Intraoperative high-dose-rate brachytherapy using dose painting technique: Evaluation of safety and preliminary clinical outcomes

Lisa K. Morikawa 1, Michael J. Zelefsky 1, Gil’ad N. Cohen 2, Marco Zaider 2, Johnny Chiu 2, Nitin Mathur 2, Michael F. Worman 2, Karyn A. Goodman 1,*

1 Department of Radiation Oncology, Memorial Sloan—Kettering Cancer Center, New York, NY
2 Department of Medical Physics, Memorial Sloan—Kettering Cancer Center, New York, NY

ABSTRACT

PURPOSE: Intraoperative radiation therapy (IORT) allows delivery of tumoricidal doses of radiation to areas of potential residual microscopic disease while minimizing doses to normal tissues. IORT using high-dose-rate (HDR) brachytherapy allows dose modulation and delivery of concomitant boosts to high-risk areas. This study describes a novel technique of HDR-IORT with dose painting (DP) (HDR-IORT-DP) and evaluates the clinical outcomes.

METHODS AND MATERIALS: Sixteen patients with recurrent cancers received HDR-IORT-DP at the time of radical resection. Of these patients, 13 had colorectal cancer, 2 had head and neck cancer, and 1 had a gynecologic malignancy. All received external beam radiation previously. Negative margin (R0) was obtained in 12 patients (75%) and microscopically positive margins (R1) in 4 patients (25%).

RESULTS: The median total target and boost area were 45 and 8.5 cm², and HDR-IORT and boost dose were 1500 and 1750 cGy, respectively. Median followup was 14.9 months. The 2-year local control and overall survival were 80% and 20%, respectively. Eleven patients (69%) developed distant metastasis and were deceased at the time of the last followup. A total of 13 patients (19%) developed Grade 3 toxicity related to HDR-IORT; no grade 4+ toxicities were observed.

CONCLUSIONS: HDR-IORT-DP technique is feasible, safe, and allows for dose escalation in locally advanced or recurrent previously irradiated tumors. To our knowledge, this is the first clinical report on HDR-IORT-DP. Further studies are warranted to evaluate efficacy in a larger patient cohort. Local control was encouraging in our patients. © 2013 American Brachytherapy Society. Published by Elsevier Inc. All rights reserved.

Keywords: Intraoperative radiotherapy; High-dose-rate brachytherapy; Reirradiation; Dose painting

Introduction

Management of recurrent neoplasms remains a clinical challenge. Despite aggressive surgery, chemotherapy, and/or radiotherapy, locally advanced cancers recur in 15—50% of patients (1). Locoregional relapse after resection of colorectal cancer is associated with poor prognosis, with median survival of 11—15 months, and often as few as 5% of patients survive 5 years (2). Intraoperative radiotherapy (IORT) has been advocated (3) as a component of an aggressive multidisciplinary management in T4 or recurrent tumors. It seems to provide improvement in tumor local control (LC), while limiting dose to normal adjacent structures and minimizing toxicity; this has been the rationale for its use. It is given as a single fraction with doses ranging from 10 to 20 Gy, which has been estimated to have the cell-killing equivalence of two to three times the dose using conventional external beam radiotherapy (EBRT) (3).

IORT can be delivered by several different techniques: electron beam therapy, orthovoltage radiotherapy, and high-dose-rate (HDR) brachytherapy. Most centers use intraoperative electron radiotherapy (IOERT) where the radiation is delivered by a linear accelerator thorough a rigid cone directed to the tumor bed. For HDR brachytherapy technique, a flexible applicator is placed in direct contact to the area to be treated and source guide tubes are
connected to an afterloader system to deliver the radiation via a $^{192}\text{Ir}$ source.

At our institution, IORT is delivered with HDR brachytherapy using the Harrison–Anderson–Mick (HAM) applicator (Mick Radio-Nuclear Instruments, Inc., NY) that allows a very conformal treatment even on curved and deep body surfaces (4). The use of HDR-IORT is also ideal in particular sites, such as the lateral pelvic sidewall or deep in the pelvis, as well as in pediatric patients, where an electron rigid cone could be relatively inaccessible. Usually, a square/rectangular area is treated. This multiple-channel applicator and the use of computerized treatment planning systems allow for dose optimization by varying source positions and dwell times. The dose can be sculpted inside of the target area permitting dose escalation or de-escalation, allowing for planned nonhomogenous dose distributions or dose painting (DP). This DP technique allows the sites highly suspicious for positive microscopic disease or close margins to be treated to higher doses, while minimizing dose to areas of subclinical spread; normal organs could also be more effectively spared from high or unnecessary doses of radiation.

