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Adjuvant radiation therapy for bladder cancer: A dosimetric comparison of techniques

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ABSTRACT

Trials of adjuvant radiation after cystectomy are under development. There are no studies comparing radiation techniques to inform trial design. This study assesses the effect on bowel and rectal dose of 3 different modalities treating 2 proposed alternative clinical target volumes (CTVs). Contours of the bowel, rectum, CTV-pelvic sidewall (common/internal/external iliac and obturator nodes), and CTV-comprehensive (CTV-pelvic sidewall plus cystectomy bed and presacral regions) were drawn on simulation images of 7 post-cystectomy patients. We optimized 3-dimensional conformal radiation (3-D), intensity-modulated radiation (IMRT), and single-field uniform dose (SFUD) scanning proton plans for each CTV. Mixed models regression was used to compare plans for bowel and rectal volumes exposed to 35% ($V_{35\%}$), 65% ($V_{65\%}$), and 95% ($V_{95\%}$) of the prescribed dose. For any given treatment modality, treating the larger CTV-comprehensive volume compared with treating only the CTV-pelvic sidewall nodes significantly increased rectal dose ($V_{35\%\ rectum}$, $V_{65\%\ rectum}$, and $V_{95\%\ rectum}$; $p < 0.001$ for all comparisons), but it did not produce significant differences in bowel dose ($V_{95\%\ bowel}$, $V_{65\%\ bowel}$, or $V_{35\%\ bowel}$). The 3-D plans, compared with both the IMRT and the SFUD plans, had a significantly greater $V_{65\%\ bowel}$ and $V_{95\%\ bowel}$ for each proposed CTV ($p < 0.001$ for all comparisons). The effect of treatment modality on rectal dosimetry differed by CTV, but it generally favored the IMRT and the SFUD plans over the 3-D plans. Comparison of the IMRT plan *vs* the SFUD plan yielded mixed results with no consistent advantage for the SFUD plan over the IMRT plan. Targeting a CTV that spares the cystectomy bed and presacral region may marginally improve rectal toxicity but would not be expected to improve the bowel toxicity associated with any given modality of adjuvant radiation. Using the IMRT or the SFUD plans instead of the 3-D conformal plan may improve both bowel and rectal toxicity.

Introduction

Patients with urothelial carcinoma found to have primary tumors invading through the bladder muscle (≥pT3) at the time of radical cystecomy have an estimated 5-year overall survival rate of less than 40%.[1] Approximately one-third of these patients develop a recurrence in the pelvis as the initial site of clinical failure after surgery.[2] Perioperative chemotherapy is not effective in preventing these pelvic recurrences,[2-4] and salvage of such failures is rarely successful.[3-5]

There is evidence that adjuvant radiation therapy reduces local-regional failures[6,7] and may even improve survival,[6,7] but adjuvant radiation has no well-defined role because of bowel toxicity reported decades ago with such treatments. Improvements in radiation techniques coupled with increased recognition of those patients who are at highest risk for pelvic failures have rekindled interest in the potential benefits of adjuvant radiation. Several cooperative groups are developing clinical trials to reassess adjuvant radiation after radical cystectomy, including NRG Oncology

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and cooperative groups in France and the United Kingdom (Paul Sargos, personal communication, April 12, 2015 and Amit Bahl, personal communication, May 15, 2015). However, the radiation techniques and the target volumes that are most likely to optimize outcomes in these trials have not been clearly defined. The purpose of this study was to evaluate the radiation techniques to be used in these clinical trials by comparing the bowel and rectal doses associated with 3 different treatment modalities [3-dimensional conformal radiation (3-D), intensity-modulated radiation (IMRT), and single-field uniform dose (SFUD) proton therapy] applied to 2 different clinical target volumes (CTVs) that have been proposed for adjuvant radiation (pelvic sidewall nodes ± cystectomy bed and presacral nodes).[8]

Methods and Materials

Simulation and contouring

Computed tomography (CT) simulation images were obtained for 7 patients who had previously received radiation after radical cystectomy, either for positive margins ($n = 5$) or pelvic failure ($n = 2$). There were 6 patients who had ileal conduit diversions, 1 patient who had an Indiana pouch, and 1 patient who had an orthotopic neobladder as their urinary diversion. Patients were simulated either prone using a belly board or supine with 15° Trendelenburg position to displace the bowel from the pelvis. For each patient, 2 different CTVs were contoured. CTV-pelvic sidewall has been proposed for patients with negative surgical margins, and it included the bilateral common, external and internal iliac nodal regions, as well as the obturator nodal regions.[8] CTV-comprehensive has been proposed for patients with positive surgical margins, and it covered the same nodal volumes as CTV-pelvic sidewall did but also included the presacral nodal region and the cystectomy bed.[8] The volumes contoured for CTV-pelvic sidewall and CTV-comprehensive are illustrated in Fig. 1.

