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The Current Status of Intraoperative Radiotherapy in Colorectal Surgery

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ABSTRACT

Colorectal cancer is the second most common malignancy in Singapore and its incidence is increasing. Results of surgery have been augmented in selected cases by the addition of radiotherapy and chemotherapy. This standard approach only offers palliation in locally advanced and locally recurrent cancers. Newer modalities and combinations are currently being investigated to improve the results in this particular group of patients. One such modality is the use of intraoperative radiotherapy (IORT). This paper discusses the rationale for using IORT, the patient selection, method of delivery and treatment, tolerance and results in centers which have been using IORT as part of a multi-modality therapy for colorectal cancer.

Keywords: colon, rectum, cancer, radiotherapy, IORT

INTRODUCTION

Colon and rectal cancer is the second most common malignancy in Singapore. Its incidence is increasing alarmingly and is predicted to overtake lung cancer as the commonest malignancy by the next century. The mainstay of treatment is surgical resection even in locally advanced and locally recurrent rectal cancer. However, in these situations, local and systemic failure rates are high with surgery alone[1], suggesting a role for radiation therapy and chemotherapy, respectively. This standard treatment approach (external beam radiotherapy and chemotherapy ± resection) can offer useful palliation in locally advanced and locally recurrent colorectal malignancies. The limiting factor is usually the tolerance of surrounding organs and tissues. External beam doses necessary to accomplish local control are in the range of 6000 to 7000+ cGy while safety limits are often in the range of 4500 to 5000 cGy. This often accounts for a dismal local control and long-term survival in this group of patients[2,3].

Intraoperative radiotherapy (IORT) refers to the delivery of irradiation at the time of surgery. This can utilise electrons (IOERT) or high dose rate brachytherapy (IOHDR) and is usually used in conjunction with surgical exploration and resection ± external beam radiotherapy (EBRT) and chemotherapy. Both IORT methods therefore achieve a higher more effective dose of irradiation to the area of concern while dose limiting structures are surgically displaced. IORT thus aims not only at improvement of palliation in situations of locally advanced tumor and in locally recurrent cancers but in improved local control which subsequently translates to an improved survival. The most useful area is deep in the pelvis where, anatomically, resection may be compromised. This manuscript reviews the rationale of the modality of therapy, describes the method of surgical approach and IORT in these situations and examines the results to determine the exact role of IORT in colorectal surgery.

RATIONALE

In locally advanced or recurrent rectal cancer where negative margins cannot be obtained surgically, external beam irradiation is usually palliative because doses above 5000 cGy cannot be delivered safely, leaving persisting disease or resulting in recurrence.

Residual microscopic disease requires about 6000 cGy in 180 to 200 cGy fractions to achieve local control. When gross residual disease is left behind, even higher doses are required. At doses greater than 6000 cGy, the radiation tolerance in the abdomen and pelvis would be exceeded. Therefore, while local control will benefit from an aggressive approach with external beam radiotherapy, severe treatment related complications may result including fistulae and perforation which often require further surgery. Mortality may also result.

Excellent long-term results have been reported using a combined external beam irradiation plus a boost technique in breast, gynaecological as well as head and neck tumours using interstitial and intracavitary techniques. IORT is therefore a logical extension. Tolerable external beam doses of 4500 to 5000 cGy is delivered pre-operatively and the remaining irradiation delivered as a supplement intra-operatively.

This combination improves the local recurrence rates while keeping the complications acceptably low because the volume of the irradiated boost field is decreased by direct tumour field visualisation and appositional treatment and all or part of dose sensitive structures are mobilised and shielded. In

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addition, by using appropriate electron beam energies, the depth of penetration can be controlled. The effectiveness of the radiation therapy is therefore optimised.

Selection of patients

The specific criteria for eligibility varies from institution to institution but general guidelines prevail. These include: 1) surgery alone will not achieve acceptable local control (ie. the patient would likely have positive microscopic margins); 2) external beam doses would be 6000 – 7000 cGy or greater for a curative attempt but is unsafe to deliver in the particular patient; 3) IORT and external beam irradiation in combination would produce a more suitable cure versus complication ratio, and 4) there is no evidence of disease outside the localised area.

