Use of combined intraoperative radiotherapy and ^{125}I brachytherapy in incompletely resected recurrent colorectal carcinoma

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RESUMEN: *Se describe una nueva técnica terapéutica, que combina la braquiterapia con I^{125} y la radioterapia intraoperatoria, en el tratamiento del adenocarcinoma colorrectal recurrente. La radioterapia intraoperatoria se aplica al área que previsiblemente puede estar extendido el cáncer, aplicando una dosis inferior a la que puede provocar una neuropatía grave. La braquiterapia con I^{125} se utiliza para eliminar la zona central, pues si se aplicara la radioterapia intraoperatoria únicamente, requeriría una dosis radioterápica con efectos neurotóxicos. Los resultados a más largo plazo, obtenidos en los pacientes tratados, serán objeto de una futura publicación.*

SUMMARY: This technique paper describes a new treatment strategy which involves the combination of ^{125}I brachytherapy and intraoperative radiotherapy (IOERT) in the treatment of recurrent colorectal adenocarcinoma. IOERT is used to encompass the areas of presumed microscopic disease with the IOERT dose being kept below the threshold for severe neuropathy. Brachytherapy with ^{125}I is used to boost areas of gross disease within the IOERT treated area that would otherwise require potentially neurotoxic IOERT doses to achieve local control. The outcome results of patients treated with this technique will be reported at a later date after further patient actual and longer follow-up.

Key words

Intraoperative radiotherapy, iodine-125, colorectal cancer.

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IOERT and ^{125}I brachytherapy.

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Introduction

Intraoperative Electron Beam Radiotherapy (IOERT) has been used in the management of recurrent rectal cancer during the last two decades. Although the lack of randomized trials does not allow firm conclusions regarding effectiveness, toxicity patterns have been elucidated from prior phase I-II trials (1-6). High-dose IOERT (≥15 Gy) has been associated with clinically significant toxicity in late-responding tissues, especially limb neuropathy and ureteral stricture (1-3, 6). Patients routinely treated with high-dose IOERT include those with gross residual disease and/or prior pelvic irradiation. However, the results in terms of local control and survival have been suboptimal regardless (1, 4-6). Current trends in IOERT practice include the use of lower IOERT doses (10-20 Gy) to minimize late-responding tissue toxicity and the addition of low-dose external beam radiation therapy (EBRT) with or without chemotherapy to improve treatment efficacy, even in previously irradiated patients.

A new option to maximize the therapeutic ratio is to combine IOERT with other radiation modalities with different toxicity patterns, such as permanent ^{125}I brachytherapy. ^{125}I releases radiation very slowly over several months (half life=59.4 days) with an initial dose rate of 7.7 cGy/h and a favorable ratio between biologically equivalent dose (BED) in acute and late reacting tissues (Table 1) (7). In addition, the very sharp fall-off of ^{125}I outside the implant volume allows a geometric sparing of sensitive neighboring normal tissues (lumbosacral nerve plexus). ^{125}I brachytherapy has also the advantage of being curative for gross residual disease (as demonstrated in other human malignancies, e.g., prostate cancer), provided the whole tumor burden is identified and homogeneously implanted (8). It is however, not practical to use I-125 to cover a large target area.

This technical report shows the potential for complementary use of ^{125}I brachytherapy and IOERT. ^{125}I brachytherapy is currently used in our institution if gross residual disease remains after surgery. IOERT is used to treat areas of suspected microscopic disease around or adjacent to the ^{125}I implanted area.

Table 1

Biologically equivalent dose (BED) for different radiation modalities

Modality	Dose (Gy)	BED acute-tumor effect (α/β = 10)	BED late effect (α/β = 2.5)	Ratio of BED (acute-tumor/late effect)
I-125[1]	144	140	146	0.96
EBRT[2] 50.4 (1.8Gy x 25)		59	87	0.68
EBRT[2] 59.4 (1.8Gy x 33)		70	102	0.68
IORT[2]	10	20	50	0.40
IORT[2]	15	37	105	0.35
IORT[2]	20	60	180	0.33

