

Consensus Statement

# Intraoperative high-dose-rate brachytherapy: An American Brachytherapy Society consensus report

S. Lloyd<sup>1</sup>, K.M. Alektiar<sup>2</sup>, S. Nag<sup>3</sup>, Y.J. Huang<sup>1</sup>, C.L. Deufel<sup>4</sup>, F. Mourtada<sup>5,6</sup>, D.K. Gaffney<sup>1,\*</sup>

<sup>1</sup>Huntsman Cancer Institute, Department of Radiation Oncology, University of Utah, Salt Lake City, UT

<sup>2</sup>Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York City, NY

<sup>3</sup>Department of Radiation Oncology, Northern California Kaiser Permanente, Santa Clara, CA

<sup>4</sup>Department of Radiation Oncology, Mayo Clinic, Rochester, MN

<sup>5</sup>Department of Radiation Physics—Patient Care, The University of Texas MD Anderson Cancer Center, Houston, TX

<sup>6</sup>Helen F. Graham Cancer Center & Research Institute, Christiana Care Health System, Newark, DE

## ABSTRACT

**PURPOSE:** This report presents recommendations from the American Brachytherapy Society for the use of intraoperative high-dose-rate (IOHDR) brachytherapy.

**METHODS AND MATERIALS:** Members of the American Brachytherapy Society with expertise in IOHDR formulated this document based on their clinical experience and a review of the literature. This report covers the use of IOHDR in colorectal cancer, soft tissue sarcoma, gynecologic cancers, head and neck cancers, and pediatric cancers. This report does not cover intraoperative brachytherapy for breast cancer. Details about treatment planning and delivery are emphasized so this document can serve as a guide to practices implementing this technique.

**RESULTS:** IOHDR brachytherapy is generally most beneficial for patients with either close or positive margins and/or recurrent disease in a previous resection bed or previously irradiated area. IOHDR brachytherapy requires a well-coordinated multidisciplinary team. IOHDR brachytherapy is recommended in the treatment of both recurrent and primary locally advanced disease for colorectal and gynecologic malignancies, soft tissue sarcoma, and selected head and neck and pediatric malignancies. Other techniques such as perioperative fractionated brachytherapy are also acceptable in many cases with some advantages and disadvantages compared to IOHDR.

**CONCLUSIONS:** IOHDR brachytherapy is a specialized technique in radiation therapy with unique properties and advantages in cancer control. Special considerations for treatment planning and delivery are outlined herein. © 2017 American Brachytherapy Society. Published by Elsevier Inc. All rights reserved.

## Keywords:

Intraoperative high-dose-rate brachytherapy; Colorectal cancer; Gynecologic cancer; Sarcoma; Head and neck cancer; Pediatric cancer; Radiation planning

## Introduction

Intraoperative high-dose-rate (IOHDR) brachytherapy is the delivery of a single large dose of radiation via photons emitted from a sealed radionuclide brachytherapy source,

usually after maximal tumor resection of a limited area while the patient is undergoing surgery. IOHDR brachytherapy is one of the main forms of intraoperative radiation therapy (IORT). This report will focus on IOHDR; however, many reports of intraoperative electron radiation therapy (IOERT) and intraoperative orthovoltage techniques have been valuable in determining toxicities to organs at risk and defining tumor control doses, and hence, they are also considered here.

IOHDR brachytherapy allows the radiation oncologist to deliver a boost to the tumor bed while minimalizing dose to organs at risk. It is indicated when the risk of local failure is high. IOHDR brachytherapy is used for a variety of cancers either alone or as a boost in conjunction with external beam radiation therapy (EBRT). This document will focus on the

Received 8 November 2016; received in revised form 19 December 2016; accepted 2 January 2017.

Financial disclosure: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest: SL reports honoraria from Sirtex. The other authors report no conflicts of interest.

\* Corresponding author. Huntsman Cancer Institute, Department of Radiation Oncology, University of Utah, 1950 Circle of Hope, Salt Lake City, UT 84112. Tel.: 801-581-8793; fax: 801-585-3502.

E-mail address: david.gaffney@hci.utah.edu (D.K. Gaffney).

treatment of colorectal, sarcoma, gynecologic, head and neck, and pediatric cancers.

IOHDR brachytherapy is delivered with direct visualization. It allows for real-time collaboration between the surgeon and the radiation oncologist in choosing the target area. IOHDR brachytherapy is distinguished from perioperative brachytherapy procedures such as permanent  $^{125}\text{I}$  interstitial implants and temporary  $^{192}\text{Ir}$  afterloading implants in which the radiation delivery occurs after the surgery is completed. With IOHDR brachytherapy, dose-limiting structures (DLSs) may be maximally displaced with retraction or packing or protected with shields (1).

It is expected that there will be appropriate variations in practice and the recommendations in this paper are meant primarily to facilitate the use of IOHDR brachytherapy. This consensus document will review the patient evaluation and selection, treatment planning, treatment delivery, and posttreatment management of IOHDR brachytherapy.

## Methods

Members of the American Brachytherapy Society with expertise in IOHDR brachytherapy reviewed the literature. Breast cancer was excluded. The available data are compiled and presented in this document to formulate guiding principles for the use of IOHDR. This document is based both on the published literature and the clinical experience of the authors. Reviewed topics focused on the state of the art techniques in IOHDR including relevant clinical indications, patient evaluation and selection, treatment planning, and treatment delivery. All authors reviewed and edited the final manuscript for consensus.

## Preoperative patient evaluation

Patients should undergo an evaluation by a surgeon and a radiation oncologist, with assessment of the patient's ability to tolerate surgery and radiation therapy. Preoperative assessment by the anesthesia team is also necessary as the total time under anesthesia is generally increased by 1–2 hours when IOHDR is added to a surgical resection. A thorough history and examination should be conducted. Other tests may include flexible and/or rigid endoscopy (colorectal cancer) and blood work including tumor markers. Complete staging should be performed to rule out distant disease. The treating physicians should make a decision preoperatively whether the proposed IOHDR treatment is technically feasible with available techniques. Optimal imaging should be employed to aid in patient selection. In general, MRI has superior soft tissue discrimination and is the preferred imaging technique for evaluating local extent of tumor. Notably, CT is recommended for determining bone invasion and hepatic involvement.

## Patient selection/contraindications

Patients selected for IOHDR will have either (1) expected close, microscopic, or grossly positive margins, (2) recurrent disease in a previous resection bed, and/or (3) recurrent disease in a previously irradiated area in which full dose reirradiation with EBRT is felt unsafe. IOHDR brachytherapy is generally used in a curative approach, that is, in patients without metastatic disease. However, there may be select patient scenarios where IOHDR can measurably contribute to definitive local control in a patient with metastatic disease such as a young patient with a large, low-grade retroperitoneal sarcoma with small volume lung involvement.

Although the feasibility of IOHDR is determined preoperatively, intraoperative data are used to guide treatment. For example, the availability of frozen section pathology is critical to estimate the margin status and make final decisions about whether to use IOHDR and the appropriate dose and treatment volume during surgery. Intraoperative findings of tumor adherence to surrounding tissues or difficult resection can also direct treatment.

## Special considerations

### *External beam radiation therapy*

EBRT can complement IOHDR by enabling larger dose volumes to be treated than could be delivered with IOHDR brachytherapy alone. EBRT also enables elective dosing of areas considered at lower risk of recurrence. In these circumstances, IOHDR is used as a boost to areas of potential microscopic disease. EBRT can be delivered before or after surgery. The benefits of delivering EBRT preoperatively are the possibility of tumor volume reduction and increased chance of resectability, a potential reduction in postoperative complications compared to postoperative EBRT, and delivery of radiation to an oxygenated tumor. The benefits of waiting to deliver EBRT until after surgery include the benefit of intraoperative exploration to define the extent of disease including regional or distant disease such as peritoneal implants and the placement of clips to help define target volumes. Intraoperative radiation alone has also been used in patients who have refused EBRT but is generally thought to be inferior to a combined approach when feasible (2).

### *Alternative IORT techniques*

IORT may also be administered via electrons or orthovoltage photons produced by equipment that can be introduced or built into the operating room (OR). IOERT is most common. By varying the electron beam energy along the range of 6 MeV–20 MeV, radiation can be delivered to depths up to 5 cm. Bolus is applied when dose is desired at superficial tissues. The operative suite must be

equipped with shielding. Electron applicators are bulky and can be difficult to apply if an angled approach into the operative bed is desired. High-dose-rate (HDR) afterloaders in the OR are mobile and less expensive than a linear accelerator and allow for use in other procedures in the outpatient setting when not needed in the OR (3).

### Perioperative brachytherapy

Perioperative HDR brachytherapy is an alternative to IOHDR in many instances. With this technique, catheters are placed in the target area and radiation is delivered in a nonoperative setting. The details of the clinical factors and treatment planning and delivery of this technique are beyond the scope of this report. For the disease sites covered in this report, perioperative brachytherapy may be more appropriate than IOHDR when (1) the OR time required for IOHDR would unacceptably increase the risk of complications, (2) more time is desired for individualization of the dose distribution, or (3) when more than one fraction is desired. In many cases, IOHDR and perioperative brachytherapy are both appropriate options. It is recognized that, because of the need for a shielded OR or nearby vault, IOHDR may be associated with higher costs. Perioperative brachytherapy should not be selected when correct catheter placement cannot be attained or verified as may be the case for some deep pelvic tumors.

## Clinical indications for IOHDR brachytherapy

### Colorectal cancer

Locoregional relapse after primary treatment of colorectal cancer portends a poor prognosis with median survival ranging from 11 to 15 months, with fewer than 5% surviving 5 years. Options for the treatment of local recurrences are limited and include surgery and radiation therapy. In previously radiated patients, retreatment with EBRT can lead to high rates of toxicity. For these reasons, IOHDR is an appropriate option both to prevent local recurrences in the up-front treatment of locally advanced colorectal cancer and as a treatment for recurrent colorectal cancer with good results (Table 1).

As with EBRT, the majority of colorectal cancer patients treated with IOHDR have primary rectal cancers. When IOHDR is used for colon cancer originating in the sigmoid colon or more proximal, it is often for a recurrence in the pelvis. However, it can also be for adherence to abdominal structures such as the abdominal wall and retroperitoneum where there is a concern for incompletely resected margins.

Consistent with other disease sites discussed in this review, much of the literature deals with electron beam therapy, although a handful discuss brachytherapy uniquely (4, 7, 8). Although this review focuses on IOHDR, it is useful to discuss the electron beam experience as well to draw

conclusions about the appropriate dose and tolerance of surrounding structures. A meta-analysis found no difference in the incidence and severity of complications between IOERT and IOHDR in colorectal cancer (20).

Two randomized controlled trials have been conducted to evaluate the addition of IOERT in locally advanced, nonrecurrent rectal cancer (5, 6). In the study by Dubois *et al.* (5), high rates of local control were found in both arms of the trial (92% in patients receiving IOERT vs. 93% in those receiving standard care,  $p = 0.60$ ). Surgical margin status is not stated but given the relatively early stage of most patients in the study, it is likely that the majority of patients achieved a complete resection, thus minimizing the potential benefit of IOERT. Similarly, IOERT did not affect outcomes in a smaller trial by Masaki *et al.* (6) that included early-stage patients and none with T4 disease.

A meta-analysis of comparative studies including both IOHDR and IOERT showed improved local control ( $p = 0.03$ ), disease-free survival ( $p = 0.009$ ), and overall survival (OS) ( $p = 0.001$ ) in patients with both recurrent and locally advanced disease treated with intraoperative radiation (20). IORT is most beneficial for patients with R1 resections or recurrent disease. Studies that report no benefit have often, but not always, consisted of patients with R0 resections (9, 21) or early-stage patients with exceptionally good outcomes in both arms (5). However, several studies including patients with R0 resections have shown a benefit to IOHDR or IOERT (10, 22).