Therapeutic approach to patients

The optimal sequence of therapy is discussed and determined at the time of joint multidisciplinary consultation involving the surgeon(s), radiation oncologist and medical oncologist.

Preoperative radiation therapy and chemotherapy

Radiation therapy administered alone does not offer any chance for cure but combined with surgery for locally advanced primary rectal tumours, local recurrence rates are reduced and resectability rates increased[4-7]. In the same manner, radiation therapy can be employed for locally recurrent rectal cancer. The recent demonstration of added benefit from combined radiation therapy and fluorouracil chemotherapy[7,8] prompts us to use the same basic regimen to reduce local and systemic failures. To further reduce the risk of local recurrence while avoiding dose-related toxicities, we can combine external beam radiation preoperative radiation therapy plus chemotherapy with intraoperative electron radiation therapy (IOERT). IOERT offers the advantages of localised tumour-directed therapy, limited normal tissue exposure, single fraction, high biological equivalence, with improved control for high risk sites.

Patients with local recurrence who have not undergone previous pelvic radiation therapy receive a full course of external beam radiotherapy (4500 – 5000 cGy) in conjunction with 5 fluorouracil (5-FU). Since maximum synergy between external and intraoperative radiation therapy is accomplished within an 8-week period, patients are re-staged and taken for surgery and IOERT within 4 to 8 weeks following external beam and chemotherapy treatments. Patients with local recurrence who received adjuvant postoperative adjuvant radiation therapy as part of their primary tumour treatment are treated with low dose (2000 cGy) preoperative radiation plus 5-FU based chemotherapy, when possible. When low dose radiation therapy is used, surgery can be scheduled within one to two weeks.

Pre-operative EBRT (± chemotherapy) followed by resection in 3 – 5 weeks offer theoretical advantages over resection, IORT followed by EBRT. These include: 1) the exclusion of patients who have metastases detected at re-staging or laparotomy after the initial EBRT; 2) possibility of tumour shrinkage with an increased possibility of achieving gross total resection; 3) potential alteration of implantability of cells that may be disseminated at the time of a marginal or partial surgical resection, and 4) possible reduction in treatment interval between EBRT and IORT. (When resection is done initially, EBRT may be delayed if post-operative complications occur).

Surgery

This description will concentrate on locally recurrent rectal cancer but the basic principles can be applied to locally advanced rectal cancers. Before embarking on resective pelvic surgery, it is essential that patient and family members understand the magnitude of the planned procedure. Sphincter-preserving surgery may not be possible in cases of local failure, therefore, patients must be willing to accept a permanent colostomy. Those with anterior or posterior fixation must understand the consequences of an ileal conduit or sacrectomy, respectively.

Preferably all cases of locally recurrent rectal cancer should be scheduled in a dedicated IOERT suite. This suite, within operating room facilities, houses a linear accelerator, standard operating room equipment, and special anesthesia equipment that facilitates moving from operating to radiating positions. For pelvic cases, patients are placed in the legs up position taking precautions to avoid compartment syndrome which can occur during these long cases[9]. Under cystoscopic guidance, bilateral ureteral stents are placed at the beginning of the case. Abnormalities of the bladder may be appreciated at the time of cystoscopic stent placement.

If a rectus abdominus flap is anticipated, care must be exercised in preserving epigastric vessels during the celiotomy. Adhesions are typically present and must be lysed to allow full abdominal exploration. Careful examination of the liver, peritoneal surfaces, retroperitoneum, and wound, should be performed to establish the absence of extrapelvic disease which would contraindicate radical resection. Rarely, in very young patients with limited pelvic disease, liver metastases, and pelvic recurrence have simultaneously been resected, but this is the exception rather than the rule.