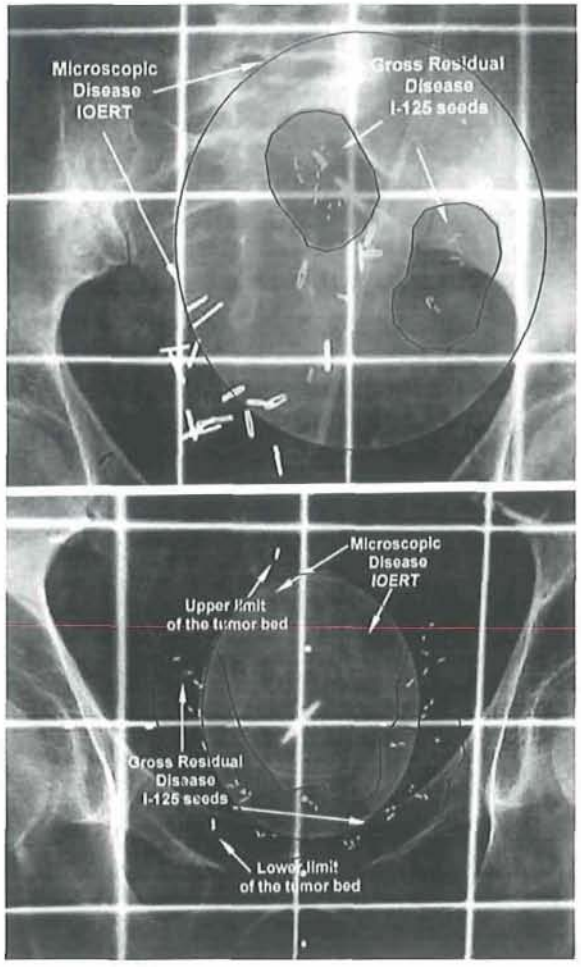
(1) I-125 values calculated according to BED= $Ro/\lambda[1+(\lambda/\mu+\lambda)Ro/\lambda(\beta/\alpha)]$ (7); Ro: initial dose rate; λ: radioactive decay constant, m: repair constant, taken 1.46 h^{-1} for acute-reacting tissues and 0.46h^{-1} for late-reacting tissues.
(2) IORT and EBRT values calculated according to BED=$nd[1+d/(\alpha/\beta)]$.

Materials and Methods

Four patients with recurrent pelvic tumors were treated during the period between July 1996 and June 1998. These previously irradiated patients were selected for combined IOERT and ^{125}I brachytherapy due to the presence of gross residual disease after maximal surgical resection. Patients with only microscopic disease were treated with intraoperative radiation alone. The area of microscopic residual disease to be treated with IOERT and the area of gross disease to be treated with ^{125}I brachytherapy were jointly determined by the oncologic surgeon and the brachytherapist. The boundaries of the suspected residual microscopic tumor were delineated and marked with radiopaque inactive gold marker seeds to guide additional postoperative low-dose EBRT, if required. These markers can be easily distinguished in simulation radiographs from the ^{125}I seeds by their different size and density (figure 1b). The IOERT applicator was inserted into the pelvic cavity to encompass the target volume, and the adjacent normal tissue was excluded from the target by retraction and/or by packing with gauze. Sometimes, the IOERT applicator itself was useful in keeping radiosensitive structures out of the target. A soft-docking system was used, i.e., the IOERT applicator was not attached to the linear accelerator (9). The applicator was positioned over the target volume and secured with a Bookwalter clamp. The annulus (secondary collimator) was attached to the accelerator head. The applicator was aligned with the radiation beam using a laser alignment system located in the linear accelerator head. The laser system also helped to maintain the nominal 100 cm treatment distance. A dose of 10-15 Gy prescribed at the 90% isodose line was then delivered to the tumor bed with 6 MeV electrons. The median time to complete the IOERT procedure was 30-45 minutes, including the actual treatment of three to five minutes.

Once the IOERT procedure was completed, the total activity and the number of ^{125}I seeds to be implanted was determined using the Memorial Sloan-Kettering Nomograph (10). This calculation system, used before November 1995, ensured a minimal peripheral dose (MPD) of 160 Gy to the target volume. After November 1995 and the implementation of the AAPM TG-43 report, this dose was reported as 144 Gy, due to measurements of the Air Kerma Strength (11). Interstitial needles (17-gauge stainless steel, hollow needles, 15 cm long) were then inserted into the gross residual tumor (with a 0.5 centimeter margin), about 1 centimeter apart. A Mick applicator (Mick Radiological Instruments, Bronx, New

Fig 1



Post-implant pelvic radiographs show the location of the implanted ^{125}I seeds and its relationship with the area treated with IOERT. Fig 1a shows the IOERT field completely encompassing the ^{125}I implant. Fig 1b shows the IOERT field adjacent to ^{125}I implanted area.