Toxicity has been low in studies of IOHDR for colorectal cancer, even though patients are often exposed to multiple treatment modalities including retreatment in the recurrent setting. In the above-mentioned meta-analysis, the most frequently reported morbidities were wound-related problems (incidence ranging from 3% to 46%), gastrointestinal complications such as fistulae (incidence 1% to 8%), ureteric obstruction (incidence 2% to 12%), and late neuropathy (incidence 2% to 22%) (20). There was no increase in total, urologic, or anastomotic complications, but there was an increased rate of wound complications ( $p = 0.049$ ). In a review of 607 patients with recurrent colorectal cancer treated with IOERT by Haddock *et al.*, the rate of Grade 3 or higher toxicity was 11% (19). Neuropathy (any grade) was observed in 15% and was associated with doses exceeding 12.5 Gy (Gy). Delayed sacral osteonecrosis has been reported infrequently (21).

The IOHDR application should be targeted to the area considered to have the greatest risk of recurrence (12). In their review of 243 patients treated with IOERT for locally advanced rectal cancer, Roeder *et al.* (13) reported seven (3%) in-field recurrences in the presacral space, five (2%) recurrences in the retrovesical/retroprostatic area, two (<1%) recurrences in the anastomotic site, and one (<1%) recurrence each at the promontorium, ileocecal area, and perineal area. Some centers always irradiate the presacral space (13). Some have alternately suggested that presacral recurrences result from spill from surrounding high-risk areas that are

Table 1  
Literature summary—colorectal cancer

Author	N	Median followup (mo)	Intraoperative dose (Gy)	Surgical margins	EBRT	Outcomes	Comments
Locally advanced colorectal cancer							
Alektiar (MSKCC) 2000 (4)	74	22	10–18	21/74 had positive margins	29 patients received additional EBRT	5-yr LC 39%; 5-yr OS 23%	Negative margin and use of IOHDR brachytherapy correlated with improved survival.
Dubois (France) 2011 (5)	142	60	18	—	40 Gy preop	5-yr LC 92% vs. 93% ± IOERT; no difference in LC, OS, or DFS	Phase 3 RCT. T3 or T4 rectal cancer. All cases treated with IOERT.
Masaki (Tokyo) 2008 (6)	44	34	18–20	—	None	No difference in LC, OS, DFS	Japanese RCT. Surgery alone vs. surgery plus IOERT. Inclusion of patients with T1/2 disease. None with T4 disease.
Huber (Germany) 1996 (7)	38	26	15	R0 in 27 R1 in 6 R2 in 5	19 postop (T3 tumors) 19 preop (T4 tumors)	5-yr LC 84% (T3), 90% (T4) 5-yr in-field LC 100% 5-yr OS 28%	IOHDR. Postop morbidity 68%, mostly delayed sacral wound healing.
Nuyttens (The Netherlands) 2004 (8)	37	34	10	—	All received preop	5-yr LC 81% 5-yr in-field LC 94% 5-yr OS 61%	IOHDR, margins ≤ 2 mm. Primary locally advanced rectal cancer in 18 pt and recurrent disease in 19 pt. Dose prescribed to 1 cm. LF greater for recurrent disease (52% vs. 19%, <i>p</i> = 0.004).
Ferenschild (The Netherlands) 2006 (9)	27	25	10	—	Preop 50 Gy	5-yr LC 72% (R0), 58% (R1/2) 5-yr OS 66% (R0), 38% (R1/2)	IOHDR given if R1 or ≤ 2 mm margins. Compared to non-IOHDR cohort, IOHDR improved 5-yr LC (58% vs. 0%) and 5-yr OS (38% vs. 0%) in R1/2 patients.
Valentini (Rome) 2009 (10)	29	31	10–15	All R0	100% preop	In-field LC 100%	All T4 rectal cancers. 29/100 received IOERT. IOERT improved LC when R0 resection (100% vs. 81%, <i>p</i> = 0.014).
Kusters (The Netherlands) 2010 (11)	605	56 (for surviving pts)	10–12.5	Varied	36% preop (45–50.4 Gy)	5-yr LC 88% 5-yr OS 67%	Multinational review, advanced T3 or T4 tumors. IOERT. 55% of pts with +SM did not develop LR.
Mannaerts (The Netherlands) 2000 (12)	38	21	10–17.5	—	100% preop	5-yr LC 82% 5-yr LC (in-field) 92% 5-yr OS 72%	IOERT
Roeder (Heidelberg) 2007 (13)	243	59	10 (median)	R0 in 93%	36% preop 50% postop	5-yr LC 92%	IOERT. Recurrence most common in presacral space.
Recurrent colorectal cancer							
Pezner (City of Hope) 2002 (14)	15	>20	15	R0 in 4 R1 in 8 R2 in 3	3 received postop RT to 25.2 Gy/14 fractions	3-yr OS 29% MOS 9 months in patients fixed or bulky tumors	IOERT for salvage in previously irradiated patients with rectal and sigmoid colon cancer. Concluded that the value of IOERT may be greater in less extension of disease.
Hashiguchi (Japan) 2003 (15)	39	36	15–30	—	31% preop 38% postop	3-yr OS 44%	IOERT for pelvic recurrences.
Martinez-Monge (Ohio State) 1999 (16)	51	48	10–20	—	Postop in 47%	5-yr LC 26% 5-yr OS 4%	IOERT (28 pt), IOHDR (23 pt), or <sup>125</sup> I brachytherapy (29 pt). Colorectal recurrences in the pelvis or paraaortic lymph nodes. Over 50% had previous RT.

Table 1 (continued)

Author	N	Median followup (mo)	Intraoperative dose (Gy)	Surgical margins	EBRT	Outcomes	Comments
Shoup (MSKCC) 2002 (17)	100	23	12.5–17.5	R0/R1/R2	37% preop	In-field LC 67%	IOERT. 50% had previous radiation. R0 resection predicted for improved OS and LC.
Vermaas (The Netherlands) 2008 (18)	11	22	10–12.5	R0/R1/R2	55% preop	5-yr LC 27% 5-yr OS 51%	IOHDR (9), IOERT (1)
Haddock (Mayo) 2011 (19)	607	36	15 (median)	R0 (37%) R1 (37%) R2 (26%)	96% before or after IOERT	Median OS 36 months 3-yr “central” relapse 12%	All received IOERT. Distant relapse much more common. Improved survival associated with R0 resection, no prior chemotherapy, and later years of the study (entire study was 1981–2008). Grade 3 + toxicity partially due to IOERT found in 11% of patients.

EBRT = external beam radiation therapy; OS = overall survival; IOHDR = intraoperative high-dose-rate; IOERT = intraoperative electron radiation therapy; LC = local control; DFS = disease free survival; RCT = randomized controlled trial; LF = local failure; SM = surgical margin; LR = local recurrence; RT = radiation therapy; MOS = median overall survival.

not optimally treated when only the presacral space is targeted (23). Either of these strategies may be appropriate.

Colorectal cancer consensus recommendations:

- IOHDR brachytherapy is an appropriate component of the treatment of colorectal cancer for likely positive margins or recurrent disease.
- Given a meta-analysis of prospective and retrospective studies showed a benefit locally advanced (nonrecurrent) patients, IOHDR may be appropriate but is not uniformly recommended for up-front use in colorectal cancer (20).
- Doses of 10–17.5 Gy to depths of 0 cm–1.0 cm are usually most appropriate as they are most frequently reported with good results and acceptable toxicity (IOHDR Treatment Planning Basics for further dose depth guidance).
- A strategy of increasing doses incrementally according to resection status is also recommended with 10–15 Gy given for microscopic residual disease and 15–17.5 Gy given when gross residual disease is suspected (12,13,21,22,24).

#### Soft tissue sarcoma

The use of brachytherapy for soft tissue sarcoma is well established with a wide range of brachytherapy techniques including low dose rate, HDR, and intraoperative techniques. Although perioperative brachytherapy is more widely reported in the literature, IORT is an appropriate option to limit local recurrence when direct visualization of the tumor bed and/or shielding of surrounding tissue is desired. As in other sites, it is most beneficial for cases where surgical margins are likely to be positive. It is frequently used with neoadjuvant or adjuvant fractionated EBRT as the doses needed to sterilize relatively radioresistant sarcomas usually surpass normal tissue tolerance. IOHDR brachytherapy doses should range from 10 to 17.5 Gy in the abdomen and 10 to 20 Gy in the extremities, to depths of 0 cm to 1 cm. Doses at the higher end of these ranges are recommended when the risk of positive margins is high if tissue tolerance allows.

Retroperitoneal sarcomas represent about 15% of all soft tissue sarcomas. Seventy-two percent of these tumors recur at 5 years and 91% recur at 10 years even after complete gross resection (25). This group of sarcomas presents unique challenges in treatment for several reasons. Complete surgical resection is difficult due to their tendency to invade into surrounding structures. Likewise, EBRT for retroperitoneal sarcomas is challenging because of their proximity to vital organs and the relative radioresistance of sarcomas. Finally, perioperative brachytherapy may not be possible due to their location.

One of the few published prospective series of IOHDR for retroperitoneal sarcoma showed good local control but some concern about wound complications with 8 of 39 patients requiring revision surgery (26) (Table 2). One

Table 2  
Literature summary—soft tissue sarcoma

Author	<i>N</i>	Median followup (mo)	Intraoperative dose (Gy)	Surgical margins	EBRT	Outcomes	Comments
Retroperitoneal soft tissue sarcoma							
Rachbauer (Austria) 2003 (26)	39	26 (mean)	Not listed	All “marginal resections”	Yes	2-yr DFS 84%	Prospective study or IOHDR. 32 high grade and 7 low grade. 35 were >5 cm. Treatment-related wound morbidity in 11 patients with revision surgery in 8.
Alektiar (MSKCC) 2000 (27)	32	33	12–15		78% of patients (45–50.4 Gy)	5-yr LC 62% 5-yr DFS 55% 5-yr OS 45%	Outcomes improved for primary (not recurrent) disease, low grade. 18% GI obstruction, 9% fistula formation, 6% peripheral neuropathy.
Sindelar (multiple institutions) 1993 (28)	35	96	20	All patients considered to have microscopic residual disease	Yes, postoperative. 35–40 Gy for IOERT, 50–55 Gy for no IOERT	Median OS in IOERT group: 45 months Median OS in control group: 52 months (not statistically different) IOERT improved local control ( $p < 0.05$ )	Randomized trial of IOERT with “low-dose” adjuvant EBRT vs. no IOERT with “high-dose” adjuvant EBRT. IOERT group experienced less radiation enteritis (40% vs. 80%) but more neuropathy (60% vs. 5%).
Peterson (Mayo) 2002 (29)	87	42	12 (primary treatment) 15 (recurrent tumors)	64% had microscopic residual tumor 17% had gross residual disease	77 received EBRT (53 neoadjuvant, 12 adjuvant) Median dose was 47.6 Gy (range 10–65 Gy)	5-yr OS 47% 5-yr LC 59%	Grade 3 or higher GI toxicity in 12 cases (14%).
Roeder (Heidelberg) 2014 (30)	27	33	10–12	R0 in 22% R1 in 74%	Neoadjuvant RT to 45–50 Gy with boost to 50–56 Gy	3-yr LC 72% 3-yr OS 74%	Interim analysis of a Phase I/II trial of IOERT for primary and recurrent disease. Grade 3 + toxicity in 15%. Severe postoperative complications in 33%.
Sweeting (North Carolina) 2013 (31)	18	42	10–15 depending on margins 12.5–20 if no EBRT	R0 in 89% R1 in 11%	Neoadjuvant 45 Gy for most patients	5-yr LC 64% 5-yr OS 72%	Two perioperative deaths not included in outcomes.
Tran (Stanford) 2008 (32)	50	35	6–16	R0 in 15% R1 in 70% R2 in 15%	Postoperative EBRT in 37%	5-yr LC 55% 5-yr DSS 25%	Orthovoltage intraoperative radiation to recurrent sarcomas of the retroperitoneum (78%), extremity (8%), and other sites (14%). 5-yr Grade 3 or 4 complication-free survival rate of 85%. Disease-free interval before recurrence of >12 months associated with favorable outcomes.
Lehnert (Heidelberg) 2000 (33)	92		15–18 for retroperitoneum 12–15 for extremities				Review of 251 pt with STS, 92 of whom received IOERT. IOERT associated with reduced relative risk of death or recurrence by 40% ( $p < 0.02$ ). Infectious complications higher in patient receiving IOERT ( $p = 0.03$ ).