To our knowledge, this is the first clinical report on HDR-IORT using a DP technique (HDR-IORT-DP). The aim of this study is to describe the HDR-IORT-DP technique and report on the preliminary clinical outcomes of patients treated with this approach.

Methods and materials

Beginning in 2007, the DP technique was introduced for HDR-IORT cases at Memorial Sloan–Kettering Cancer Center; thus the treatment plans for all patients who received IORT after January 2007 were reviewed to identify IORT plans using DP. A total of 207 patients with locally advanced or recurrent neoplasms, who underwent IORT between January 12, 2007 and August 25, 2010 were identified. Among this group, 16 patients (7.7%) received HDR-IORT-DP and comprised our study group: 13 patients had recurrent colorectal cancer, 2 patients had recurrent cancer of the head and neck region, and 1 had a gynecologic malignancy. All patients in this group had undergone surgical resection and EBRT previously and had areas within the field that were identified by the surgeon to be at higher risk of microscopic residual disease or were adjacent to critical structures such as the ureter, where adequate shielding could not be achieved owing to geometric constraints. DP was indicated in these cases to either achieve modulation of the dose and delivery of a concomitant boost to higher-risk areas within the resection bed, while delivering a lower dose to the regions closest to normal structures or to achieve even more conformal dosimetry to a more complicated geometric region within the square or rectangular treatment region created by the HAM applicator. At the time of HDR-IORT-DP, patients were undergoing radical resection with expected close margins owing to locally advanced/recurrent nature of the tumors. Final resection margins were negative (R0) in 12 patients (75%) and microscopically positive margins (R1) in 4 patients (25%). Patient and treatment characteristics are shown in Table 1.

The HDR-IORT-DP was delivered using the HAM applicator, a flexible pad of silicone rubber that has 8-mm thickness and 22 cm in length (Fig. 1). Multiple catheters (3–24) are embedded parallel to each other spaced 10-mm apart, while a fixed source-to-tissue distance of 5 mm is maintained. All procedures were performed in a dedicated shielded operating room. The HDR-IORT-DP technique can be summarized as follows: After tumor resection, the decision to proceed with IORT is based on the radiation oncologist’s and the surgeon’s impression of the risk for close or microscopically positive margins. If deemed necessary, the area at risk is mapped out by the surgeon and radiation oncologist, and the HAM applicator is chosen with the number of channels to cover the target area appropriately. A sterile, transparent, and flexible template that mimics the HAM applicator and varies in number of channels from 3 to 24 is used to define the “DP” regions within the treatment area (Fig. 2). The region for dose escalation and/or de-escalation is demarcated by the radiation oncologist using a surgical pen. The same template is also used when changes in the shape of the radiation field are desired. The template containing this information is given to the physicist to incorporate within the intraoperative treatment planning system. The orientation of the applicator and the template must be established to implement such dose prescriptions correctly. The dose to a larger area (Dose 1) and to the boost region (Dose 2) is determined by the radiation oncologist and prescribed to 0.5 cm from the applicator’s surface. The HAM applicator is positioned in direct contact with the area at risk using either sutures or packing to hold the applicator in place (Fig. 3a). Packing is also used to displace normal

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<th>Table 1 Patient and dosimetric characteristics</th>
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adjacent organs (e.g., large bowel, bladder, and small intestines) away from the field, as well as lead shields to reduce the dose to normal structures in close contact with the applicator (Fig. 3b). The HAM applicator catheters are then connected to the HDR machine (Fig. 4), the staff leaves the room, and the patient is prepared for treatment via remote afterloader control. Treatment planning is performed while the applicator is secured in the treatment position using the Abacus HDR planning software (GammaMed, Inc., North Jackson, OH). It is especially efficient for planning treatments using applicators with fixed or predefined geometry as it allows the import of the implant geometry. Such a program was developed in-house to interface with Abacus and transfer the treatment geometry as defined in the operating room. The treatment geometry includes source stopping positions and dose reference points, required for dwell-time optimization. A secondary dose calculation algorithm for quality assurance of HDR treatment planning is also performed (5, 6). Figure 5 shows a coronal view of dose distribution using the DP for dose-escalation and also dose distribution in an irregular field. After the plan is evaluated and approved by the physician, a second physicist performs an independent check of the treatment plan. The process of planning and checking the plan has been streamlined and takes approximately 5 min. Once the plan is checked and approved, the treatment proceeds and patient vital signs are monitored remotely.

