next trial*
Brain metastases	(119) Curry 2005	eIORT	16 Gy (10–20 Gy) to 2 mm depth beyond tumor
	(120) Pantazis 2009	eIORT	18 Gy (15–18 Gy) to tumor margin or 1 mm depth beyond
	(121) Weil 2015	eIORT	14 Gy to 2 mm depth from resection the cavity
	(126, 127) Wernicke 2014, 2016	IORT-LDR	80 Gy to 5 mm depth from resection cavity with Cs-131
Gynecologic			
Locally advanced/recurrent cervical cancer	(130) Barney 2013	IOERT	15 Gy (6.25–25 Gy), 6–18 MeV, 90% IDL
	(131) Mahe 1996	IOERT	18 Gy (10–25 Gy) after complete resection, 19 Gy (10–30 Gy) after partial resection, 6–24 MeV, 90% IDL
Recurrent Endometrial	(132) Dowdy 2006	IOERT	15 Gy (10–20,59–63) Gy
Pediatrics			
Solid tumors	(146) Merchant 1998	IORT-HDR	12 Gy to 0.5 cm depth from the applicator surface
	(147) Schomberg 1997	IOERT	10–25 Gy, 6–15 MeV, 90% IDL
Neuroblastoma	(148) Gillis 2007	IOERT	10 Gy (7–15 Gy), 4–16 MeV electrons, 80–90% IDL
	(149) Kunieda 2008	IOERT	8–15 Gy, 4–6 MeV
	(150) Rich 2011	IORT- HDR	15 Gy (8–18 Gy) to 0.5 cm depth from the applicator surface
Sarcoma	(151) Folkert 2014	IORT-HDR	12 Gy (4–17.5 Gy) to 0.5 cm depth from the applicator surface
	(152) Calvo 1991	IOERT	10–20 Gy, 6–20 MeV
	(153) Sole 2015	IOERT	10 Gy (7.5–20 Gy), 9 MeV (6–18 MeV), 90% IDL

HDR = high-dose-rate; IORT = intraoperative radiation therapy; IOERT = Electron beam IORT; LDR = low-dose-rate, IDL= isodose line.

approaches. In the TARGIT-A randomized trial, 3,451 patients received either whole-breast irradiation (WBI) or eIORT (20 Gy to the surface). Patients in the IORT arm could receive their IORT at the time of surgery before final pathology was available (prepathology cohort) or as a second procedure (postpathology cohort); in addition, patients in the IORT arm received supplemental WBI if they had margins < 1 mm, extensive intraductal component, lobular carcinoma, or met institutional criteria (21.6% prepathology, 3.6% postpathology). With short followup (median 29 months), IORT was associated with an increase in local recurrence (3.3% vs. 1.3%, $p = 0.04$, within noninferiority criteria) with higher rates seen in the postpathology cohort (5.4% vs. 1.7%, $p = 0.07$) (13); in addition, concerns have been raised regarding the statistical methods from this trial including the noninferiority criterion and the use of subgroup analyses (14). Long-term followup from this trial is awaited and 5-year outcomes were reported with a median followup of only 29 months. Similarly, the ELIOT trial randomized 1,305 women to WBI or IORT, which was delivered with electrons (21 Gy), with no supplemental WBI. Similar to TARGIT-A, at 5 years, IOERT was associated with increased rates of local recurrence (4.4% vs. 0.4%) as compared with WBI; however, a subset analysis did find low rates of recurrence in ASTRO suitable risk patients (15, 16). More recently, data from the TARGIT registry, which included 935 patients including 822 with at least 6-month followup had a 2.3% recurrence rate with only 23 months of followup (17). At this time, IORT, unlike other partial breast options (e.g., brachytherapy, EBRT) or hypofractionated WBI, has been found to have inferior local control compared with WBI (Table 1) (13, 15, 18–23). Doses used for IORT in breast cancer and by treatment site are presented in Table 2. It is important to recognize that all clinical results were based on a prescription to water as the medium (24). However, breast tissue density and composition (fat/adipose tissue content) varies up to 30% with a ratio of 70% adipose/30% glandular breast tissue (25). This variation has minimal impact with high-energy sources such as Ir-192 but may impact dosimetry for eIORT.

Recommendation. Consistent with the ABS consensus statement for accelerated partial breast irradiation, IORT, as monotherapy, after breast-conserving surgery, should not be offered to patients outside of prospective clinical trials, regardless of IORT technique used (Table 3) (12). Patients interested in IORT should have an informed discussion with their treatment team regarding the differences in local recurrence between techniques and the pros/cons of the approach. Clinicians should evaluate the dose prescription (to water vs. to tissue) because of the current dose calculation formulation limitations (26).