(Continued)

Table 2 (continued)

Author	<i>N</i>	Median followup (mo)	Intraoperative dose (Gy)	Surgical margins	EBRT	Outcomes	Comments
Extremity soft tissue sarcoma							
Tinkle (UCSF) 2015 (34)	26	35	10–18	R0 in 54% R1 in 46%	58% received EBRT before IOERT (median dose 63 Gy) 42% received adjuvant IOERT (median dose 52 Gy)	5-yr LC 58% 5-yr amputation free 81% 5-yr DFS 35% 5-yr OS 50%	IOERT for locally recurrent extremity sarcoma. Grade 3 + acute and late toxicities seen in 23% and 31%, respectively.
Niewald (Germany) 2009 (35)	38	28	8–15	R0 in 39% R1 in 32% R2 in 11%	Adjuvant EBRT in 82% 50 Gy if R0 56 Gy if R1	5-yr LC 63% 5-yr OS 57%	IOHDR for 29 primary tumors and 9 recurrences. 72% in the extremities, the rest in the retroperitoneum or chest. Late skin toxicity 42%, wound healing problems in 16%. No neuropathy seen.
Calvo (Spain) 2014 (36)	103	57	10–20 (median 12.5)	R0 in 60% R1 in 40%	62% received RT	5-yr LC 60% 5-yr IOERT in-field control 73% 5-yr OS 52%	Joint analysis of three Spanish centers. Recurrent patients and those with positive had higher rates of LC when treated with EBRT.
Azinovic (Spain) 2003 (37)	45	93	12–15		Adjuvant EBRT 45–50 Gy	5-yr LC 88% if negative or close margins 5-yr LC 57% if positive margins Extremity preservation in 88%	IOERT for extremity STS. Peripheral nerves were displaced or dose limited to 10 Gy. 11% developed neuropathy.

EBRT = external beam radiation therapy; OS = overall survival; IOHDR = intraoperative high-dose-rate; IOERT = intraoperative electron radiation therapy; GI = gastrointestinal; STS = soft tissue sarcoma; DSS = disease specific survival.

prospective randomized trial examining the role of IOERT for retroperitoneal soft tissue sarcoma has been completed (28). Patients were randomized to IOERT to 20 Gy followed by adjuvant “low-dose” EBRT to 35–40 Gy or no IOERT and adjuvant EBRT to 50–55 Gy. Although there was no difference in survival or cancer-free survival, fewer patients in the IOERT group recurred locally. Side effects differed between treatment arms: patients in the IOERT group were less likely to experience enteritis but more likely to experience radiation-related peripheral neuropathy.

Soft tissue sarcomas of the extremities present different anatomic challenges but may be amenable to treatment with several brachytherapy techniques including both perioperative low-dose or high-dose-rate brachytherapy, IOHDR, or IOERT. The choice of optimal therapy should be individualized and is dependent on the available equipment, experience, and expertise. IOHDR brachytherapy is also an attractive option for pediatric sarcomas as small children will not have to be anesthetized again for treatment after surgery (38). This topic is covered in the pediatric section of this manuscript.

The addition of IOHDR to surgery increases toxicity, but this is usually acceptable given the local control benefit. In the treatment of retroperitoneal sarcomas, Grade 3 or higher gastrointestinal toxicity has been reported to occur in 14% (29). In a review of 251 patients from Germany with soft tissue sarcoma of any site, in which 92 received IOERT, IOERT was associated with reduced relative risk of death or recurrence by 40% ( $p < 0.02$ ) (33). However, infectious complications were higher in patients receiving IOERT ( $p = 0.03$ ) with a trend of surgical complications being more common (33% vs. 23%,  $p = 0.1$ ).

Sarcoma consensus recommendations:

- IOHDR brachytherapy is an appropriate option to limit local recurrence when direct visualization of the tumor bed is possible. As in other sites, it is most beneficial for cases where surgical margins are likely to be positive.
- IOHDR brachytherapy is frequently used with neoadjuvant or adjuvant fractionated EBRT as the doses needed to sterilize relatively radioresistant sarcomas usually surpass normal tissue tolerance.
- IOHDR brachytherapy doses should range from 10 to 17.5 Gy in the abdomen and 10 to 20 Gy in the extremities, to depths of 0 cm to 1.0 cm (IOHDR Treatment Planning Basics for further dose depth guidance). Doses at the higher end of these ranges are recommended when the risk of positive margins is high if tissue tolerance allows.

### Gynecologic cancers

IOERT has been employed mostly for recurrent disease in gynecologic cancers, often with good results. It has also been used as a strategy in the initial management of gynecologic cancers (39) (Table 3). Many reports on gynecologic cancers

include uterine, cervix, vulvar, vaginal, and ovarian cancers, and hence, these data are summarized here. Also, many reports include IOHDR with Harrison-Anderson-Mick (HAM) applicators (discussed below); however, there are also many reports of IOERT use (44, 47). On review of the literature, several valuable issues are manifest.

For large pelvic tumors, local-regional control (LRC) is reasonable high. Of the 16 reports in Table 3, the median LRC is 67% with a range of 93–21%. In-field local control is as high as 100% in some series (42). More contemporary series have higher local control rates which are likely due to better patient selection via modern imaging and perhaps due to greater surgical expertise at achieving an R0 and R1 resection. Large tumor volume is an adverse factor in numerous series (43). LRC is higher when RT was not used previously (46). Martinez-Monge *et al.* (49) showed a 33% and 77% LRC rate in the presence and absence of a previous course of EBRT, respectively. As in many other recurrent disease settings, a greater time interval between diagnosis and recurrence is also prognostic (49). An R0 and R1 resection was markedly better than an R2 resection emphasizing the importance of a macroscopic complete resection (45, 48). In a report by Barney *et al.* (52) in ovarian cancer patients, all local relapses were in margin positive cases. Importantly, Cambeiro *et al.* (45) demonstrated a dose response on multivariate analysis for LRC. LRC was superior when the sum of EBRT and IOERT was  $\geq 62$  Gy EQD2. A recent report by Barney *et al.* from the experienced Mayo Clinic team documented an excellent LRC rate of 93% in uterine sarcomas with no failures in the intraoperative field with a median EBRT dose of 50.4 Gy and median intraoperative dose of 12.5 Gy. They concluded that IOHDR or IOERT should be used if the surgical margin will be questionable (42).

It is challenging to ascribe toxicities specifically to IOHDR when patients are also treated with multiple modalities including chemotherapy, EBRT, and aggressive resection. In Table 3, nine series documenting IOHDR, IOERT, or both reported toxicities (most reporting Grade 3 and 4) ranging from <10% to 33%. The incidence of any grade neuropathy ranged from 7% to 33% in six different reports. Toxicities solely attributable to intraoperative treatment were 10% and 29% in two series from the Mayo Clinic (48, 52).

Gynecologic cancer consensus recommendations:

- IOHDR brachytherapy is an appropriate component of the treatment of gynecologic cancers for likely positive margins or recurrent disease.
- Doses of 10–17.5 Gy to depths of 0 cm–1.0 cm are recommended as they are most frequently reported with good results and acceptable toxicity (IOHDR Treatment Planning Basics for further dose depth guidance).
- In patients who have not previously received EBRT, it is appropriate to combine IOHDR with fractionated EBRT with a recommended equivalent dose in 2 Gy per fraction (EQD2)  $\geq 62$  Gy (45).



Table 3  
Literature summary—gynecologic cancers

Author	N	Median followup (mo)	Intraoperative dose (Gy)	Surgical margins+/total	EBRT	Outcomes	Comments
Backes (Ohio State) 2014 (40)	32	NS	15–17.5	10/32	100%	LRC 66%	66% cervical, 25% vaginal, 9% vulvar. 21/32 received IOERT, IOERT did not change outcome, but IOERT patients had worse prog.
Giorda (Italy) 2011 (39)	35	NS	10–15	0/35	100%	11% in-field 17% other pelvic	Stages IIA bulky IVA. Intraoperative radiation seems to be active.
Tran (Stanford) 2007 (41)	36	20	11.5	80%	72% prev. 53% post	44% 5 yr LRC	Orthovoltage, 47% cervix, 31% uterine, 14% vulvar, 6% vaginal. IORT useful in select patients, 28% G3-4 complications.
Barney (Mayo) 2012 (42)	16	NS	12.5	6/16	100%	LRC 93% 3 yr	All uterine sarcomas. 19% G3 toxicity. IOHDR or IOERT should be used if margin is questionable. 19% G2 peripheral neuropathy.
del Carmen (Mass General) 2000 (43)	15	3–36	10–20.5		9/15 prev. EBRT	LRC 53%	Volume may be important for relapse.
Konski (Ohio) 1990 (44)	9		20		100% postop	25% OS, 2 yr	IOERT. 33% (3 of 9) developed neuropathy.
Cambeiro (Spain) 2015 (45)	128	19 mo	15		61% EBRT	LRC 31%, 5 yr OS 31%, 5 yr	24% G3-5 complications. R0/R1 better than R2, EQD2 $\geq$ 62 Gy sig on MVA for LRC. All sites, 22% gyn.
Sole (Spain) 2015 (46)	35	55	12.5		51%	79% LRC, 5 yr	No prior EBRT and time interval sig on MVA for LRC, only R1 sig for OS on MVA.
Mahe (France) 1996 (47)	70	15	18–19	53%	43%	LRC 21%	65 e beam and 5 supervoltage. Feasible. Intraoperative radiation toxicity in 14%: 5 neuropathies, 4 ureteral obstructions, and 1 rectal stricture.
Garton (Mayo) 1993 (48)	21		12.5–25	100%	67%	71% LRC, 5 yr 80% LC in IOERT field	Toxicity acceptable. 29% toxicity attributable to IOERT. 9% neuropathy. R2 did worse. R1 did well. 69% cervix.
Martinez-Monge (Spain) 1993 (49)	26		10–25			LRC 33% with prev RT LRC 77% with no RT	IOERT study. Combining chemo, surgery, EBRT, and IOERT may render some long-term survivors.
Gemignani (MSKCC) 2001 (50)	17	20	14		59%	67% LRC, 3 yr	53% cervix, 41% uterine, 6% vaginal. S + IOHDR provides good LRC. 5 G3, 0 G4 toxicities, 18% peripheral neuropathy.
Dowdy (Mayo) 2006 (51)	25		15	72%	84% LC in IOERT field	84% LRC	R0 better survival than R1/2. Predictors of OS are concurrent EBRT, grade, tumor size, and age. Combining surgery, EBRT, and IOERT may render some long-term survivors.
Barney (Mayo) 2011 (52)	20	76	12.5		80%	LRC 59%, 5 yr 76% in IOERT field	All local relapses were in margin pos. cases. 29% toxicity in G3 or higher. 10% attributable to IOERT, 3 patients experienced G1-2 neuropathy.