It is typical to find pelvic fibrosis, and for this reason, the pelvic dissection is commenced at the level of the aortic bifurcation. Ureters and iliac vessels are dissected from the level of the pelvic brim to the sidewalls, this allows safe dissection in the posterior pelvis along the sacrum. It is generally necessary to trace the ureters all the way to their insertion into the bladder, this allows safe lateral dissection in a reoperative pelvis. When sacrectomy or cystectomy is required, the ureters are actually dissected for their entire pelvic length, to prevent injury from the posterior dissection, or to allow insertion into an ileal conduit, respectively. The intraoperative management of these lesions are determined by the findings at surgery. These can be classified into non-fixed (FO),

fixed resectable (FR anterior, FR posterior) and fixed non-resectable (FNR)[10].

Non-fixed lesions (FO)
A completion abdominoperineal resection is performed. As is true for all locally recurrent rectal cancer cases, it is very often difficult to distinguish between normal scar and tumour-infiltrated scar. When fibrosis is encountered, particularly in areas that are outside the realm of possible resection, such as along the sacral promontory or high along the lateral sidewalls, frozen section should be obtained. If tumour cells are identified within samples of the fibrosis by frozen section, complete resection is not feasible.

Fixed-resectable, posterior lesions
Posterior fixation (FR) is best managed by distal sacretomy. As discussed above, the proximal limit of sacral resection is around the S2-3 junction. Removing portions of sacrum proximal to S2 requires elaborate internal fixation and reconstructive procedures for sacroiliac stability and this is beyond what is reasonable for locally recurrent rectal cancer. Furthermore, preserving one S3 nerve root is generally sufficient bladder function.

Distal sacrectomy, performed in four consecutive stages, includes anterior procedures, posterior procedures, IOERT and pelvic reconstruction. Anterior and lateral lines of resection are delineated and adherent organs or structures are dissected and removed en bloc with the posterior-based tumour. The posterior dissection stops just proximal to the level of fixation. Frozen section biopsies, at this point, will help determine whether the lesion is resectable and establish the site at which a negative sacral margin can be accomplished. This maneuver facilitates the ease of completing the posterior sacral transsection.

Next, internal iliac artery and vein ligation is performed to reduce blood loss when sacral transsection proximal to the S3-S4 junction is anticipated. Finally, before closing the abdomen, gastrointestinal and/or urinary stomas are fashioned, as required, and either the omentum or rectus abdominus flap are mobilised and placed in the pelvis for subsequent pelvic reconstruction.

The patient is repositioned flex-prone and a posterior midline incision is made. The sacrum is exposed and the sacrotuberous and sacrospinous ligaments divided. The pyriformis muscle is divided taking extreme care to protect the sciatic and pudendal nerves. At this time, the level of sacral transection can be identified by palapating the sacrum anteriorly. While the orthopaedic surgeon performs the laminectomy, dural sac ligation and bony transsection, the pelvic surgeon assists in the final dissection of the lateral pelvic sidewalls to protect the ureters, bladder, urethra and sciatic nerve from injury. It is occasionally necessary to sacrifice lateral sacrospinous ligament attachments to accomplish clear lateral margins. Intraoperative radiation therapy and closure are performed as described below.

Fixed-resectable, anterior lesions
The extent of resection required for anterior fixation depends on whether the patient has a uterus and/or a rectum. Most often the presence of a uterus ensures that the bladder will not be tumour-adherent. In contrast, when there is no uterus or rectum, such as in the male who has previously undergone APR, there is a much greater likelihood that the bladder will be involved with tumour. If the tumour is confined to a portion of the bladder that can be sacrificed and primarily repaired, then partial cystectomy will suffice. Having said that, caution should be exercised when primary repair of a radiated bladder is being considered. If the tissues are poor, it may be safer to remove the entire bladder. When the trigone or prostate are tumour-involved, cystectomy and an ileal conduit are required.

Intraoperative Electron Radiation Therapy (IOERT)
The resected specimen and additional patient-side biopsies, as required, are reviewed with the pathologist and radiation oncologist to determine margins and the need for IOERT. When IOERT is required, a lucite cylinder is placed into the pelvis to expose tissues at risk, and the patient is repositioned beneath the linear accelerator. Typically, a dose of 1,000 cGy is recommended for minimal residual disease, 1,500 cGy for gross residual $\leqslant$ 2 cm, and 2,000 cGy reserved for unresected or gross residual disease of $\geqslant$ 2 cm. These single-dose radiation treatments are biologically equivalent to the same quantity delivered as external beam fractions[11].