Lumpectomy cavity boost. A lumpectomy cavity boost has been found to reduce the rates of local recurrence after breast-conserving surgery and is recommended for appropriately selected patients (27, 28). An area of growing interest is the role of IORT to deliver a tumor bed boost. At this time, there are a lack of randomized data comparing boost techniques. However, several prospective studies have found that IORT boost is associated with low rates of recurrence and acceptable toxicity profiles (29–31). Kaiser *et al.* reported on 770 cases treated with IOERT, with 10-year followup, the in-breast recurrence rate was 2.7% (29). In addition, with the increased utilization of oncoplastic techniques, IORT boost represents a strategy where the tumor bed boost can be delivered before the oncoplastic procedure distorts the anatomy of the breast, allowing higher risk patients to receive a boost while maximizing their cosmetic outcomes in cases where boost offers a large potential local control benefit (32).

Recommendation

IORT can be considered for use as a boost technique in patients requiring a tumor bed boost. IORT may be considered a favorable option in patients undergoing oncoplastic procedures.

Future directions

More recently, a novel intraoperative approach for breast radiotherapy has been evaluated (33). With this technique, patients undergo CT-based planning, something lacking from most current IORT approaches in breast cancer, followed by a single fraction of IORT-HDR brachytherapy. A series of 28 patients underwent such an approach, receiving 12.5 Gy prescribed to a depth of 1 cm. Rates of toxicities were low with 21% Grade 2 toxicities and no Grade 3 events (33) Further data are needed regarding local recurrences with this approach before considering it a standard treatment option.

Sarcoma

Radiation therapy has been part of the treatment paradigm for soft tissue sarcoma since the advent of limb preservation (34). Traditionally, radiotherapy was delivered with postoperative EBRT, but today multiple options exist including preoperative EBRT, postoperative EBRT, brachytherapy (monotherapy/boost), and IORT. IORT is typically not used as monotherapy because of the high doses required with sarcoma but can be used to provide a boost in patients undergoing preoperative or postoperative EBRT. Data and guidelines for IORT boost are presented in the ABS Sarcoma Guidelines (35). In addition, IORT can be considered in cases with local recurrence after primary therapy (35).

The IORT dose given in conjunction with EBRT is typically 10–20 Gy, delivered in a single fraction with IORT-HDR, IOERT, or eIORT (36–38). Low energy IORT (50 kVp) may be used in cases not requiring great depth of penetration (approximately 25% of prescription dose at 1 cm) and for field sizes that are limited (<5 cm) because of applicator sizing. IOERT allows for greater options with respect to

Table 3
Summary of recommendations for intraoperative radiation by treatment site

	Recommendation	Future directions
Breast cancer		
Monotherapy	Should not be offered to patients outside of prospective clinical trials	Single-fraction IORT-HDR
Boost	Can be considered for use as a boost technique in patients requiring a tumor bed boost	In conjunction with oncoplastic surgery
Sarcoma		
Extremity	Consider in cases with close/positive margin, recurrence with reirradiation	Risk stratify high-risk patients in conjunction with EBRT
Retroperitoneal	Consider in conjunction with EBRT, particularly for cases where close/positive margins expected	
Thorax	Can be considered for appropriately selected patients. Consider placing patients on institutional registries or prospective studies to allow for greater data and follow up; consider in cases with concern for positive margin	Prospective studies in close/positive margin cases
Head and neck	Can be considered for appropriately selected patients. Consider placing patients on institutional registries or prospective studies to allow for greater data and follow up	
Pancreas	Consider in cases with concern for close/positive margin	Prospective studies in close/positive margin cases
Colorectal	Consider in cases with concern for positive margin	
CNS		
High-grade gliomas	Can be considered for appropriately selected patients. Consider placing patients on institutional registries or prospective studies to allow for greater data and follow up	INTRAMET Study
Brain metastases	Can be considered for appropriately selected patients. Consider placing patients on institutional registries or prospective studies to allow for greater data and follow up	IORT-LDR
Gynecologic	Consider in recurrent cases with concern for close/positive margins	
Pediatric cancers	Consider for pediatric sarcomas upfront when concern for close/positive margins or in recurrent sarcomas	

EBRT = external beam radiation therapy; HDR = high-dose-rate; IORT = intraoperative radiation therapy; LDR = low-dose-rate.

penetration (can select from a range of energies) but can be limited by the ability to orient the device in the treatment field. IORT-HDR is delivered with an applicator (e.g., Harrison-Anderson-Mick applicator). The applicator is sutured/packed into the tumor bed with single-fraction delivery as IORT or fractionated brachytherapy (35). Lead shielding can be used for areas at risk and organs can be displaced with packing as well. Dose constraints are provided in the ABS Sarcoma guidelines with particular attention paid to the skin, nerves, vascular structures, and bone (35).