EBRT = external beam radiation therapy; OS = overall survival; IOHDR = intraoperative high-dose-rate; IOERT = intraoperative electron radiation therapy; LRC = local-regional control; IORT = intraoperative radiation therapy; IVA = as in stage IV-A (4A); MVA = multivariable analysis.

Table 4  
Literature summary—head and neck

Author	N	Median followup (mo)	Intraoperative dose (Gy)	Surgical margins+/total	EBRT	Outcomes	Comments
Nag (Ohio State) 2005 (53)	65		7.5–15		17 pt (45–50 Gy)	5-yr LC 59% 5-yr OS 42% mOS 50 months	Base of skull involvement from various sites. No major intraoperative or postoperative complications.
Nag (Ohio State) 2004 (54)	34	72	10–12.5 if with EBRT. 15–20 if no EBRT		27 pt (45–63 Gy) Prior EBRT in 7 and they were treated with IOHDR alone.	5-yr OS 44% 5-yr LC 65%	Paranasal sinus tumors. IOHDR given after maximal surgical excision. Presence of gross disease after surgical resection was the biggest predictor of survival.
Teckie (MSKCC) 2013 (55)	57	16				3-yr PFS 57% 3-yr OS 50%—when achieving in-field control	All patients with recurrence cancer, various primary sites. Dose > 15 Gy improved survival. Grade 3 toxicity in 37%—unrelated to dose.

EBRT = external beam radiation therapy; OS = overall survival; IOHDR = intraoperative high-dose-rate; DFS = disease free survival.

Head and neck

Unfortunately, there are only a few institutions that have reported their experience with IOHDR in head and neck cancer. IOHDR brachytherapy is useful in the base of skull and the paranasal sinuses as these areas are difficult to treat with IOERT or perioperative brachytherapy due to their inaccessibility, and the narrow cavities and bony structures which impose geometric constraints to electron beam applicators. Shielding of adjacent critical structures is also problematic with high-energy electrons. IOHDR brachytherapy permits delivery of a single high dose of brachytherapy, gaining access to the tumor bed after resecting bony structures (e.g., maxilla) and retracting or shielding critical structures like the eyes. For these reasons, IOHDR may be more appropriate than perioperative brachytherapy for base of skull or deeper head and neck tumors. Bones can be regrafted in place after the radiation has been delivered. Unfortunately, there are a few institutions that have reported the use of IOHDR in head and neck tumors (Table 4).

Skull base IOHDR was reported by Nag *et al.* (56) from The Ohio State University originally in 29 patients with base of skull involvement from various sites. All patients were able to undergo gross total resection. Patients were then treated with IOHDR (7.5–15.0 Gy) with (*n* = 17) or without (*n* = 15) EBRT (45–50 Gy) as part of the treatment plan. At a median followup of 21 months, local failure was 11% in patients receiving combined IOHDR and EBRT. Local failure was 67% (8/12) among patients treated with IOHDR only, 83% (5/6) in patients receiving previous EBRT, and 50% (3/6) if patients could not complete EBRT. No major complications occurred during the delivery of IOHDR. Chronic complications were reported in 5 patients and included cerebrospinal fluid leak with bone exposure, hematoma, septicemia, otitis, and severe xerostomia. No episodes of carotid blowout or osteoradionecrosis were reported. This experience was updated in 2005 in 65 patients (53). The 1-, 3-, and 5-year local control rates for the entire group were 77%, 69%, and 59%, respectively. The 1-, 3-, and 5-year OS rates were 83%, 63%, and 42%, respectively, with a median OS of 50 months. There were no major intraoperative or postoperative complications.

Tumors of the paranasal sinus can also be successfully treated with IOHDR after maximal surgical resection as reported by Nag *et al.* (54). Twenty-seven patients with new primaries underwent gross resection and 10–12.5 Gy IOHDR followed by 45–50 Gy EBRT. Seven previously irradiated (45–63 Gy) patients with recurrent disease were treated with 15–20 Gy of IOHDR alone after gross excision. After a mean followup of 6 years (range 34–120 months), the 1-, 3-, and 5-year actuarial survival rate was 80%, 62%, and 44%, respectively. The overall local control rate at 1 and 5 years was 75% and 65%, respectively. Subgroup analysis revealed that the presence of gross disease after surgical resection was the strongest prognosticator, with a 5-year survival and local control rate of 17% and 50%,

respectively, compared with 60% and 68%, respectively, for microscopic disease. The addition of EBRT to IOHDR increased the 5-year disease-free survival rate from 27% to 44% but had no effect on local control (64% vs. 65%). They concluded that IOHDR could be safely used to deliver a high radiation dose to locally advanced and recurrent tumors in the paranasal sinuses. They recommend considering chemosensitization in previously irradiated patients and in those with gross residual disease. Furthermore, they advocate considering interstitial boosting techniques, which can deliver higher doses at depth, in patients with gross residual disease. IOHDR brachytherapy is not recommended alone in previously irradiated patients as it achieves poor local control (57).

Teckie *et al.* (55) from the Memorial Sloan-Kettering group reported their experience with single fraction IOHDR in 57 patients with recurrent head and neck cancer treated between 1998 and 2011. One- and 3-year in-field progression-free survival (IFPFS) was 67% and 57%, respectively. In a multivariate model, IOHDR dose >15 Gy (hazard ratio [HR] = 0.11;  $p = 0.02$ ) and prerecurrence disease-free interval >12 months (HR = 0.29;  $p = 0.04$ ) independently predicted for superior IFPFS; nodal extracapsular extension (HR = 4.62;  $p = 0.003$ ) predicted for inferior IFPFS. Three-year OS was 50% vs. 32% in those achieving in-field control vs. those not achieving in-field control ( $p = 0.04$ ). Grade 3 + toxicity occurred in 37% and was unrelated to IOHDR dose. They concluded that IOHDR dose >15 Gy should be used to increase the likelihood of disease control.

Head and neck cancer consensus recommendations:

- It may be appropriate to use IOHDR for head and neck cancers involving the base of skull or paranasal sinuses in cases of likely positive margin or when resecting recurrent disease.
- Doses of 10–15 Gy of IOHDR (prescribed 1 cm from the plane of the catheters or 0.5 cm from the applicator–tissue interface) are appropriate in conjunction with 45–50 Gy of EBRT for the treatment of microscopic disease in previously unirradiated patients (58).
- For previously irradiated patients, when no or only limited dose of EBRT can be given, IOHDR dose >15 Gy is required (55).

### Pediatric cancers

IOHDR brachytherapy has special relevance in pediatric cancers because young children may not be able to lie still and hence may need to be anesthetized for fractionated HDR brachytherapy treatments. Although anesthesia is still required for IOHDR, the problem is minimized because it is given in a single fraction directly to the tumor site under direct vision. In general, IOHDR is reserved for sites not amenable to IOERT if both techniques are available. These sites include, but are not limited to, the base of skull, thorax, abdomen, pelvic side walls, and the retropubic area. Narrow

cavities and corners/curves in these areas pose geometric constraints to the IOERT applicator, and steeply sloping surfaces affect dose build up and induce dose inhomogeneities. IOHDR brachytherapy techniques circumvent these constraints through the use of surface applicators which can be cut to encompass the target area adequately.

The late sequelae of brachytherapy depend not only on the dose given to the target volume but more importantly on the volume irradiated both within and outside the target. This is of utmost importance in children as their growing tissues are susceptible to radiation. Hence, the volumes implanted are smaller than those in adults. For example, in adult soft tissue sarcomas, the entire muscle compartment may be implanted (from the origin to the insertion of the muscle group); however, in children, only the area at high risk for recurrence (usually the postchemotherapy residual volume with a variable margin) is implanted. The volume to be implanted may vary: Margins can be generous if there are no radiosensitive surrounding normal tissues, but they must be smaller if adjacent to critical normal tissues (e.g., epiphyseal plates).

An initial report on single IOHDR to treat soft tissue malignancies in six children was reported by Nag, *et al.* (59) in 1998 (Table 5). The children were treated with IOHDR in conjunction with EBRT, chemotherapy, and radical surgery at nine sites not treatable by standard IOHDR techniques. The IOHDR dose was 10 Gy (at seven sites with microscopic residual disease) or 12.5 Gy (at two sites with minimal gross residual disease) prescribed at 0.5 cm depth. The EBRT dose was limited to 27–30.6 Gy (median dose 27.4 Gy) postoperatively in all patients to minimize growth retardation or altered organ function. After a median followup of 40 months (range 22–62 months), all the patients were alive, five of them without evidence of disease. Toxicity was seen in 2 patients. Adverse effects included recurrent urinary infections and ureteral stenosis after requiring a left nephrectomy and mild to moderate loss of visual acuity and impaired orbital growth. They concluded that tumor beds not treatable with standard IOERT could be satisfactorily encompassed with IOHDR to obtain local control and long-term disease-free survival with acceptable morbidity.

The same group reported their updated experience with IOHDR of 13 pediatric patients treated at 21 sites in 2001 (60). After a median followup of 47 months (range 12–97 months), 11 patients were alive and without evidence of disease (OS rate = 85%, 4-year actuarial survival = 77%). There was one local failure, which occurred in a patient with gross residual disease after incomplete resection for pulmonary blastoma. The local control rate was 95%, and morbidity was observed in 3 patients (23%). Adverse effects included orbital growth with mild ptosis in 1 patient, femoral subcapital epiphysis and requiring surgical pinning and construction of a neobladder secondary to urethral obstruction in 1 patient, and reimplantation of an autotransplanted kidney secondary to chronic urinary tract infections and ureteral reflux in 1 patient.

Memorial Sloan-Kettering Cancer Center has documented a long experience using IOHDR in pediatric tumors (61–63). In the last update of their 20-year experience with 75 pediatric patients treated with IOHDR from May 1993 to November 2013 (63), the median age was 9 years old (36 patients were 6 years old). HDR IORT was part of initial therapy in 37 patients (49%) and for recurrent disease in 38 patients (51%). Forty-one patients (55%) received IOHDR and postoperative external beam RT, and 22 patients (29%) were previously treated with EBRT to the IOHDR site. At a median followup of 7.8 years for surviving patients, 5-year projected rates of local control, event-free survival, and OS were 63%, 33%, and 43%, with a median survival of 3.1 years. The 5-year LC, EFS, and OS rates for patients with recurrent disease were 46%, 30%, and 36%. Grade 3 acute toxicity occurred in two (2.5%) treatments; Grade 3 late toxicity occurred in 4 (5.3%) patients 0.3–9.9 years after IOHDR. All Grade 3 or higher toxicity occurred in patients less than 6 years treated with IOHDR doses greater than 12 Gy. They concluded that doses between 8 and 12 Gy are appropriate for IOHDR in patients less than 6 years of age.

Schuck *et al.* (64) reported the role of IOHDR after preoperative chemoradiation in the treatment of 20 Ewing's sarcoma patients. Six patients presented with distant metastases on presentation. All patients were treated with neoadjuvant chemotherapy followed by concurrent chemotherapy with split-course hyperfractionated EBRT then resection with IOHDR. After that, patients were treated with further adjuvant chemotherapy for 1 year. Location of tumors included pelvis ( $n = 9$ ), upper extremity (humerus = 4, ulna = 1), and lower extremity (femur = 5 and fibula = 1). The dose of EBRT was 45–55 Gy. Chemotherapy consisted of vincristine, adriamycin, ifosfamide, and actinomycin D with or without etoposide. The amount of residual disease at the time of IOHDR was not reported. At a median followup of 24 months, local failure occurred in 1 patient, whereas distant metastases occurred in seven including the patient with local failure. No intraoperative complications related to IOHDR occurred, and the overall complication rate of 40% did not seem increased compared to those not receiving IOHDR.