All patients in this study were followed by the surgeon and/or radiation oncologist at 3- to 6-month intervals. All information related to clinical outcome was obtained from the patient electronic medical record system. This was a retrospective study approved by the Institutional Review Board.

Treatment-related complications were classified using the Common Toxicity Criteria of Adverse Effects version 3.0. Overall survival (OS) and LC rates were calculated by the Kaplan–Meier method. Local failure was defined as recurrent disease inside of the IORT field and distant failure included any extra-IORT site described by the physician on physical examination, radiographic, and/or pathologic findings.

Results

The median total target and boost area were 45 and 8.5 cm², respectively. The median Dose 1 and 2 (boost) were 1500 cGy (range, 1250–1750 cGy) and 1750 cGy (range, 1750–1850 cGy), respectively. In all cases, the dose was prescribed to 0.5-cm depth from the applicator surface. The median treatment time was 36.5 min (range, 12–98 min). The median followup was 14.9 months (range, 1–41 months) and OS was 17.5 months (range, 6–34 months). The 2-year actuarial LC and OS for all patients were 80% and 20%, respectively (Figs. 6a and 6b). Eleven patients (68.7%) developed distant metastasis (DM) and had died owing to the progression of disease at the time of last followup.

Among the 4 patients who had an R1 resection, 3 died of DM disease (75%) and 2 (50%) had evidence of local recurrence. None of the patients who underwent an R0 resection had a definitive local recurrence as of the time of last followup or death.

IORT-specific complications were identified by any description in the medical record of sign or symptom that could specifically be related to previous radiation treatment. Three patients (19%) developed toxicity Grade 3 described as “related to HDR-IORT.” All of them also
had recurrent colorectal neoplasm. One patient developed ureteral stricture requiring nephrostomy and stent placement. The second patient developed a pelvic abscess and ileal pouch/colonic fistula and a third patient developed a rectovaginal fistula. No Grade 4 or 5 toxicity was identified.

Discussion

Local failure after combined modality therapy remains a clinical challenge for many types of cancer, as further local options are often limited owing to postoperative and postradiation fibrosis and adhesions, the absence of intact fascial planes, and highly infiltrative disease. Systemic therapy may also be less effective in the setting of prior surgery and radiotherapy owing to poor vascular supply to the irradiated postoperative bed. Locally recurrent malignancies can cause severe pain owing to compression or nerve involvement, bleeding, or obstruction of adjacent structures such as gastrointestinal or urinary tract. Retreatment using EBRT is limited by dose constraints for previously treated normal tissue adjacent to the tumor bed. Surgical resection of a recurrent tumor in a previously irradiated field may be very challenging and outcomes have historically been poor, with 5-year survival rates of 0% for patients undergoing surgery alone for pelvic recurrence from rectal cancer (3). Thus, at most institutions, patients are treated with palliative intent; however, this subset of patients should be considered for salvage treatment using a multimodality approach. Radical resection with IORT has the advantage of delivering tumoricidal doses of radiation to areas with very high risk for local failure, while minimizing the dose to adjacent normal organs (7, 8).

The DP technique adds additional flexibility in delivering HDR-IORT to complex, deep, and previously irradiated areas, especially in recurrent colorectal tumors. The technique described in our study allows for HDR-IORT delivery to almost any complex area or anatomy because dose can be optimized and treatment field can be modulated to achieve ideal geometric coverage. Not only suspicious areas for microscopic disease can be boosted but also critical normal structures such as bowel, nerves, and ureters can be protected from unnecessary radiation. The DP expands the limitation of the retangular HAM applicator and makes it possible to create more geometrically complex treatment areas. However, this entails the use of a template to delineate the target area as well as more complex treatment planning, which could potentially result in a slightly lengthened procedure; thus, one should carefully identify the ideal candidate to use this nonuniform HDR-IORT technique. Finally, another drawback of this more complicated approach is that there is a greater potential for error regarding directionality of the HAM because it was no longer a uniform dose distribution.