Recommendation

IORT as a boost can be considered in patients where concern regarding close/positive margins exists or in cases of local recurrence where previous EBRT has been given. IORT technique chosen will depend on location and depth of dose needed. BED at the prescription depth should be calculated for dose summation of IORT-HDR, IOERT, or eIORT with EBRT dose.

Retroperitoneal sarcomas. Retroperitoneal sarcomas represents a clinically challenging treatment site because of normal tissue toxicity concerns and the need for higher doses. Although preoperative EBRT represents a standard approach, there is a role for IORT in the management of these sarcomas, particularly with data suggesting a benefit to dose escalation, and the ability to target areas at high-risk for microscopic residual disease (39, 40). IORT techniques used in retroperitoneal sarcomas include IOERT, IORT-HDR, and eIORT (41–43). A randomized trial compared postoperative EBRT (50–55 Gy) with IOERT and a lower postoperative dose of EBRT (35–40 Gy); the addition of IOERT was associated with a significant increase in local control (60% vs. 20%) (39). More modern studies have evaluated preoperative intensity-modulated radiotherapy with IOERT, demonstrating excellent local control (5 year 72%) and an acceptable toxicity profile (Grade 3 15%) (44–46). Toxicity remains a concern with the use of IORT as rates of severe complications can exceed 15% (39, 43, 47–50). The traditional IORT dose is 10–20 Gy; however, for retroperitoneal sarcomas, doses less than 15 Gy are recommended to reduce toxicities including bowel toxicity and neuropathy (35).

Recommendation

IORT may be considered in conjunction with preoperative radiotherapy for retroperitoneal sarcomas particularly for those cases where margins may be an issue. Multiple techniques (eIORT, IOERT, IORT-HDR) can be used.

Future directions

As hypofractionated EBRT regimens are evaluated for extremity soft tissue sarcomas, brachytherapy and IORT represent an option that can be used in a risk-stratified way for patients with high-risk features at surgery. Increased use of brachytherapy as monotherapy may also reduce the risk of complications as compared with EBRT in high-risk locations (51). With respect to retroperitoneal sarcomas, increased use of IORT should be considered as rates of local control remain low with EBRT alone.

Thorax

Although external beam is most commonly used, there are roles for brachytherapy and IORT in the treatment of non–small-cell lung cancer (NSCLC). Calvo *et al.* presented early findings using IORT as a boost at the time of surgical resection of NSCLC in addition to preoperative or postoperative EBRT more than 25 years ago (52). At this time, no prospective randomized trials have been conducted evaluating IORT for the treatment of lung cancer but a number of institutions have reported on cohorts of patients treated with IOERT to doses of 10–20 Gy (53). Although no standardized approach has been defined, areas at high risk of residual microscopic disease are frequently targeted for an IORT boost such as the hilar and mediastinal lymph nodes, and chest wall especially in the case of Pancoast tumors (54, 55).

At this time, sublobar resections are commonly used for patients with stage I NSCLC who do not have adequate pulmonary reserves to undergo a lobectomy, although this is changing with the emergence of stereotactic body radiotherapy. Local recurrence after a sublobar resection is more common than after a lobectomy, and as such IORT-LDR has been combined with sublobar resections at some centers to reduce the risk of a local tumor recurrence (56, 57). The most common form of LDR brachytherapy used for NSCLC is I-125 embedded in a mesh and sutured to the lung along the staple line at the time of resection. A number of centers have reported retrospective series that indicate that sublobar resections in combination with intraoperative LDR brachytherapy are safe, with local control outcomes similar to those seen after lobectomies (57–62). The only randomized trial of IORT-LDR for patients with lung cancer was the ACOSOG Z4032 Phase III trial which randomized 244 high-risk operable patients with NSCLC and tumor size <3 cm to sublobar resection with or without intraoperative brachytherapy (I-125 seeds, 100 Gy at 5–7 mm). The study found no significant difference in local tumor recurrence (HR, 1.01; 95% CI, 0.51 to 1.98; log-rank $p = 0.98$) but did find a trend for improved local control in the 14 patients with positive staple line cytology (HR 0.22; $p = 0.24$) (63).

Recommendation

IORT can be considered for appropriately selected patients. Consider placing patients on institutional registries or prospective studies to allow for greater data and follow up. IORT can be considered at the time of surgical resection in cases with concern for a positive margin. Intraoperative LDR brachytherapy may improve local control outcomes in patients undergoing sublobar resections for stage I NSCLC when there is a concern for a positive margin.

Future directions

Additional prospective studies are needed, including randomized trials comparing IORT-LDR to non-IORT techniques, particularly in margin-positive patients.