York) was then sequentially attached to the distal end of the needles to place the ^{125}I seeds into the tumor, usually 1 cm apart along the needle. The I-125 procedure was done after IOERT to minimize radiation exposure to the medical personnel. An omental pedicle flap was used to cover the implanted area to displace bowel away from the high dose area. The median time to complete the ^{125}I implant was 30 minutes.

Discussion

In the pelvis, high IOERT dose may cause severe ureteral damage and neuropathy. The latter may range from pain in the ipsilateral limb to sensory disturbances or motor loss, alone or combined. Although ureteral damage can be successfully managed in a variety of ways, clinical neuropathy may become a permanent and irreversable condition. The incidence of clinical neuropathy increases with IOERT dose (3) and has been reported to occur in 25% to 34% of the treated patients in the Mayo series with IOERT doses in the 10 to 30 Gy range (3). In the same series, however, severe neuropathy was documented in only 6% of these patients with a threshold dose of 15 Gy and with most of them occurring after IOERT doses of ≥20 Gy. A NCI retroperitoneal sarcoma trial (12) reported a 60% incidence of neuropathy with the use of 20 Gy IOERT followed by 35-40 Gy. It is therefore, unlikely, that dose escalation in IOERT can offer a substantial advantage for those patients with subtotally resected recurrent colorectal cancer. Hence, current trends in IOERT practice tend towards reducing IOERT doses (10-20 Gy) and then supplementing with EBRT with or without chemotherapy, even in previously irradiated patients. However, even a combination of IOERT and EBRT may be insufficient to control gross residual disease in previously irradiated patients because the prior radiation given limits delivery of meaningful EBRT doses.

The limited experience reported in two ^{125}I brachytherapy series on recurrent colorectal carcinoma show no neurological toxicity (13,14). The BED for standard doses of iodine-125 used is high, however, it has a favorable acute to late effect ratio (table 1) (7). Further, the exponentially sharp fall-off of the radiation dose outside the implanted volume reduces the dose to the neighboring sensitive structures (lumbosacral plexus, ureter), thus minimizing the probability of severe damage unless these structures are intentionally implanted due to tumor invasion. The local control results, however, have been very poor. Fourquet et al. (13), at Memorial Sloan-Kettering Cancer Center, New York, reported a 55% 1-year local control for 51 patients with colorectal cancers treated with brachytherapy in the pelvis. Seventy-five percent of these patients had ^{125}I implants; 25% received EBRT. Data from The Ohio State University (OSU) reveal 1, 2, and 4-year local control rates of 38%, 17%, and 17%, respectively (median to local failure 11 months) in a series of 29 patients with colorectal cancer recurrent in the pelvis or the paraortic nodes (15). These local control results are

remarkably poor when compared with local control rates exceeding 90% in other human malignancies treated exclusively with ^{125}I brachytherapy (e.g., prostate) (8). In the post-irradiated pelvis, it is very difficult to differentiate tumor from areas of radiation fibrosis, which may lead to an underestimation of the target volume. In addition, the high-dose of radiation delivered with ^{125}I brachytherapy requires that the target volume be implanted with little (0.5 cm) or no margin. Furthermore, the sharp fall-off of ^{125}I outside the implanted volume, which is an advantage for normal tissue sparing, becomes a disadvantage in terms of target coverage because any area left unimplanted will receive very little irradiation. The interim OSU data in 80 patients treated intraoperatively for recurrent colorectal cancer show that the median treatment volume for ^{125}I brachytherapy was 25 cc; whereas, patients treated with IOERT or intraoperative high-dose brachytherapy had median treatment volumes of 66 cc and 50 cc, respectively. So, in this regard, ^{125}I is used to treat gross disease while IOERT is used to treat microscopic disease adjacent to the implanted area (Figure 1a and 1b). This report is restricted to the technics of this strategy. The results of patients treated with this strategy will be reported separately after further followup with more patients.

Conclusions

This technical report shows the potential for complementary use of ^{125}I brachytherapy and IOERT in recurrent colorectal cancer patients. ^{125}I brachytherapy is used if gross residual disease remains after surgery while IOERT is used to treat areas of suspected microscopic disease around or adjacent to the ^{125}I implanted area.

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