Pediatric cancer consensus recommendations:

- Although there is limited published experience, it may be appropriate to use IOHDR for pediatric malignancies because of the benefits of fewer episodes of anesthesia, direct visualization of the tumor bed, lower integral dose compared to EBRT, and better protection (direct shielding) of tissue in growing patients.
- For pediatric soft tissue sarcomas, IOHDR doses of 10–15 Gy (prescribed at 0.5 cm) are recommended with a standard dose of 40–45 Gy EBRT; however, consideration may be given for a lower dose of EBRT (27–30 Gy) if severe growth abnormality would ensue after conventional dose of EBRT (60).

- Doses between 8 and 12 Gy are most appropriate for IOHDR in patients less than 6 years of age.
- Because there is only limited data, specific recommendations cannot be made for each pediatric site.

### IOHDR applicators

Two main IOHDR devices are available in the market, Freiburg Flap applicator (Nucletron, Veenendaal, The Netherlands) and HAM applicator (Mick-Radio-Nuclear Instruments Inc., Mount Vernon, NY). Both devices consist of flexible plastic material into which flexible treatment catheters may be placed. The plastic material maintains the source wire at a fixed distance (i.e., 5 mm) from the patient tissue surface to reduce the dose gradient and safely minimize surface dose while delivering the therapeutic dose at target depth. Depending on the applicator, the devices may be single use (should be disposed of after treatment) or reusable if an appropriate sterilization process is used as per the manufacturer's specification.

#### Freiburg Flap applicator

The Freiburg Flap applicator consists of soft plastic spheres, each with a diameter of 1.0 cm, which are joined in tandem to create a flexible surface applicator that may be placed directly over the treatment site (Fig. 1a). The

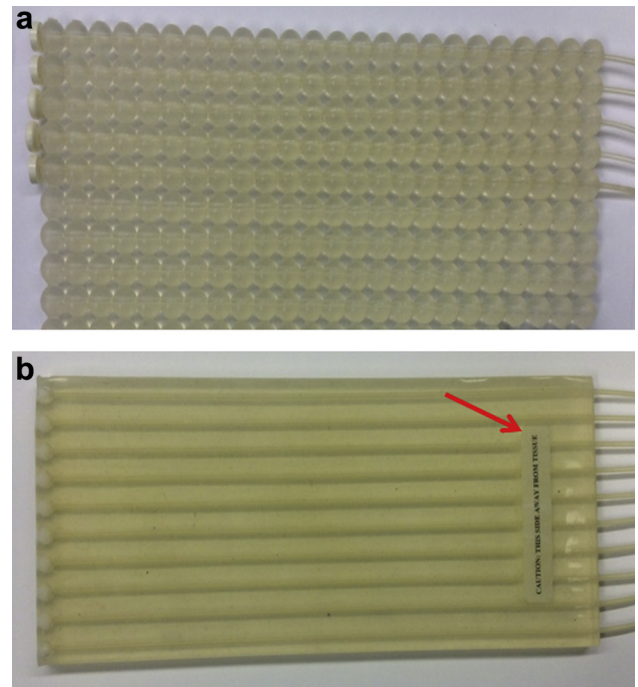


Fig. 1. Example of Freiburg Flap and HAM applicator systems. (a) Freiburg Flap applicator with five treatment catheters inserted; (b) HAM applicator with embedded treatment catheters spaced 1 cm apart. The label (red arrow) should indicate the orientation of the applicator for use. HAM = Harrison-Anderson-Mick. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

flap may be cut to a custom size in increments of 1 cm. Treatment catheters are inserted through the center of the plastic spheres along one direction for connection of the device to the HDR afterloader. The spheres function to evenly space the treatment catheters and also to maintain the source wire at a fixed distance (i.e., 5 mm) from the patient tissue surface. The Freiburg catheters are 6-French and are shipped with sealed ends. The user is required to trim the catheter end and remove a plastic stylet before use.

#### HAM applicator

Standard HAM applicators are 0.8 cm thick and 22-cm-long rectangular slabs (Fig. 1) with a variable number of channels, ranging from 3 to 24. The HAM applicators may be ordered with or without embedded flexible treatment catheters. With embedded catheters, the catheters are placed in 1 cm spacing. The HAM applicators without embedded catheters work similarly to the Freiburg applicators as they require the internal catheters to be trimmed and threaded by the user either before the surgery or inside the OR after the size of the HAM for treatment is determined.

In contrast to the Freiburg applicator, the HAM applicator has an asymmetric thickness by design, with 5 mm on the bottom layer and 3 mm on the top layer. The orientation of the applicator is indicated with an embedded label (Fig. 1b). With the eccentric catheter position, it is important for the user to pay attention in placing the HAM applicators in relationship to the tumor bed. Standard placements use a 5-mm thickness layer to be in contact with the tumor bed.

#### Ancillary devices

The HAM and Freiburg applicators may be connected to the afterloader directly with transfer guide tubes (Fig. 2a). Alternatively, the user may purchase 45-cm-long 4Fr catheters (Mick-Radio-Nuclear Instruments Inc., Mount Vernon, NY) that can be fully inserted into each channel. The 4Fr catheters may be secured with collets (Mick-Radio-Nuclear Instruments Inc., Mount Vernon, NY) that lock to both the applicator and the 4Fr catheters (Fig. 2b). The treatment team should visually verify that the 4Fr catheters are inserted completely and reach the end of applicator channels. The 4Fr catheters provide a redundant barrier keeping the radioactive source wire from contacting patient fluid. The catheters also standardize the applicator channel lengths and reduce the likelihood of incorrect source placement due to catheter measurement error.

Lead sheets may be used to reduce dose to nearby structures.  $^{192}\text{Ir}$  has a half-value layer equal to 4.8 mm in lead. The lead sheets should be wrapped in gauze to reduce backscatter and prevent direct contact of the lead with patient tissue (65).

#### IOHDR treatment planning basics

The treatment planning goal is to create a plan that achieves a uniform prescribed dose over the tumor bed area at the desired depth of treatment. Common treatment depths are at the surface of the applicator and depths of 0.3 cm, 0.5 cm, or 1.0 cm from the applicator surface. A dose uniformity of  $\pm 5\%$  is desired. The DLS is typically the surface of the tissue, which should be maintained at

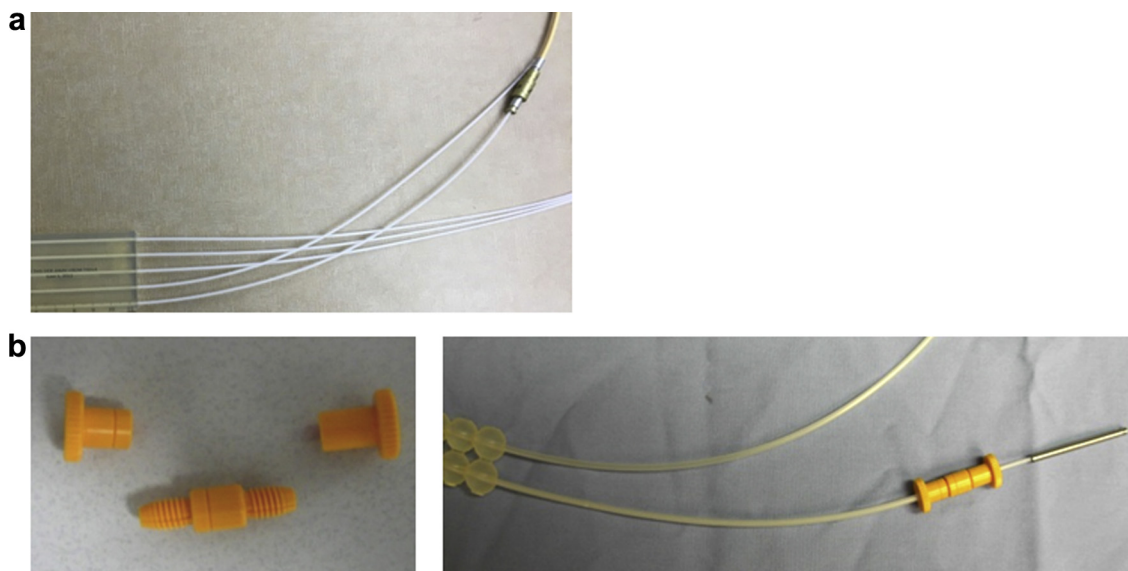


Fig. 2. (a) Example of a HAM applicator connects directly with a transfer guide tube. (b) Example of collet system and 4Fr click fit catheters in use with a Freiburg Flap applicator. HAM = Harrison-Anderson-Mick.

no greater than 200% of the prescribed dose when possible. It may not be possible to achieve both the uniformity and surface dose limits for prescriptions depths greater than 0.5 cm from the applicator surface, and input from the radiation oncologist should be sought on how to compromise between the target and DLS. Some institutions advocate using preplanned equal dwell weight treatment plans for its simplicity, ease of quality assurance, and ability to deliver a higher central dose where the risk of residual disease is higher (66).

In an IOHDR procedure, the patient will be under anesthesia with an opened cavity during applicator placement, treatment planning, and treatment delivery. Therefore, one of the most important factors to consider in creating the treatment plan for an IOHDR patient is efficiency as the patient is in a vulnerable state where there is a risk of infection or anesthesia-related death. In this section of the report, we will outline several treatment planning options that ensure quick planning time. Readers may choose to adapt any method they deem most appropriate for their own clinical setting.

*IOHDR simulation*

In general, no image acquisition is performed for treatment planning for IOHDR patients, and users are encouraged to consider generating a library, or atlas, of treatment plans beforehand that accommodates a range of applicator sizes and treatment depths (Fig. 3) (67, 68).

For example, treatment plans may be created for rectangular applicator sizes ranging from 2 cm × 2 cm up to 36 cm × 36 cm and to deliver a nominal dose at the applicator surface or at fixed depths from the surface. However, radiographic images may be obtained for verification of the catheter position within the treatment site (66).

*IOHDR dosimetry*

Absorbed dose calculations for IOHDR use the TG43 formalism (69). However, recently, model-based dose calculation algorithms (MBDCA) such as ACUROS Grid-based Boltzmann Solver in Brachy Vision or ACE collapsed cone in Oncentra (70) have been FDA approved. Compared to TG43, MBDCA algorithms may provide a more accurate dose distribution because they account for tissue interface and IOHDR applicator heterogeneity (71). However, MBDCA will require real-time imaging to capture applicator curvature and the tissue/air interface, and as of this writing, the application of MBDCA for IOHDR is still under evaluation. Furthermore, physicians should carefully consider whether prescription changes are warranted when using MBDCA because prior patient studies were likely done with TG43 or similar water-based dosimetry.