Head and neck cancer

Head and neck cancers represent a heterogeneous group of diseases with varied histologies, treatment paradigms, and clinical outcomes. Despite treatment, up to 30–40% of patients will recur locoregionally (64–69). Management of locoregional recurrences are challenging and usually involve surgery, reirradiation, or a combination of these options. IORT has been used for over 30 years in the treatment of primary and recurrent head and neck cancers. However, studies are limited by small numbers, varied histologies, and long periods of time over which treatment paradigms have changed (70, 71). Schuller *et al.* evaluated 123 patients with primary untreated head and neck cancer of the oral cavity, oropharynx, or hypopharynx. Patients received perioperative chemoradiation followed by resection with IOERT with a locoregional control rate of 91% (72). From the same group, Nag *et al.* evaluated 65 patients treated with IORT-HDR that was inaccessible with IOERT; at 5 years, the rate of local control was 59% with no major intraoperative or postoperative complications (72). Similar results have been seen from several other small studies (74–76). Zeidan *et al.* evaluated 231 patients with cervical node metastases undergoing neck dissection as part of primary treatment or salvage. IORT was delivered (primarily IOERT, 51% of cases) to a dose of 15 or 20 Gy. Overall, recurrence free survival was 49% at 5 years (77). A more recent series from Loyola University evaluated 22 patients with advanced or recurrent head and neck cancer treated with eIORT between 2014 and 2016; 7 cases were primary parotid tumors and the rest recurrent in the parotid or neck. Patients received 12–14 Gy definitively or a 5 Gy boost prescribed to 5 mm. With a median followup of 16 months, in-field local control was seen in 19 of 22 patients with 1 wound healing complication, 2 neuropathies, and 1 case of fat necrosis (78).

Recommendation

IORT can be considered for appropriately selected patients. Consider placing patients on institutional registries or prospective studies to allow for greater data and follow up.

Future directions

In light of the utilization of intensity-modulated radiotherapy and volumetric modulated arc therapy as well as

the use of stereotactic body radiation therapy in the recurrent setting, the role of IORT in head and neck cancers has decreased (79, 80). Future studies are needed to evaluate the role that IORT may have when combined with modern radiotherapy techniques in the salvage setting (77).

Pancreatic cancer

Pancreatic cancer represents a unique clinical challenge with its high rate of mortality, the difficulty in assessing resectability, and the risk of systemic and local recurrence after treatment. With respect to local recurrence, IORT as an adjunct to EBRT or stereotactic body radiotherapy represents an opportunity to improve local control and has been studied for more than 30 years (81, 82). Willet *et al.* presented a series of 150 patients with unresectable pancreatic cancer treated with 5-fluorouracil–based chemotherapy, EBRT, and IOERT between 1978 and 2001. Median survival was 13 months with long-term survival observed in 8 patients, including 5 beyond 5 years. In this series, use of smaller applicators was associated with improved survival (83). Updated results confirmed these findings, with multivariate analysis finding that applicators ≤8 cm were associated with improved survival (84). A modern series that evaluated the role of IOERT after neoadjuvant chemotherapy and chemoradiation included 68 patients with 41 undergoing resection; 22 patients underwent IOERT for close/positive margins. Median survival was 26.6 months for all resected patients and 35.1 months for those who received IOERT as compared with 24.5 months for those who did not. Of the 18 unresectable patients, 17 received IORT with median survival of 24.8 months (85). Similar results have been seen with additional series with limited toxicity reported (86–91).

Recommendation

IORT can be considered at the time of surgical resection in cases with concern for a close/positive margin.

Future directions

Future prospective studies with larger patient numbers are needed to determine which subgroups of patients benefit from IORT.

Colorectal malignancies

Despite multimodality treatment with preoperative radiotherapy/chemoradiation, total mesorectal excision and adjuvant chemotherapy, rectal cancers recur locally in approximately 10% of patients and in up to 20% of patients with positive surgical margins (92, 93). Local tumor recurrences can lead to significant morbidity and can be challenging to treat (94). In patients who have recurred despite prior pelvic EBRT, further full-dose EBRT is typically not feasible due to toxicity concerns, making IORT alone or in conjunction with lower EBRT doses a potential treatment option to prevent further local recurrence after surgery while minimizing morbidity. In addition, IORT has been delivered at some centers as a radiation dose escalation technique with the goal of decreasing the risk of local tumor recurrence for patients at high risk for recurrence such as those with expected positive surgical margins or with recurrent disease. IORT has been delivered most commonly as IOERT or eIORT but also with IORT-HDR. Guidelines on the use of HDR brachytherapy for colorectal cancers were published previously and as such we will review additional IORT techniques (1).