The common iliac nodes were contoured from the aortic bifurcation superiorly down to the common iliac bifurcation inferiorly, creating the CTV by adding a 7-mm margin around the vessels and carving out bone but not soft tissue. Our decision to include the full common iliac nodes was based on the results of our prior patterns of failure analysis in our cohort of 442 cystectomy patients that reported 10% to 15% 5-year cumulative incidence of failure in the common iliac nodes for patients with pT3 category or higher category disease.[8] We defined the CTV for the internal and the external iliac nodes as the volume encompassing the internal and the external iliac vessels with a 7-mm margin carving out bone. For the obturator node CTV, the volume was a 5-mm expansion around the tissue extending 5 to 10 mm medial to the medial border of the internal obturator muscle with its superior margin located at the inferior border of the internal/external iliac nodal volume and its inferior border at the cephalad edge of the pubic symphysis. Anteriorly, the obturator volume approached the anterior extent of the ischium, while posteriorly the CTV extended to the posterior extent of the ischium. The cystectomy bed was contoured beginning 1 cm cephalad to the apex of the pubic symphysis, extending inferiorly to the bottom of the pubic ramus. Anteriorly, the cystectomy bed was contoured to the pubic ramus bone, posteriorly to the tissues just anterior to the rectum and the vagina when present, and laterally 5 mm into the obturator muscles bilaterally. The contours of the cystectomy bed were defined based on the results of our prior patterns of failure analysis and encompassed the sites of failure in the cystectomy bed in our cohort of 442 cystectomy patients.[8] The presacral region was contoured to include 1 to 1.5 cm of tissue anterior to the sacrum between the iliac contours. The superior border of the presacral region was just below the L5 protuberance, whereas the inferior border was at the bottom of the S2 vertebrae. For all plans, planning target volumes were created to account for setup and motion uncertainties by uniformly expanding CTVs by 5 mm. For the SFUD plans, a beam-specific optimization volume was created to account for both lateral and range uncertainties, as has been previously described.[9]

There were 2 organs at risk contoured for each patient: the bowel and the rectum. The bowel contour included the individual loops of both the small bowel and the large bowel because these are difficult to distinguish in the post-cystectomy setting. The rectal contour included the entire rectum and its contents from the sigmoid flexure inferiorly to the level of the ischial tuberosities.

Treatment planning

For 3-D conformal radiation, a 4-field box technique with 15-MV photon beams was used for patients in both the prone and supine positions. For the IMRT plans, 8 photon beams of 15 MV at 0°, 30°, 50°, 70°, 90°, 270°, 300°, and 330° were used to reduce dose to the anterior abdomen to spare the bowel. 15-MV energy was chosen based on the body habitus of the patients and the central location of the target. For the SFUD plans, a posterior-anterior and 2 posterior oblique fields angled 30° off the vertical axis on each side were used for improved plan robustness and to avoid anterior beams going through the bowel to reduce bowel toxicity and dose inhomogeneity because of day-to-day variations in the gas distribution in the bowel. Beam weights varied by patient. For illustration, Fig. 2 shows the isodose distribution for each treatment modality for a typical post-cystectomy patient.

For all plans, the CTVs were prescribed to receive a dose of 50.4 Gy in 1.8-Gy fractions. All proton doses assumed a relative biological effectiveness of 1.1. All treatment planning was performed using Eclipse.

Statistical analysis

Mixed models regression was used to compare mean volumes of bowel and rectum exposed to different dose levels (continuous outcomes), with treatment method as a categorical predictor with 3-D conformal as the reference. Separate regressions were fitted for sidewall *vs* comprehensive plans and for low, intermediate, and high dose levels. The 3 dose levels were defined as 35% ($V_{35\%}$), 65% ($V_{65\%}$), and 95% ($V_{95\%}$) of the prescribed dose, respectively, according to CTV and treatment modality.

Results

For all plans, at least 99% of the CTVs were covered by 98% of the prescription dose.

Effect of CTV on bowel and rectal dosimetry

The mean volumes of bowel receiving at least 35%, 65%, and 95% of the prescribed dose according to treatment modality for

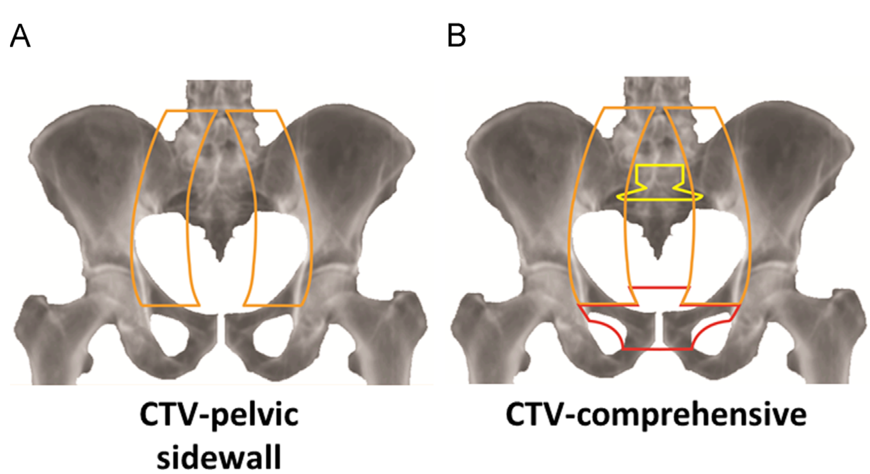

Fig. 1. An idealized representation of CTV-pelvic sidewall and CTV-comprehensive. (A) CTV-pelvic sidewall includes the pelvic sidewall nodes, which consist of the common iliac, external/internal iliac, and obturator nodes (from top to bottom). (B) CTV-comprehensive includes all of CTV-pelvic sidewall plus the medial structures shown in 1(B), the presacral nodes (superiorly), and the cystectomy bed.