*Digitization of applicator channels*

The IOHDR brachytherapy team may elect to digitize the applicator channels using a stylized model of the

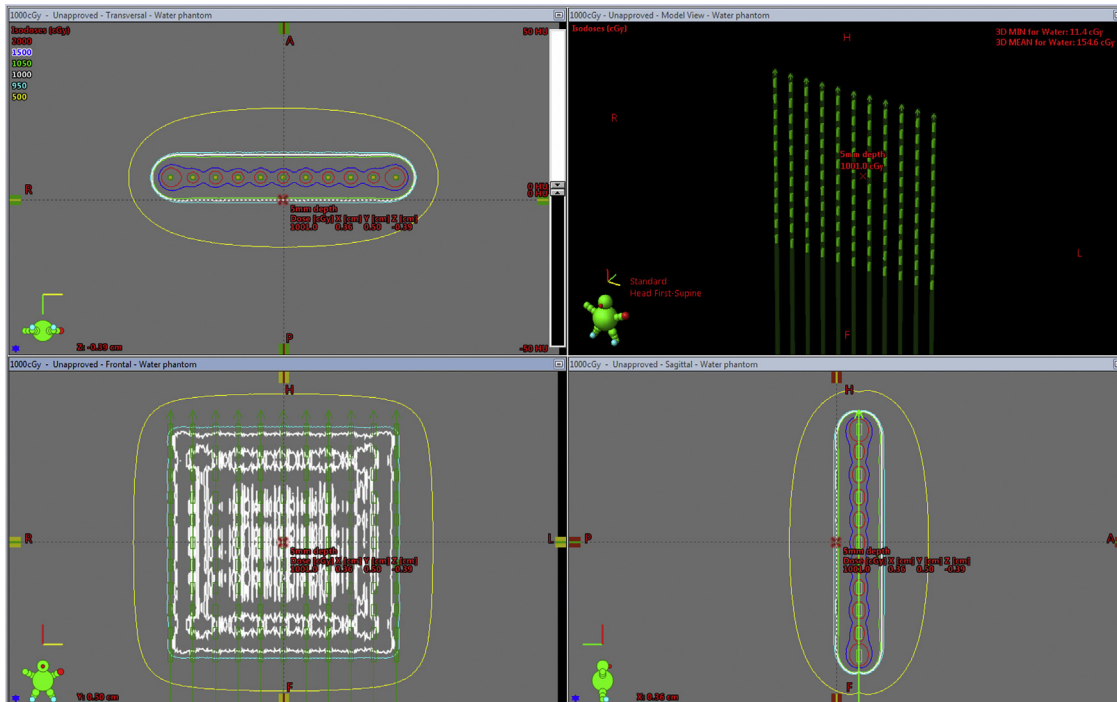


Fig. 3. Example library plan for a 10 cm × 10 cm treatment site prescribed to 0.5 mm from the surface of the applicator.

applicator by first measuring the applicator at hand to verify the vendor drawings or by reconstruction of the treatment catheters using a CT scan of the applicator (axial CT with 1–2 mm slice thickness recommended) (Fig. 4). A predigitized or prereconstructed plan with a large number of catheters (e.g., 24 channels) may also be created and saved in the treatment planning system (TPS) as a template. This Digital Imaging and Communications in Medicine-Radiation Therapy plan can be imported into any future IOHDR patient so that the catheter reconstruction time can be eliminated. This method also allows flexibility in generating dose distribution in any size and shape, also known as “dose painting” (72). To use DP, a sterile transparency film with the image of an applicator along with possible dwell positions in 1:1 magnification factor should be prepared. Once the applicator is affixed on top of the treatment area, this transparency film is overlaid onto the applicator and the area of dose painting can be defined by drawing on the film. The dwell positions inside the area of interest will be activated to create the dose shape the physician desires.

#### Plan optimization

Plan optimization may be used to identify the dwell times for each source dwell position to deliver a uniform prescription dose to the target and limit excessive dose to the patient surface. During optimization, it is helpful to have structures that represent the applicator and target surfaces. These surfaces may be contoured as structures or represented by reference lines that are positioned at fixed distances from the applicator channels. Volumetric, geometric, and graphical optimization methods may be used.

Volumetric optimization methods require that the user delineate points, lines, and/or surface structures to represent the target and patient surfaces. Several different algorithms have been used for HDR volume optimization, including stochastic, deterministic, and exact methods (73). Volume-based approaches typically require the user to specify constraints on the dose to the applicator surface and desired dose to the target surface. For example, using the commercial algorithm in BrachyVision TPS, the user may specify that 0% of the patient surface structures receive >200% of the prescription dose; 100% of the target surface structure should be receiving at least 95% of the prescription dose; and 0% of the target surface structure should receive >105% of the prescription dose.

Geometry-based optimization (74) is a deterministic algorithm that may be used to optimize the dose to one or more dose points at a set distance from the source. Geometric optimization generates an approximately uniform target surface dose. The algorithm is implemented directly in Varian Brachytherapy as well as in Oncentra TPS. An advantage of geometric optimization is that it only requires a single or a single set of prescription points and the calculation is very fast. A disadvantage is that the dose to the target surface is not as uniform as volume optimization methods.

Graphical optimization is an approach in which the user employs graphical tools, such as dragging isodose lines, to produce the desired dose distribution. Graphical optimization is a qualitative approach that is often used in combination with other optimization methods (e.g., geometric optimization).

Just as the catheter reconstruction time can be eliminated by preparing template plans in advance, optimization time may be eliminated by generating optimized plans in

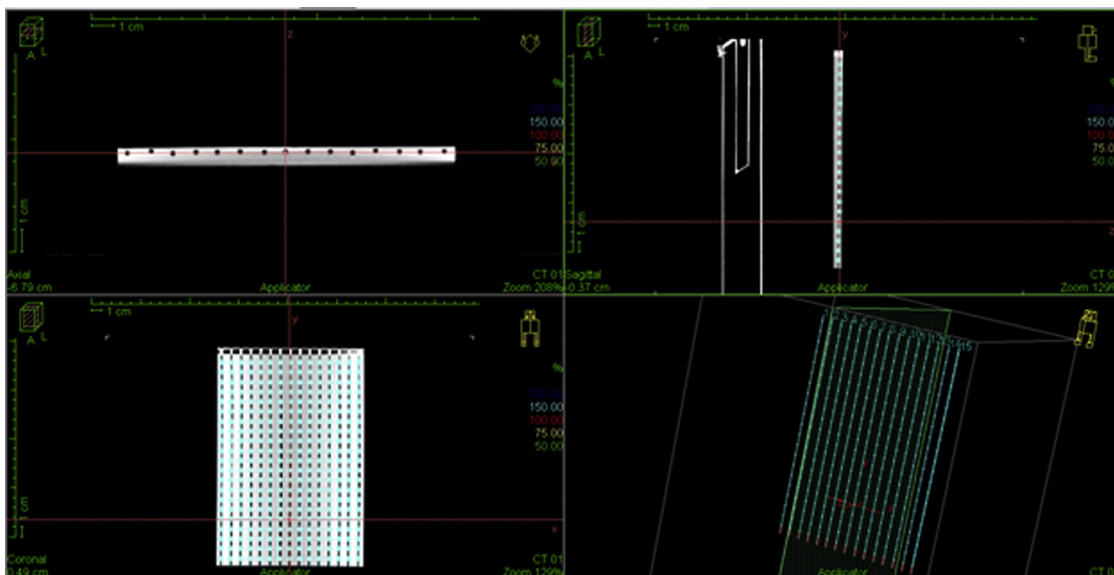


Fig. 4. Example of the Oncentra TPS applicator digitization reconstructed on a HAM applicator CT image set (axial CT, 1.25 mm, 120 kVp). HAM = Harrison-Anderson-Mick; TPS = treatment planning system.

Table 5  
Literature summary—pediatric cancers

Author	N	Median followup (mo)	Intraoperative dose (Gy)	Surgical margins+/total	EBRT	Outcomes	Comments
Nag (Ohio State) 1998 (59)	6	40	10–12.5		Yes (27–30.6 Gy)	At 40 months, all pts alive, 5/6 without recurrence	Soft tissue sarcomas.
Nag (Ohio State) 2001 (60)	13	47	10–12.5		Yes	OS 77% LC 95%	Variety of tumor histologies. Morbidity observed in pts (23%)
Merchant (MSKCC) 1998 (61)	16	18	12		EBRT in 4. Previous EBRT in 5.	2-yr LC 61% 2-yr PFS 51% 2-yr OS 54%	7 thoracic, 6 pelvis, 3 abdomen. Ages 5–24 years
Goodman (MSKCC updated) 2003 (62)	66	12	12			2-yr LC 56% 2-yr OS 54%	Variety of tumor histologies. Ages 9 months to 24 years. 26 pt died from progressive disease
Folkert (MSKCC updated) 2014 (63)	75	7.8	8–12+			5-yr LC 46% 5-yr EFS 30% 5-yr OS 36%	Variety of tumor histologies. IOHDR part of initial therapy in 37 and recurrent disease in 38. 20-yr experience
Schuck (Germany) 1997 (64)	20	24			45–55 Gy	1 pt with LF	Acute Grade 3 toxicity in 2.5% Late Grade 3 toxicity in 5.3% Ewing's sarcoma 9 pelvis, 5 upper extremity, 6 lower extremity No complications due to IOHDR

EBRT = external beam radiation therapy; OS = overall survival; IOHDR = intraoperative high-dose-rate; EFS = event free survival.

advance. Because this process may be time-consuming, the reader may consider homegrown solutions to improve efficiency (67). Other institutions advocate using pre-planned equal dwell weight treatment plans rather than optimized plans for their simplicity, ease of quality assurance, and ability to deliver a higher central dose where the risk of residual disease is higher (66).

*Treatment planning quality assurance*

Treatment planning quality assurance (QA) should be performed before patient treatment. QA should include a check of applicator digitization, channel lengths, inspection of the DLS and target doses, and verification of the dose calculation using an independent dwell-time calculation, comparison of total reference air kerma, or Ci-s with a nomogram. The use of checklists is recommended to reduce the likelihood of errors due to distraction or fatigue.

*Treatment delivery times*

Treatment delivery times vary depending upon the applicator size, treatment depth, and remote afterloader source strength. Example delivery times for various sizes of applicator and treatment depth are found in Table 6.

*Other treatment planning considerations*

Readers should be aware that plans generated with flat applicator geometry, such as library plans, may not represent the true dose distribution to the tumor bed. The curvature of the applicator when affixed to the treatment area may cause a discrepancy between the planned dose and delivered dose (75, 76). The treatment team may attempt to estimate the effects of the surface curvature using commissioning measurements or by generating an atlas of applicators of various curved geometries rather than standard flat geometry for IOHDR planning.

**IOHDR treatment delivery**

The radiation team should consist of at least one radiation oncologist, one authorized medical physicist (AMP), and one dosimetrist or a second physicist. Other members that will be involved in this procedure may include but not

Table 6  
Example delivery times for various sizes of applicator and treatment depth

Target size (cm × cm)	Time (min) to deliver 1000 cGy to various treatment depths from the applicator surface using a 40300U source		
	0 cm depth	0.5 cm depth	1.0 cm depth
3 × 3	2.6	5.2	6.9
5 × 5	5.0	8.3	11.3
10 × 10	12.8	19.9	22.3
20 × 20	37.5	53.3	66.6



are limited to surgeons, anesthesiologists, nurses, OR technicians, residents, and other trainees. The radiation oncologist and surgery team will identify the treatment site and place a correctly sized applicator device in the patient. Depending on the applicator, the radiation oncologist may also need to trim catheters with a sterile cutting tool, and if using 4Fr catheters, insert them completely into the applicator channels. Sterile stickers with numbers may be used to label each catheter to facilitate the proper connection with the remote afterloader. The AMP should assist the radiation oncologist with connecting the applicator to transfer guide tubes. The arrangement of the catheters should be such that there will be no bending or twisting of the catheters to eliminate possible obstruction error during treatment. Sterile plastic wrapping or tubes, such as ultrasound transducer covers, may be used to prevent the nonsterile transfer guide tubes from contacting sterile patient drapes. Using the vendor-specific measurement device, the AMP should measure the length of each applicator channel which later will be input into the plan. This measurement should be double checked by a second physicist or another trained staff member. The AMP is responsible to connect the transfer guide tubes to the HDR treatment machine and perform the pretreatment QA. Care should be taken to prevent blood or other body fluids from accumulating between the applicator and the tumor bed.