A recent systematic review of over 3,000 patients receiving IOERT or IORT-HDR for colorectal cancer found a significant improvement in local control (OR 0.22; $p = 0.03$), disease free survival (DFS) (HR 0.51; $p = 0.009$), and overall survival (OS) (HR 0.33; $p = 0.001$) with no increases in total (OR 1.13; $p = 0.57$), urologic (OR 1.35; $p = 0.47$), or anastomotic complications (OR 0.94; $p = 0.98$), although increased wound complications (OR 1.86; $p = 0.049$) were noted in patients receiving IORT compared with patients who did not (95). It should be noted that neuropathy has been reported as occurring in 23% of patients when ≥15 Gy is delivered with IOERT vs. 3% when ≤12.5 Gy is delivered (96). However, a large single-institution series of IORT-HDR for colorectal cancer using a median dose of 15 Gy (range: 10–20 Gy) demonstrated a 2% rate of Grade ≥3 neuropathy, and no association between IORT-HDR dose and toxicity was observed (97).

IORT has been evaluated in two randomized clinical trials for patients with locally advanced rectal cancers. The largest trial, a French multicenter study, randomized 142 patients after 40 Gy of preoperative EBRT to either surgical resection alone or in combination with 18 Gy IOERT. There were no significant differences found in 5-year local control ($p = 0.60$), OS ($p = 0.26$), DFS ($p = 0.78$), or postoperative complications ($p = 0.15$) between the two groups (98). Similarly, a previous smaller randomized trial of 44 patients with low rectal cancers also demonstrated no difference in oncologic outcomes with the inclusion of IORT (99). Neither of the studies reported on surgical margin status, and therefore, they were unable to determine if patients with positive surgical margins benefited from IORT. In addition, retrospective series have reported local control rates of 65–75% in patients with gross residual disease who receive preoperative EBRT and IOERT (96, 100).

Recommendation

IORT can be considered at the time of surgical resection of locally advanced or recurrent colorectal cancer in cases with concern for a positive margin, particularly when pelvic EBRT has already been delivered. A dose of 15 Gy in a single treatment to 5 mm depth in tissue using IORT-HDR has been used. However, doses less than or equal to 12.5 Gy in a single fraction should be used to reduce the risk of neuropathy when IOERT is used.

Future directions

Future prospective studies with larger patient numbers are needed to determine which subgroups of patients with primary or recurrent colo rectal cancer may benefit from IORT.

Central nervous system malignancies

High-grade gliomas

IORT represents an attractive means of improving outcomes for patients with high-grade gliomas, owing to the fact that most tumor progression occurs within 1–2 cm of the surgical margins (101–103). Furthermore, as greater extent of resection is an important predictor of outcomes, IORT may theoretically account for scenarios in which gross total resection is unable to be achieved because of proximity to eloquent areas within the brain (104, 105). Finally, IORT may also theoretically account for delays in initiation of adjuvant chemoradiation after surgery during which time tumor cells may be actively proliferating, although data vary as to whether delayed adjuvant treatment has worse outcomes than earlier adjuvant treatment (106–108). Data evaluating IORT in the pre-temozolomide era largely consist of retrospective single-institutional series. Reported IORT doses have ranged from 10 to 50 Gy prescribed to 0.5 to 3 cm, most commonly using IOERT, followed by adjuvant EBRT. Although initial reports demonstrated promising outcomes and potential improvements in OS (109-111), subsequent studies were unable to replicate the previously observed improved outcomes (112,113).

In the temozolomide era, the INTRAGO study was the first to prospectively use eIORT in a single-arm Phase I/II dose escalation study for patients with glioblastoma. The IORT doses were 20, 30, and 40 Gy prescribed to the applicator surface, which was followed by standard EBRT with concurrent and adjuvant temozolomide. At a median followup of 13.8 months, 15 patients received IORT, 3 of whom did not complete adjuvant therapy (1 did not receive EBRT). No dose limiting toxicities were observed, and of the five Grade 3 events, two were classified as ''probably'' related and three as ''possibly'' related to IORT. Radiation necrosis occurred in 33% of cases, which is higher than the 5–10% rates reported with standard of care therapy, but there was no obvious correlation with increasing IORT dose. Although conclusions regarding efficacy are unable to be made, among the 12 who completed per protocol treatment, median local progression free survival (PFS) (''local'' defined as within 1 cm of the resection cavity) was 17.8 months and median PFS was 11.3 months. Patterns of failure analysis demonstrated local recurrence in just 2 of the 15 patients, both of whom were in the lowest IORT dose group (20 Gy) and one of whom did not receive adjuvant chemoradiation. The rest of the patients failed ''distantly,'' which was presumably outside 1 cm from the resection margin. Median OS was 17.8 months in the per protocol group. Overall, the study provides data in the temozolomide era and demonstrated safety and tolerability as intended, although with higher than expected rates of radiation necrosis (114). This study has led to INTRAGO II, a European multinational randomized Phase III study evaluating standard of care EBRT with concurrent and adjuvant temozolomide, with or without 30 Gy IORT prescribed to the applicator surface, and allowing a dose reduction to 20 Gy for proximity to critical structures (115). The primary endpoint is median PFS.

