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Advancing Techniques of Radiation Therapy for Rectal Cancer

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Since the advent of radiation therapy for rectal cancer, there has been continual investigation of advancing technologies and techniques that allow for improved dose conformality to target structures while limiting irradiation of surrounding normal tissue. For locally advanced disease, intensity modulated and proton beam radiation therapy both provide more highly conformal treatment volumes that reduce dose to organs at risk, though the clinical benefit in terms of toxicity reduction is unclear. For early stage disease, endorectal contact therapy and high-dose rate brachytherapy may be a definitive treatment option for patients who are poor operative candidates or those with low-lying tumors that desire sphincter-preservation. Finally, there has been growing evidence that supports stereotactic body radiotherapy as a safe and effective salvage treatment for the minority of patients that locally recur following trimodality therapy for locally advanced disease. This review addresses these topics that remain areas of active clinical investigation.
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Introduction

More than 40,000 individuals are diagnosed with rectal cancer in the United States each year with a mortality rate near 40%.[1] Surgery with or without chemo-radiation therapy (CRT) is the primary treatment for these patients. Both local recurrence and distant metastasis are a major concern in rectal cancer, and each is associated with substantial morbidity and mortality.[2] Advancements in surgical technique and neoadjuvant therapies, however, have resulted in reduced local and distant recurrence, with subsequent improvement in overall survival over the past decade.[1,3]

Since 2004, preoperative CRT followed by surgery and adjuvant chemotherapy remains the standard of care for locally advanced rectal cancer (cT3-4 or node-positive). The inclusion of CRT in addition to surgery results in improved local control and disease-free survival.[4,5]Furthermore, preoperative CRT results in improved local control and toxicity profile compared with postoperative therapy, and it may allow for downstaging to facilitate a sphincter-sparing low anterior resection for a tumor that may otherwise require abdominoperineal resection.[5]

Radiation Technique

The clinical utility of 3-dimension conformation RT (3DCRT) for rectal cancer has been established. The most important contributions of 3D planning include target localization and normal tissue dose analysis via dose volume histograms. Advancing technologies of therapy are currently being investigated that permit improved conformation of radiation dose to target structures whereas limiting irradiation of surrounding normal tissues. Application of these technologies in the treatment of rectal and anal cancer is attractive, based on the potential reduction in radiation treatment toxicities that are frequently incurred in the pelvis and perineum. Thus, modern highly conformal RT planning and delivery techniques could potentially reduce the radiation dose to the bowel and other adjacent organs at risk, thus reducing subsequent acute and late side effects that limit the ability to escalate the tumor dose. Furthermore, more conformal RT techniques might also allow for dose escalation to target areas, leading to improved tumor control.

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Intensity-Modulated RT

Intensity-modulated RT (IMRT) produces dose distributions that are able to conform to the shape of target with concave or convex isodose lines or both. The benefit of this modality of therapy is to reduce high dose to organs at risk, thereby reducing both acute and late toxicity without compromise to target coverage. The radiosensitivity of the bowel is well known, and acute radiation enteritis occurs in most patients undergoing RT for rectal cancer; severe acute toxicity (ie, grade 3-4) is reported in up to 23% of patients treated with preoperative RT with concurrent chemotherapy, escalating to 37% with doses >50 Gy to the pelvis.[6,7] There is also risk of late bowel toxicity, presenting with diarrhea, bowel stricture, hemorrhage, or perforation, as high as 5% at 5 years with doses between 45 and 50 Gy.[7] Most studies show that the incidence of both acute and late effects is directly related to the maximum dose and total volume of irradiated bowel.

The ability of IMRT to reduce bowel irradiation has been demonstrated in prostate, cervical, and endometrial cancers. Planning studies in these disease sites show a 13%-18% reduction in volume of bowel treated to 45 Gy. The clinical benefit of IMRT compared with 3DCRT or conventional 2-dimensional treatment delivery in rectal cancer still remains to be determined. However, research into potential benefits has recently been undertaken. Urbano et al[8] performed a dosimetric analysis of patients with rectal cancer, who were all simulated prone with a full bladder. They found that the use of inverse planning IMRT was associated with a 64% reduction in percentage of bowel volume irradiated to 45-50 Gy compared with 3DCRT. This study found that with IMRT, absolute bowel volume irradiated to 45 Gy and 50 Gy was reduced to 69 cm^3 and 20 cm^3, respectively, compared with 214 cm^3 and 51 cm^3 with 3DCRT. The differences in improvement between 5-field, 7-field, and 9-field IMRT plans in decreasing the amount of bowel volume receiving high doses was minimal, but all were significantly better at sparing bowel compared with 3-field IMRT. This study, therefore, concluded that a 5-field custom segmented IMRT plan appears clinically promising as well as favorable in terms of treatment time to reduce intrafractional prone position variation.