#### *IOHDR in the OR setting*

If a dedicated shielded OR is available in the facility, IOHDR treatment delivery may be delivered in the OR. A treatment console will need to be installed in the OR control room, along with all necessary interlocks and radiation monitoring devices. Audio and video communications, as well as radiation monitors, should be installed, and storage should be available for accessories and emergency supplies. Physics should also confirm that the OR room is listed on the radioactive materials license.

Depending on the hospital setting, the dedicated shielded OR may be used for other surgical procedures as well that means limited accessible time for the physicist to perform QA. The physicist may need to complete daily QA early on the morning of the IOHDR procedure before the OR staff arrive to prepare the room for surgical procedures. One may consider performing daily warm-up QA the night before the surgery, if the licensee obtained such agreement with the Nuclear Regulatory Commission (NRC) or Agreement State. When possible, to ensure the system stays in the same status between QA and treatment delivery, the afterloader should be secured in the OR and the console should remain on until the procedure.

On the day of the procedure, the AMP should confirm that the HDR afterloader, treatment room, and patient-specific QA have been performed before each treatment.

Safety equipment, such as portable shields or a lead emergency safety container should also be positioned appropriately for treatment delivery. American Association of Physicists in Medicine Task Group 56 guidelines should be followed (77).

#### *IOHDR in the HDR treatment room setting*

When a dedicated shielded OR is not available, an alternative is to take the patient to the HDR treatment room for treatment delivery. One of the most serious concerns in this setting is the risk of infection. Therefore, any measure to reduce the possibility of infection such as various types of sterile adhesive films and drapes should be used properly. When getting the patient ready for treatment, care must be taken to confirm that organs and applicators inside the open surgical cavity are well packed and fixed to prevent relative motion while transporting patient between the OR and the treatment room. Furthermore, any surgical or anesthesiologic-related device mobility should also be considered before the procedure to prevent possible patient transfer/transportation difficulties.

#### *IOHDR emergency procedures*

In the IOHDR procedure, once the location and the direction of the applicator are decided, the radiation oncologist or surgeon may either suture or use packing materials to stabilize the applicator in the tumor bed. If sutures are used, it is important for the radiation oncologist to record the number and location of the sutures used in the patient. In the case of an HDR emergency where the  $^{192}\text{Ir}$  remains inside the applicator, the radiation oncologist should be able to identify where the sutures are located and remove them in the shortest possible amount of time to keep radiation exposure as low as reasonably achievable. A portable safe should be available in the OR for emergency storage of the radiation source. The vendor information regarding how to secure the source in case of a radiation event should be followed; such information can be found in the instructions for use and the vendor's required annual radiation training per the NRC 10 CFR Part 35 guidance.

In any treatment delivery environment, it is critical for every team member involved in the IOHDR treatment to understand the workflow and possible risks in every step. If possible, a thorough walk through of the procedure should be communicated before each IOHDR case starts. Each team member should be made aware of the possibility of an HDR emergency and their role when an emergency occurs. It is recommended that standard operating procedures are written, and drills are practiced on an annual basis. In the United States, following the NRC regulations or agreement state regulations for reporting a medical event are required.

## Posttreatment management and toxicity

Toxicity can vary depending on the site of IOHDR delivery and is covered in the individual disease sections of the document. Patients should be seen in followup by the surgeon and radiation oncologist to assess and manage adverse effects. Toxicities are graded using the latest version Common Terminology Criteria for Adverse Events criteria. Short-term adverse effects can include infection, poor wound healing, pain, gastrointestinal (diarrhea, nausea, vomiting, cramping), and genitourinary (symptoms of obstruction, hematuria, infection) problems; and long-term adverse effects can include necrosis, vascular complications, secondary malignancy, fibrosis, pain, gastrointestinal (bleeding, diarrhea, obstruction, fistulae), and genitourinary (obstruction, hemorrhagic cystitis, fistulae) problems. Institutions starting IOHDR programs should measure toxicity, and reporting outcomes in the literature is recommended given the small numbers of published reports, especially in some disease sites. It can be difficult to measure excess toxicity from IOHDR brachytherapy as patients are also subject to the complications of surgery and often EBRT and/or chemotherapy. Tumor progression itself causes injury that can be similar to the toxicity of treatment.

## Summary

IOHDR brachytherapy can aid in achieving tumor control in a multidisciplinary setting. Advantages include a well-defined tumor bed and the ability to shield surrounding tissues although the surgical field is open. It is appropriate in cases of positive margins and for recurrent disease for colorectal and gynecologic malignancies, and soft tissue sarcoma. IOHDR brachytherapy may also be appropriate as a boost option in base of skull and paranasal sinus cancers. Finally, IOHDR may be appropriate as a boost option for several pediatric malignancies. This document also outlines best practices for dose depth, dose uniformity, simulation, dosimetry, and QA in IOHDR.

## Acknowledgments

The authors would like to acknowledge the help of Michelle Denney for proof reading this manuscript.

## References

- [1] Hu KS, Enker WE, Harrison LB. High-dose-rate intraoperative irradiation: current status and future directions. *Semin Radiat Oncol* 2002;12:62–80.
- [2] Calvo FA, Sole CV, Lozano MA, et al. Intraoperative electron beam radiotherapy and extended surgical resection for gynecological pelvic recurrent malignancies with and without external beam radiation therapy: long-term outcomes. *Gynecol Oncol* 2013;130:537–544.
- [3] Harrison LB, Enker WE, Anderson LL. High-dose-rate intraoperative radiation therapy for colorectal cancer. *Oncology (Williston Park)* 1995;9:737–741. discussion 742–748 passim.
- [4] Alektiar KM, Zelefsky MJ, Paty PB, et al. High-dose-rate intraoperative brachytherapy for recurrent colorectal cancer. *Int J Radiat Oncol Biol Phys* 2000;48:219–226.
- [5] Dubois JB, Bussieres E, Richaud P, et al. Intra-operative radiotherapy of rectal cancer: results of the French multi-institutional randomized study. *Radiother Oncol* 2011;98:298–303.
- [6] Masaki T, Takayama M, Matsuoka H, et al. Intraoperative radiotherapy for oncological and function-preserving surgery in patients with advanced lower rectal cancer. *Langenbecks Arch Surg* 2008;393:173–180.
- [7] Huber FT, Stepan R, Zimmermann F, et al. Locally advanced rectal cancer: resection and intraoperative radiotherapy using the flab method combined with preoperative or postoperative radiochemotherapy. *Dis Colon Rectum* 1996;39:774–779.
- [8] Nuyttens JJ, Kolkman-Deurloo IK, Vermaas M, et al. High-dose-rate intraoperative radiotherapy for close or positive margins in patients with locally advanced or recurrent rectal cancer. *Int J Radiat Oncol Biol Phys* 2004;58:106–112.
- [9] Ferenschild FT, Vermaas M, Nuyttens JJ, et al. Value of intraoperative radiotherapy in locally advanced rectal cancer. *Dis Colon Rectum* 2006;49:1257–1265.
- [10] Valentini V, Coco C, Rizzo G, et al. Outcomes of clinical T4M0 extra-peritoneal rectal cancer treated with preoperative radiochemotherapy and surgery: a prospective evaluation of a single institutional experience. *Surgery* 2009;145:486–494.
- [11] Kusters M, Valentini V, Calvo FA, et al. Results of European pooled analysis of IORT-containing multimodality treatment for locally advanced rectal cancer: adjuvant chemotherapy prevents local recurrence rather than distant metastases. *Ann Oncol* 2010;21:1279–1284.
- [12] Mannaerts GH, Martijn H, Crommelin MA, et al. Feasibility and first results of multimodality treatment, combining EBRT, extensive surgery, and IOERT in locally advanced primary rectal cancer. *Int J Radiat Oncol Biol Phys* 2000;47:425–433.
- [13] Roeder F, Treiber M, Oertel S, et al. Patterns of failure and local control after intraoperative electron boost radiotherapy to the presacral space in combination with total mesorectal excision in patients with locally advanced rectal cancer. *Int J Radiat Oncol Biol Phys* 2007;67:1381–1388.
- [14] Pezner RD, Chu DZ, Ellenhorn JD. Intraoperative radiation therapy for patients with recurrent rectal and sigmoid colon cancer in previously irradiated fields. *Radiother Oncol* 2002;64:47–52.
- [15] Hashiguchi Y, Sekine T, Kato S, et al. Indicators for surgical resection and intraoperative radiation therapy for pelvic recurrence of colorectal cancer. *Dis Colon Rectum* 2003;46:31–39.
- [16] Martinez-Monge R, Nag S, Martin EW. Three different intraoperative radiation modalities (electron beam, high-dose-rate brachytherapy, and iodine-125 brachytherapy) in the adjuvant treatment of patients with recurrent colorectal adenocarcinoma. *Cancer* 1999;86:236–247.
- [17] Shoup M, Guillem JG, Alektiar KM, et al. Predictors of survival in recurrent rectal cancer after resection and intraoperative radiotherapy. *Dis Colon Rectum* 2002;45:585–592.
- [18] Vermaas M, Nuyttens JJ, Ferenschild FT, et al. Reirradiation, surgery and IORT for recurrent rectal cancer in previously irradiated patients. *Radiother Oncol* 2008;87:357–360.
- [19] Haddock MG, Miller RC, Nelson H, et al. Combined modality therapy including intraoperative electron irradiation for locally recurrent colorectal cancer. *Int J Radiat Oncol Biol Phys* 2011;79:143–150.
- [20] Mirnezami R, Chang GJ, Das P, et al. Intraoperative radiotherapy in colorectal cancer: systematic review and meta-analysis of techniques, long-term outcomes, and complications. *Surg Oncol* 2013;22:22–35.
- [21] Willett CG, Shellito PC, Tepper JE, et al. Intraoperative electron beam radiation therapy for primary locally advanced rectal and rectosigmoid carcinoma. *J Clin Oncol* 1991;9:843–849.
- [22] Mathis KL, Nelson H, Pemberton JH, et al. Unresectable colorectal cancer can be cured with multimodality therapy. *Ann Surg* 2008;248:592–598.