Recommendation. IORT can be considered for appropriately selected patients. Consider placing patients on institutional registries or prospective studies to allow for greater data and follow up.

Future directions. Additional prospective studies are ongoing to determine whether IORT improves outcomes, as well as the optimal dose and technique to deliver IORT for patients with high-grade gliomas.

Brain metastases

Among patients with brain metastases, recent studies have demonstrated postoperative radiosurgery improves local control compared with surgery alone and also better preserves neurocognition as compared with the addition of whole-brain radiotherapy (116, 117). IORT may provide similar benefits, while minimizing changes that occur between surgery and adjuvant radiosurgery, including enlargement of the postsurgical cavity and the theoretical advantage of immediate radiotherapy to prevent tumor cell proliferation (118).

One method of IORT is interstitial radiosurgery using the photon radiosurgery system (PRS, Photoelectron Corp., Inc., Lexington, MA), which is a miniature x-ray generator with a dose rate in tissue that can reach 1–2 Gy per minute at a depth of 1 cm. The largest retrospective series using the PRS for brain metastases treated 72 lesions in 60 patients with a median peripheral dose of 16 Gy (range, 10–20 Gy). At median 6-month followup, local control was 81%. Three patients developed symptomatic radiation necrosis, three developed cerebral edema, two had hemorrhagic events, and four developed postoperative seizures (119). A subsequent prospective study treated 35 patients with PRS for brain metastases to a median dose of 18 Gy (range 15–18 Gy). At 6, 12, and 24 months, local control was 64.1%, 33.0%, and 33.0%, respectively. No Grade 5 toxicity occurred, and the rate of Radiation Therapy Oncology Group (RTOG) Grade 2–4 toxicity was 34.3% (120).

Investigators at the Cleveland Clinic prospectively treated 23 patients using eIORT in a nonrandomized feasibility study to a dose of 14 Gy prescribed to 2 mm depth from the resection cavity. All 23 patients underwent successful and safe IORT. Seven patients had local recurrence at a median of 9 months after IORT, and three developed radiation

necrosis (121). Three patients remained alive with a CNS progression-free survival of 90–96 months without additional treatment for their brain metastases. Pial penetration appeared to be a risk factor for leptomeningeal disease. A Phase II study (INTRAMET) is currently accruing in Germany assessing the feasibility of IORT for resected brain metastases with IORT prescribed to a dose of 20–30 Gy to the resection margin (122).

IORT-LDR after resection of brain metastases has also been evaluated. Earlier studies used I-125, and a 72-patient series reported 94% local control at a median 16-month followup with only 5% of patients developing radiation necrosis using a prescribed dose of 150 Gy with a median total activity of 16.15 mCi (123). A separate series similarly demonstrated a favorable one year local control of 92% (124). However, the median surface dose was 800 Gy with a median total activity of 31 mCi and 23% of patients developed radiation necrosis. A concern with this technique is that I-125 has a dose rate of 0.069 Gy/h and a half-life of 59.4 days; it has been suggested that the isotope may overdose the surgical cavity as it shrinks over time (125). Cesium-131 (Cs-131), with a dose rate of 0.342 Gy/h and half-life of just 9.69 days, has been evaluated as a potentially safer alternative. A phase I/II study of 24 patients received IORT-LDR with Cs-131 to a dose of 80 Gy at 5 mm depth with a median total activity of 46.91 mCi. Local control was 100%, and no patients developed radiation necrosis at a median 19.3 months of followup (126). Subsequently, the same technique was evaluated prospectively among patients with tumors larger than 2 cm, which have poor local control with conventional treatment after resection. Among the 42 patients with 46 larger tumors, the median total activity was 58.42 mCi (127). At a median of 11.9 months of follow-up, local control was 100% with 0% incidence of radiation necrosis.

Recommendation

IORT can be considered for appropriately selected patients. Consider placing patients on institutional registries or prospective studies to allow for greater data and follow up. Emerging evidence suggests benefit similar to stereotactic radiosurgery (SRS) to the resection cavity.

Future directions

Published data from the INTRAMET study are awaited with future studies required to compare IORT to traditional techniques including SRS and whole-brain radiation therapy. IORT-LDR also represents a promising strategy and should be compared with SRS.

Gynecologic cancers

The role of radiotherapy, including EBRT and LDR/HDR brachytherapy, is well-established for gynecologic malignancies in both the definitive and adjuvant settings. However, disease recurrence is not uncommon and typically occurs within the pelvis. Rates of pelvic failure for cervical cancer and early endometrial cancer range from 10-74% and 2–30%, respectively (128, 129). Management of locoregional recurrences are challenging, owing to the associated morbidity of disease, as well as the fact that many patients have undergone prior radiotherapy, putting them at increased risk for toxicities associated with reirradiation. IORT after salvage resection may allow for improved local control by eradicating residual disease while minimizing dose to normal surrounding tissue and therefore potential toxicity.