NRG Oncology RTOG 0822[9] was initiated to determine whether the use of IMRT could decrease the rate of gastrointestinal toxicity with multiagent neoadjuvant chemoradiation (concurrent capecitabine 825 mg/m^2 BID, oxaliplatin 50 mg/m^2 weekly for 5 doses) in locally advanced rectal cancer. The basis of this study stemmed from RTOG 0247, a phase II randomized trial comparing capecitabine and oxaliplatin with 3DCRT vs capecitabine and irinotecan with 3DCRT; however, there was unexpectedly high grade 3-4 toxicity in both arms, largely gastrointestinal and appeared consequent to the compounding toxicity from both chemotherapy and radiation. This resulted in premature closure of the study, although it was later re-opened with dose de-escalation of the chemotherapy. In RTOG 0822, radiation delivery included an inverse-planned IMRT phase to the rectum and lymphatics at risk to 45 Gy (1.8 Gy fractions) followed by a 3D chemoradiation boost to the gross disease with a 2-cm margin including all of the presacral space to 5.4 Gy (1.8 Gy fractions). Patients underwent CT simulation either supine or prone in a belly board. The RTOG anorectal atlas was used to define the pelvic clinical target volumes (CTV) for the initial phase. For T3 tumors, the CTV included all gross disease (ie, gross tumor volume [GTV]) as well as the internal iliac lymph nodes and the mesorectum (ie, perirectal fat and presacral space). For T4 tumors, the CTV included the same structures as well as the external iliac lymph nodes. With regard to GTV to CTV expansions, the rectal GTV was expanded 1.5 cm radially and 2.5 cm craniocaudally, nodal GTV expanded 1.5 cm symmetrically, and uninvolved internal and external iliac vessels expanded 1 cm symmetrically. The mesorectum and perirectal lymphatics as well as the presacral space, defined as the 8 mm of soft tissue anterior to the sacrum from mid-S1 to S5, completed the unified CTV. The planning tumor volume (PTV) resulted from a 0.5 symmetric expansion of the unified CTV. The final treatment plan was required to cover $\geq 98\%$ of the PTV with $\geq 93\%$ of the prescription ($\leq 10\%$ of the PTV could receive $\geq 105\%$ of the prescribed dose and $\leq 5\%$ of the PTV could receive $\geq 110\%$ of the prescribed dose). Organs at risk included the small bowel, ie, peritoneal space containing the small bowel ($V_{35\ Gy} < 180$ cc, $V_{40\ Gy} < 100$ cc, $V_{45\ Gy} < 65$ cc, max point < 50 Gy), femoral heads, and bladder.

The primary endpoint of this study was to determine the rate of grade ≥ 2 gastrointestinal toxicity with the goal of identifying a 12% reduction in these adverse effects compared with that seen in RTOG 0247. This study, however, showed a 51.5% rate of grade ≥ 2 gastrointestinal toxicity, which substantially exceeded the observed rate of 40% in RTOG 0247. The acute toxicity in this trial perhaps discount the theoretical benefit of IMRT that was initially seen in retrospective and dosimetric studies. However, both these trials are assessing toxicity in the setting of multiagent chemotherapy, and it is unlikely that oxaliplatin will be routinely employed with neoadjuvant chemoradiation in rectal cancer, given the lack of clinical benefit seen in phase 3 studies.[10,11] Furthermore, the volume of bowel receiving low dose radiation (ie, 15 Gy) may be more important with the compounding effects of multiagent chemotherapy; the bowel constraints used in RTOG 0822 may perhaps be insufficient, and a dosimetric constraint for volume of bowel receiving lower dose of radiation may be clinically important.

At this juncture, the role of IMRT in rectal cancer remains to be determined. This technique may be beneficial in situations where there is substantially more bowel within a conventional 3DCRT field, in patients with T4 tumors that require external iliac coverage, or in the postoperative setting. It is important to note that prone positioning, a conventionally employed maneuver used to reduce the bowel volume within treatment field, can result in setup variation. Interfraction and intrafraction variations can be problematic with IMRT as a large portion of the target volume is close to a steep dose gradient, so there is potential for underdosing. Institution-based analysis of systematic and random errors with prone position is paramount to determine adequate PTV margins before the implementation of IMRT.