Although other centers have advocated IOERT (2, 9, 10), this technique is not always feasible in certain sites owing to anatomic limitations (3, 8). Moreover, IOERT does not allow “DP” in the same manner achieved by HDR-IORT using the HAM applicator. Harrison et al. (4) initially described our results using the HAM applicator to deliver HDR-IORT in 1995. In our experience, this flexible applicator is more advantageous because it can be molded to the tumor bed and allows more conformal treatment on curved surfaces. Moreover,
the technique is relatively simple and the time to position the applicator is low. Lead shields and wet lap pads are often used to protect and displace normal organs from the target area to reduce the dose to the radiosensitive organs and structures in the pelvis. Nevertheless, complications such as ureteral stenosis, bowel obstruction, and neuropathy have been previously reported (11); thus lead shields and lap pads may not be sufficient to protect adjacent highly radiosensitive structures, and the use of the HAM applicator for dose de-escalation should be encouraged to avoid high doses to areas at higher risk of complication.

The potential for severe late complications related to a single high dose remains a concern (8, 12) because the classic principles of radiobiology, sublethal damage repair, reoxygenation of hypoxic cells, and redistribution of cells in the cell cycle are not exploited. Haddock et al. (2) reported in reirradiated patients with colorectal cancer using IOERT that doses exceeding 12.5 Gy in a single fraction were associated with increased incidence and severity of neuropathy. Other common IOERT-related complications included wound infection, gastrointestinal tract fistula, and ureteral obstruction. A recent review from Australia (13) concluded that IORT adds a benefit for LC in all common cancers when used in the multimodal treatment; however, IORT may not improve OS and has significant morbidity depending on the tumor site. In our series, all patients were treated with doses from a minimum of 15 Gy up to 18.5 Gy and no neuropathy was observed. Three patients (19%) had Grade 3 complication as reported by the physician during followup visit: one had urethral stenosis and two others had fistulas (rectovaginal and ureter). Nonetheless, it is not easy to separate treatment-related local complications in patients with recurrent tumors previously treated with surgery and radiation therapy. Previously published data from our institution described the most common type of toxicity: wound (24%), ureter (23%), and bladder (20%) complication in patients with recurrent colorectal cancer who received HDR-IORT without DP (14).

Despite the use of HDR-IORT, local failure can occur in up to 50% of patients (2, 8). Resection margin status has been shown to be the primary predictor of local failure. In a prior study from our institution, patients with R1 or R2 resections had a median time to local failure of 38 vs. 63 months for patients with an R0 resection (15). Although negative margins can be obtained microscopically in a second radical resection, in previously irradiated patients, clear margins are difficult to achieve even by the most experienced surgeons in high-volume cancer centers. The cohort of patients receiving IORT-HDR-DP was particularly high risk for positive margins as all patients had recurrent disease and previous EBRT. Yet, despite positive microscopic margins in 25% of our patients, the 2-year LC was excellent (80%), suggesting that IORT was effective as an adjuvant treatment. Given the small cohort of patients and its retrospective nature, we cannot draw definitive conclusions related to survival outcomes. Also, owing to the lack of a control group, we cannot evaluate the real impact of HDR-IORT-DP in LC compared with regular HDR-IORT without DP.

The largest single-institution experience in IOERT on recurrent colorectal cancer (n = 607) from the Mayo Clinic showed a 3-year local and distant relapse incidence of 23% and 49%, respectively (2). In their series, 37% of the resections were R1. Interestingly, despite comparable LC rates to the Mayo Clinic series, the DM rate (69%) was higher in our cohort, potentially demonstrating more advanced disease at the time of surgery or more aggressive tumor

![Fig. 5. Dose distribution of high-dose-rate intraoperative radiation therapy with dose painting used for dose escalation (a) and irregular field (b).](image-url)
evaluate the benefit of IORT in the setting of radical resections and to determine the long-term effects of this therapy on quality of life for patients undergoing these procedures.

Conclusions

IORT does have a role in the multidisciplinary management of locally advanced or recurrent tumors and should be considered as an adjuvant treatment to surgery. The use of HDR-IORT-DP technique seems to be feasible and safe in patients with locally advanced or recurrent previously irradiated tumors. HDR-IORT-DP may allow for additional dose escalation in this unfavorable group of patients; further studies are warranted to evaluate efficacy of this approach in a larger patient cohort. Although LC was encouraging in this high-risk group, further improvement is needed in the management of DM disease. Advances in systemic treatments including more effective chemotherapy and/or new molecular target agents may address this issue.

References