Data assessing the impact of IORT in recurrent gynecologic cancers are limited primarily to retrospective analyses, which include heterogeneous patient populations with varying degrees of disease recurrence, extent of salvage surgery, and proportion of patients who have undergone prior radiotherapy. In addition, local recurrences pose the same challenge as other disease sites in the pelvis where accurate targeting can be severely limited by the ability to orient the IORT applicator over the treatment field deep into the pelvis. In the two largest series of recurrent cervical cancer, IORT was delivered after salvage surgery, mostly with IOERT. Doses were typically between 15–19 Gy but ranged from 6.25 to 30 Gy. Barney *et al.*, which included 73 patients with recurrent and 13 patients with advanced cervical cancer, demonstrated 3-year relapse rates within the IOERT field and locoregionally of 23% and 38%, respectively. Median survival was 15 months. Peripheral neuropathy, ureteral stenosis, and bowel fistula/perforation occurred in 16, 4, and 4 patients, respectively (130). A separate series reviewed 70 patients with recurrent cervical cancer who received IORT. Local control was 21% and median survival was 11 months. Grade 2–3 toxicity related to IORT occurred in 14% of patients, and included neuropathy, ureteral obstruction, or stricture (131).

Several smaller series specific to recurrent endometrial cancer have been reported. Dowdy *et al.* reviewed 25 patients who underwent radical resection and IOERT to a median dose of 15 Gy with a range of 10–25 Gy. Complications included peripheral neuropathy, functional ureteral obstruction, and fistula formation, although the authors note that it was challenging to determine which component of treatment caused toxicity (132). For those patients who achieved R0 resection, 5-year OS was 71% compared with 40% for those who underwent R1 resection. Local control within the IOERT field was favorable at 84%, although 2 of the 4 local failures had a simultaneous distant failure (132). Awtrey *et al.* reviewed 27 patients with recurrent endometrial cancer who underwent a nonexenteration surgery, 9 of whom received IOERT. Median PFS was no different with IOERT (12 months with IOERT vs. 15 months without), and size of residual disease was the only predictor for PFS (133). Several additional studies have reported outcomes with IORT for recurrent gynecologic

malignancies with doses ranging from 6 to 27 Gy and local control ranging from 10 to 73% (134–144). Furthermore, the addition of EBRT to IORT may improve outcomes (132, 139, 142).

The use of IORT has also been evaluated in the primary management of locally advanced cervical cancer. Giorda *et al.* enrolled 42 patients with locally advanced cervical cancer in a single-arm Phase II study designed to assess radical surgery and IORT after chemoradiation (50.4 Gy/28 fractions with 4-field box technique and concurrent IV infusion cisplatin 60 mg/m^2 on day 1 and 5-fluorouracil 750 mg/m^2 on days 2–5 during the first and fifth week of radiation) (145). No patients received brachytherapy. Surgery was laparoscopic radical hysterectomy and pelvic lymphadenectomy or pelvic exenteration if bladder involvement was present. IORT (technique not specified) was delivered to the bilateral pelvic sites, the obturator fossa, and external pelvic vessels, or nodal regions, if involved or suspicious, to a mean dose was 11 Gy (10–15 Gy). Perioperative and postoperative complications were relatively high, with 17% of patients developing lymphoceles and 14% developing pelvic sepsis. Thirty five patients completed protocol therapy, and the 5-year DFS and OS were 46% and 49%, respectively. Outcomes were significantly improved if there was no residual tumor on pathology (145).

In summary, the addition of IORT to salvage resection for isolated recurrence of gynecologic cancers has not been evaluated prospectively. Retrospective data do not conclusively suggest that the addition of IORT improves outcomes but suggest favorable local control. Extent of resection, namely R0 resection, improves outcomes, and some data suggest the addition of EBRT improves outcomes as well. In the primary management of cervical cancer, IORT has been used prospectively but is not standard of care. Neuropathy appears to be a relatively common side effect when using IORT in the pelvis.

Recommendation

IORT can be considered at the time of surgical resection for isolated recurrent gynecologic cancer in cases with concern for residual microscopic disease.

IORT after chemoradiation and surgery for primary management of locally advanced cervical cancer should not be used off protocol.

Future directions

Prospective studies are needed to determine which subgroups of patients with primary or recurrent gynecologic cancer may benefit from IORT. Use of IORT-LDR is also being evaluated for recurrent disease in conjunction with surgery.