Perineal wound closure
Finally, each procedure is completed by closing the perineal wound over drains. Since residual pelvic defects are often quite sizable and tissues of poor quality due to radiation therapy, some type of flap should be used to partition the pelvis separate from the perineum. If the omentum is not of suitable size or consistency, the rectus abdominus flap should be used. The rectus is especially preferred for sacrectomy wounds, since it not only fills the pelvic dead space, but also provides a fresh, non-radiated, vascularized skin paddle for closing the perineum. The rectus abdominus can also be used to enlarge the vagina, when narrowing or shortening occurs as a result of extensive resection.

IORT tolerance

Dose sensitive structures in the pelvis are mainly the ureter and the peripheral nerves. The ureters are not strictly dose limiting as stents can be inserted as indicated to overcome obstruction and thus preserving renal function. It has been documented that about 44% of previously unobstructed ureters become partially or completely obstructed when included in the IORT field.

The peripheral nerve is the principle dose limiting normal tissue for IORT in the pelvis. The anatomic location of these nerves make it almost impossible to shield or move out of the radiation field even if uninvolved. Prospective data collected in patients who

have undergone IORT suggest that the incidence is dose-related. When IOERT doses of $\geq$ 15 Gy are given, about 20% of the patients develop neuropathy. This drops significantly when doses of $<$ 12.5 Gy are given. This incidentally is the cut-off point of IOERT boost given depending on whether gross or microscopic residual disease is left behind.

Results of IORT in colorectal surgery

This section will review the results of IOERT in primary locally advanced cancers and recurrent cancers separately.

Primary cancers

Both the Massachusetts General Hospital and the Mayo Clinic have shown the results of EBRT, resection + IOERT to be statistically better than EBRT and resection alone. This include survival rates at 1 and 2 years. The majority of the relapses were in the non-IOERT group and occurred within 18 months of surgery. The improvements in local recurrence rates with the addition of IOERT paralleled an improved survival rate. It was also found that both the local control and survival at five years was better for patients in whom there was only microscopic disease left behind. Although it can be argued that these results may be a result of selection bias, they seem fairly conclusive. In addition, randomized trials in this area may be difficult.

Recurrent cancers

Long-term survival in patients with recurrent rectal cancers treated by standard techniques are usually $\leq$ 5%. The addition of IOERT in the treatment of this group in MGH produced an overall 5-year survival rate of 16%. When only microscopic margins were left behind, the results were clearly superior compared with gross residual disease. The 5-year local recurrence and disease free survival was 47% and 21% versus 21% and 7% respectively.

Suzuki et al[12] reported the Mayo Clinic series of locally recurrent rectal cancers treated with and without IOERT. This was a non-randomized group of patients but the 3 and 5-year survival was 43% versus 18% and 19% versus 7% in the IOERT versus non-IOERT group. Significant factors that were found to affect survival significantly were amount of residual disease (gross versus microscopic), symptoms of pain, amount of fixation to the pelvic walls and pre-operative Eastern Co-operative Oncology Group status. They found that local control was significantly better with IOERT at 3 years (40% versus 90%) but the cumulative probability of distant metastasis did not differ in the two groups.

CONCLUSION

The data available are very encouraging with regard to local control and survival when IOERT is used in combination with standard treatment for locally advanced and recurrent colorectal cancer. Further advances are necessary as the systemic failure rate still approaches 50%. It must also be kept in mind that local control is sub-optimal if gross residual tumor is left behind despite maximal surgical resection. Randomized studies comparing standard therapy $\pm$ IOERT are currently on the way in Europe and Scandinavia. In the US, attempts are being made to improve local control with 5FU $\pm$ leucovorin or other enhancing agents during EBRT. Dose modifiers like sensitizers and hyperthermia for IOERT are also being evaluated. Taking the concept to the next step would be an attempt to investigate randomized trials of (EBRT, resection, IOERT $\pm$ dose modifiers) with various chemotherapeutic regimes during and after EBRT.

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