- [23] Kusters M, Holman FA, Martijn H, et al. Patterns of local recurrence in locally advanced rectal cancer after intra-operative radiotherapy containing multimodality treatment. *Radiother Oncol* 2009;92:221–225.
- [24] Nakfoor BM, Willett CG, Shellito PC, et al. The impact of 5-fluorouracil and intraoperative electron beam radiation therapy on the outcome of patients with locally advanced primary rectal and rectosigmoid cancer. *Ann Surg* 1998;228:194–200.
- [25] Storm FK, Mahvi DM. Diagnosis and management of retroperitoneal soft-tissue sarcoma. *Ann Surg* 1991;214:2–10.
- [26] Rachbauer F, Sztankay A, Kreczy A, et al. High-dose-rate intraoperative brachytherapy (IOHDR) using flab technique in the treatment of soft tissue sarcomas. *Strahlenther Onkol* 2003;179:480–485.
- [27] Alektiar KM, Hu K, Anderson L, et al. High-dose-rate intraoperative radiation therapy (HDR-IORT) for retroperitoneal sarcomas. *Int J Radiat Oncol Biol Phys* 2000;47:157–163.
- [28] Sindelar WF, Kinsella TJ, Chen PW, et al. Intraoperative radiotherapy in retroperitoneal sarcomas. Final results of a prospective, randomized, clinical trial. *Arch Surg* 1993;128:402–410.
- [29] Petersen IA, Haddock MG, Donohue JH, et al. Use of intraoperative electron beam radiotherapy in the management of retroperitoneal soft tissue sarcomas. *Int J Radiat Oncol Biol Phys* 2002;52:469–475.
- [30] Roeder F, Ulrich A, Hahl G, et al. Clinical phase I/II trial to investigate preoperative dose-escalated intensity-modulated radiation therapy (IMRT) and intraoperative radiation therapy (IORT) in patients with retroperitoneal soft tissue sarcoma: interim analysis. *BMC Cancer* 2014;14:617.
- [31] Sweeting RS, Deal AM, Llaguna OH, et al. Intraoperative electron radiation therapy as an important treatment modality in retroperitoneal sarcoma. *J Surg Res* 2013;185:245–249.
- [32] Tran PT, Hara W, Su Z, et al. Intraoperative radiation therapy for locally advanced and recurrent soft-tissue sarcomas in adults. *Int J Radiat Oncol Biol Phys* 2008;72:1146–1153.
- [33] Lehnert T, Schwarzbach M, Willeke F, et al. Intraoperative radiotherapy for primary and locally recurrent soft tissue sarcoma: morbidity and long-term prognosis. *Eur J Surg Oncol* 2000;26(Suppl A):S21–S24.
- [34] Tinkle CL, Weinberg V, Braunstein SE, et al. Intraoperative radiotherapy in the management of locally recurrent extremity soft tissue sarcoma. *Sarcoma* 2015;2015:913565.
- [35] Niewald M, Fleckenstein J, Licht N, et al. Intraoperative radiotherapy (IORT) combined with external beam radiotherapy (EBRT) for soft-tissue sarcomas—a retrospective evaluation of the Homburg experience in the years 1995–2007. *Radiat Oncol* 2009;4:32.
- [36] Calvo FA, Sole CV, Cambeiro M, et al. Prognostic value of external beam radiation therapy in patients treated with surgical resection and intraoperative electron beam radiation therapy for locally recurrent soft tissue sarcoma: a multicentric long-term outcome analysis. *Int J Radiat Oncol Biol Phys* 2014;88:143–150.
- [37] Azinovic I, Martinez Monge R, Javier Aristu J, et al. Intraoperative radiotherapy electron boost followed by moderate doses of external beam radiotherapy in resected soft-tissue sarcoma of the extremities. *Radiother Oncol* 2003;67:331–337.
- [38] Nag S, Shasha D, Janjan N, et al., American Brachytherapy S. The American Brachytherapy Society recommendations for brachytherapy of soft tissue sarcomas. *Int J Radiat Oncol Biol Phys* 2001;49:1033–1043.
- [39] Giorda G, Boz G, Gadducci A, et al. Multimodality approach in extra cervical locally advanced cervical cancer: chemoradiation, surgery and intra-operative radiation therapy. A phase II trial. *Eur J Surg Oncol* 2011;37:442–447.
- [40] Backes FJ, Billingsley CC, Martin DD, et al. Does intra-operative radiation at the time of pelvic exenteration improve survival for patients with recurrent, previously irradiated cervical, vaginal, or vulvar cancer? *Gynecol Oncol* 2014;135:95–99.
- [41] Tran PT, Su Z, Hara W, et al. Long-term survivors using intraoperative radiotherapy for recurrent gynecologic malignancies. *Int J Radiat Oncol Biol Phys* 2007;69:504–511.
- [42] Barney BM, Petersen IA, Dowdy SC, et al. Long-term outcomes with intraoperative radiotherapy as a component of treatment for locally advanced or recurrent uterine sarcoma. *Int J Radiat Oncol Biol Phys* 2012;83:191–197.
- [43] del Carmen MG, McIntyre JF, Fuller AF, et al. Intraoperative radiation therapy in the treatment of pelvic gynecologic malignancies: a review of fifteen cases. *Gynecol Oncol* 2000;79:457–462.
- [44] Konski AA, Neisler J, Phibbs G, et al. A pilot study investigating intraoperative electron beam irradiation in the treatment of ovarian malignancies. *Gynecol Oncol* 1990;38:121–124.
- [45] Cambeiro M, Calvo FA, Aristu JJ, et al. Salvage surgery and radiotherapy including intraoperative electron radiotherapy in isolated locally recurrent tumors: predictors of outcome. *Radiother Oncol* 2015;116:316–322.
- [46] Sole CV, Calvo FA, Lizarraga S, et al. Intraoperative electron-beam radiation therapy with or without external-beam radiotherapy in the management of paraortic lymph-node oligometastases from gynecological malignancies. *Clin Transl Oncol* 2015;17:910–916.
- [47] Mahe MA, Gerard JP, Dubois JB, et al. Intraoperative radiation therapy in recurrent carcinoma of the uterine cervix: report of the French intraoperative group on 70 patients. *Int J Radiat Oncol Biol Phys* 1996;34:21–26.
- [48] Garton GR, Gunderson LL, Webb MJ, et al. Intraoperative radiation therapy in gynecologic cancer: the Mayo Clinic experience. *Gynecol Oncol* 1993;48:328–332.
- [49] Martinez Monge R, Jurado M, Azinovic I, et al. Intraoperative radiotherapy in recurrent gynecological cancer. *Radiother Oncol* 1993;28:127–133.
- [50] Gemignani ML, Alektiar KM, Leitao M, et al. Radical surgical resection and high-dose intraoperative radiation therapy (HDR-IORT) in patients with recurrent gynecologic cancers. *Int J Radiat Oncol Biol Phys* 2001;50:687–694.
- [51] Dowdy SC, Mariani A, Cliby WA, et al. Radical pelvic resection and intraoperative radiation therapy for recurrent endometrial cancer: technique and analysis of outcomes. *Gynecol Oncol* 2006;101:280–286.
- [52] Barney BM, Petersen IA, Dowdy SC, et al. Intraoperative electron beam radiotherapy (IOERT) in the management of recurrent ovarian malignancies. *Int J Gynecol Cancer* 2011;21:1225–1231.
- [53] Nag S, Koc M, Schuller DE, et al. Intraoperative single fraction high-dose-rate brachytherapy for head and neck cancers. *Brachytherapy* 2005;4:217–223.
- [54] Nag S, Tippin D, Grecula J, et al. Intraoperative high-dose-rate brachytherapy for paranasal sinus tumors. *Int J Radiat Oncol Biol Phys* 2004;58:155–160.
- [55] Teckie S, Scala LM, Ho F, et al. High-dose-rate intraoperative brachytherapy and radical surgical resection in the management of recurrent head-and-neck cancer. *Brachytherapy* 2013;12:228–234.
- [56] Nag S, Schuller D, Pak V, et al. Pilot study of intraoperative high dose rate brachytherapy for head and neck cancer. *Radiother Oncol* 1996;41:125–130.
- [57] Nag S, Schuller DE, Rodriguez-Villalba S, et al. Intraoperative high dose rate brachytherapy can be used to salvage patients with previously irradiated head and neck recurrences. *Rev Med Univ Navarra* 1999;43:56–61.
- [58] Nag S, Cano ER, Demanes DJ, et al., American Brachytherapy S. The American Brachytherapy Society recommendations for high-dose-rate brachytherapy for head-and-neck carcinoma. *Int J Radiat Oncol Biol Phys* 2001;50:1190–1198.
- [59] Nag S, Martinez-Monge R, Ruymann FB, et al. Feasibility of intraoperative high-dose rate brachytherapy to boost low dose external beam radiation therapy to treat pediatric soft tissue sarcomas. *Med Pediatr Oncol* 1998;31:79–85.
- [60] Nag S, Tippin D, Ruymann FB. Intraoperative high-dose-rate brachytherapy for the treatment of pediatric tumors: the Ohio State University experience. *Int J Radiat Oncol Biol Phys* 2001;51:729–735.

- [61] Merchant TE, Zelefsky MJ, Sheldon JM, et al. High-dose rate intraoperative radiation therapy for pediatric solid tumors. *Med Pediatr Oncol* 1998;30:34–39.
- [62] Goodman KA, Wolden SL, LaQuaglia MP, et al. Intraoperative high-dose-rate brachytherapy for pediatric solid tumors: a 10-year experience. *Brachytherapy* 2003;2:139–146.
- [63] Folkert MR, Tong WY, LaQuaglia MP, et al. 20-year experience with intraoperative high-dose-rate brachytherapy for pediatric sarcoma: outcomes, toxicity, and practice recommendations. *Int J Radiat Oncol Biol Phys* 2014;90:362–368.
- [64] Schuck A, Willich N, Rube C, et al. Intraoperative high-dose-rate brachytherapy after preoperative radiochemotherapy in the treatment of Ewing's sarcoma. *Front Radiat Ther Oncol* 1997;31:153–156.
- [65] Moningi S, Armour EP, Terezakis SA, et al. High-dose-rate intraoperative radiation therapy: the nuts and bolts of starting a program. *J Contemp Brachytherapy* 2014;6:99–105.
- [66] Nag S, Schuller D, Pak V, et al. IORT using electron beam or HDR brachytherapy for previously unirradiated head and neck cancers. *Front Radiat Ther Oncol* 1997;31:112–116.
- [67] Deufel CL, Furutani KM, Dahl RA, et al. Automated construction of an intraoperative high-dose-rate treatment plan library for the Varian brachytherapy treatment planning system. *Brachytherapy* 2016;15:531–536.
- [68] Kolkman-Deurloo IK, Nuyttens JJ, Hanssens PE, et al. Intraoperative HDR brachytherapy for rectal cancer using a flexible intraoperative template: standard plans versus individual planning. *Radiother Oncol* 2004;70:75–79.
- [69] Rivard MJ, Coursey BM, DeWerd LA, et al. Update of AAPM Task Group No. 43 Report: a revised AAPM protocol for brachytherapy dose calculations. *Med Phys* 2004;31:633–674.
- [70] Beaulieu L, Carlsson Tedgren A, Carrier JF, et al. Report of the Task Group 186 on model-based dose calculation methods in brachytherapy beyond the TG-43 formalism: current status and recommendations for clinical implementation. *Med Phys* 2012;39:6208–6236.
- [71] Raina S, Avadhani JS, Oh M, et al. Quantifying IOHDR brachytherapy underdosage resulting from an incomplete scatter environment. *Int J Radiat Oncol Biol Phys* 2005;61:1582–1586.
- [72] Morikawa LK, Zelefsky MJ, Cohen GN, et al. Intraoperative high-dose-rate brachytherapy using dose painting technique: evaluation of safety and preliminary clinical outcomes. *Brachytherapy* 2013;12:1–7.
- [73] De Boeck LB, Beliën J, Egyed W. Dose optimization in high-dose-rate brachytherapy: a literature review of quantitative models from 1990 to 2010. *Operations Res Health Care* 2014;3:80–90.
- [74] Ezzell G, Luthmann RW. Clinical implementation of dwell time optimization techniques. In: Williamson JF, Thomadsen BR, Nath R, editors. *Brachytherapy Physics*. Madison, WI: Medical Physics Publishing; 1995.
- [75] Beddar AS, Krishnan S, Briere TM, et al. The optimization of dose delivery for intraoperative high-dose-rate radiation therapy using curved HAM applicators. *Radiother Oncol* 2006;78:207–212.
- [76] Oh M, Wang Z, Malhotra HK, et al. Impact of surface curvature on dose delivery in intraoperative high-dose-rate brachytherapy. *Med Dosim* 2009;34:63–74.
- [77] Nath R, Anderson LL, Meli JA, et al. Code of practice for brachytherapy physics: report of the AAPM Radiation Therapy Committee Task Group No. 56. American association of physicists in medicine. *Med Phys* 1997;24:1557–1598.