Pediatric cancers

Pediatric cancers represent a spectrum of diseases ranging from CNS malignancies to sarcomas. IORT represents a promising technique in pediatric cancers due to the rapid fall-off seen and the potential to limit dose received by normal tissues; also, organs at risk can be shielded or displaced. With respect to treatment efficiency, due to the single fraction delivered, only one anesthesia procedure is required. The use of IORT in pediatric cancers has been studied for several decades. Merchant *et al.* reported on a series of 16 patients treated with IORT-HDR for a variety of pediatric solid tumors (Ewing's sarcoma, rhabdomyosarcoma, synovial cell sarcoma, Wilms tumor, osteosarcoma, immature teratoma, desmoplastic small round cell tumor) to a variety of sites with several having previously received EBRT and 9 undergoing resection. IORT-HDR was delivered to a dose of 11 Gy at 0.5 cm. With a median followup of 18 months, the 2-year local control was 61% (146). Schomberg *et al.* reported on a series of 11 pediatric patients with various histologies treated with IOERT (10–25 Gy with 6–15 MeV electrons) in conjunction with EBRT. With a median followup of 99 months, 73% were disease-free with all patients undergoing gross resection with IOERT being free of local recurrence. Of note, three patients required surgery secondary to complications and two developed neuropathies (147).

EBRT plays an important role in the treatment paradigm for high-risk neuroblastoma, a radiosensitive pediatric malignancy. IORT has been used in both the upfront setting to avoid the potential long-term toxicities associated with EBRT and in the recurrent setting among patients who received prior EBRT. Gillis *et al.* described 31 patients with newly diagnosed high-risk neuroblastoma who underwent IOERT (4–16 MeV electrons) to a median dose of 10 Gy (range 7–15 Gy). Estimated 3-year local control was 85%, with treatment or disease-related side effects, namely hypertension or vascular stenosis, occurring in 23% of patients (148). Kuneida *et al.* analyzed failure patterns among 27 patients with advanced neuroblastoma who received 10–15 Gy IOERT within the abdomen or retroperitoneum. Relapse occurred in 6 patients (22%), which were typically in proximity to the IOERT field or in adjacent structures which were either shielded or moved away from the electron field. These results raised caution regarding the potential for marginal failures with the use of IOERT (149). Rich *et al.* evaluated the use of IORT-HDR using a H.A.M applicator among 44 patients with recurrent or persistent high-risk neuroblastoma, 95% of whom received prior EBRT. Median dose was 15 Gy (range 8–18 Gy), resulting in a 2-year local control of 55%. Postoperative complications occurred in 41% of patients, most commonly consisting of hydronephrosis or bowel inflammation/necrosis (150).

Sarcomas represent a type of pediatric malignancy with growing data supporting the utilization of IORT. Folkert *et al.* presented a series of 75 pediatric sarcomas treated with IORT-HDR at Memorial Sloan Kettering Cancer Center. Patients were treated between 1993 and 2013, with 37 patients treated as part of initial therapy and 38 as part of

salvage therapy. The majority received IORT with postoperative brachytherapy (55%) with 29% previously treated with EBRT to the IORT site. With a median followup of 7.8 years for surviving patients, the 5-year local control was 63% overall, with local control of 46% for recurrent disease. Acute Grade 3+ toxicity was 2.5% and late Grade 3+ toxicity was 5.3%; Grade 3 + toxicity occurred in patients 6 years or younger treated with doses of 12 Gy or greater (151). A smaller series of 38 patients from Spain included 22 osteosarcomas and 16 Ewing's sarcomas with 90% of cases being primary disease. Most patients (n = 32) had not previously received radiotherapy with IORT delivered with electrons (6–20 MeV, 10–20 Gy). With a median followup of 25 months, the 5-year disease-free survival was 65% with neuropathy and soft tissue necrosis noted (152). A larger analysis from Spain included 71 pediatric sarcomas undergoing IOERT with 65% of case incorporating IORT as part of primary treatment. With a median followup of 72 months, local control was 74% at 10 years with 13% of patients having severe (Grade 3) toxicity (153).

Recommendation

For pediatric sarcomas, IORT-HDR or IOERT can be considered in the upfront setting for high-risk patients including those with concern for close/positive margins. IORT-HDR and IOERT can also be considered in the setting of recurrence. For other histologies, IORT can be considered based on clinical and surgical features on prospective trials.

Future directions

Owing to its characteristics, IORT is a potential benefit for pediatric cancers. Future studies are needed to further elucidate roles for IORT in the management of pediatric malignancies.

Conclusions

IORT is increasingly being used with a lack of consistent clinical guidelines. IOERT, IORT-HDR, and IORT-LDR are appropriate IORT modalities. The current guidelines provide recommendations for on- and off-protocol utilization of IORT; a separate guideline will be presented for use of electronic brachytherapy (eIORT) (3). Future prospective randomized clinical trials are needed to better identify appropriate patients for IORT.

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