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Clinical Investigation: Genitourinary Cancer

Postoperative Radiotherapy in Prostate Cancer: The Case of the Missing Target

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Summary

Four consensus guidelines have been published defining CTV in the postoperative setting for prostate cancer. This study shows that the current guidelines do not adequately cover the prostate and/or gross tumor volume based on preoperative MRI. Incorporating preoperative imaging into CTV delineation should lead to more accurate prostate bed coverage and, potentially, improved outcomes for prostate cancer patients treated with post-operative radiation.

Purpose: Postoperative radiotherapy (XRT) increases survival in high-risk prostate cancer patients. Approximately 50% of patients on long-term follow-up relapse despite adjuvant XRT and the predominant site of failure remains local. Four consensus guidelines define postoperative clinical target volume (CTV) in prostate cancer. We explore the possibility that inadequate CTV coverage is an important cause of local failure. This study evaluates the utility of preoperative magnetic resonance imaging (MRI) in defining prostate bed CTV.

Methods and Materials: Twenty prostate cancer patients treated with postoperative XRT who also had preoperative staging MRI were included. The four guidelines were applied and the CTVs were expanded to create planning target volumes (PTVs). Preoperative MRIs were fused with postoperative planning CT scans. MRI-based prostate and gross visible tumors were contoured. Three-dimensional (3D) conformal four- and six-field XRT plans were developed and dose–volume histograms analyzed. Subtraction analysis was conducted to assess the adequacy of prostate/gross tumor coverage.

Results: Gross tumor was visible in 18 cases. In all 20 cases, the consensus CTVs did not fully cover the MRI-defined prostate. On average, 35% of the prostate volume and 32% of the gross tumor volume were missed using six-field 3D treatment plans. The entire MRI-defined gross tumor volume was completely covered in only two cases (six-field plans). The expanded PTVs did not cover the entire prostate bed in 50% of cases. Prostate base and mid-zones were the predominant site of inadequate coverage.

Conclusions: Current postoperative CTV guidelines do not adequately cover the prostate bed and/or gross tumor based on preoperative MRI imaging. Additionally, expanded PTVs do not fully cover the prostate bed in 50% of cases. Inadequate CTV definition is likely a major contributing factor for the high risk of relapse despite adjuvant XRT. Preoperative imaging

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may lead to more accurate CTV definition, which should result in further improvements in survival for patients with high-risk prostate cancer. © 2012 Elsevier Inc.

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Introduction

Radical prostatectomy and radical radiotherapy are curative options for clinically localized prostate cancer. After surgery, approximately 15–40% of patients will relapse (1, 2). Among patients with high-risk features (positive surgical margins, extracapsular extension, and seminal vesicle involvement), the rate of biochemical failure within the first 5 years is 45–75% (3).

Three randomized controlled trials have evaluated the role of adjuvant radiation in reducing disease recurrence in men with high-risk features. All three studies demonstrate that adjuvant radiotherapy increases biochemical relapse-free survival and local control (4–6). Initial publications from these trials also indicated a trend toward improved survival that was not statistically significant. However, recently published long-term follow-up data of the Southwest Oncology Group (SWOG) 8794 trial demonstrated that at a median follow-up of 12.4 years, adjuvant radiotherapy reduces the risk of metastasis (HR 0.71, $p = 0.016$) and improves overall survival (HR 0.72, $p = 0.023$) (7).Today, adjuvant radiation to high-risk patients is considered standard of care; however, consensus on optimal radiation dose and treatment volumes is lacking.

Despite favorable results with adjuvant radiotherapy, approximately 50% of patients in long-term follow-up will eventually relapse, with the majority of patients recurring locally (8). Moreover, preliminary results indicate anti-androgen therapy improves outcome when combined with salvage radiotherapy (Radiation Therapy Oncology Group [RTOG] 96-01); however, prostate-specific antigen (PSA) disease-free survival (DFS) remains poor (7-year PSA DFS 57% vs. 40% for radiotherapy alone, $p < 0.001$) (9). Inadequate radiation doses and poor target volume delineation have been advanced to explain the high rate of local recurrence. Although it has been suggested that dose escalation in the postoperative setting may improve biochemical response (10, 11), examination of optimal clinical target volume (CTV) delineation has yet to be investigated.

CTV definition in the postoperative setting is complicated for many reasons including changes in anatomy caused by the surgery itself and the limited information on the preoperative location of the prostate. Significant variability exists between Radiation Oncologists with respect to prostate bed CTV delineation in postoperative patients (12–14). Specifically, in a study by Symon and colleagues, the interobserver variability for postoperative CTV delineation between five Radiation Oncologists on a sample of 8 patients was 16–69 cm^3. More importantly, the missed high-risk volumes ranged from 2% to 79% (12). These results emphasize the subjective nature of prostate bed CTV delineation and confirm the need to have guidelines in place for this patient population in order to optimize outcomes.

To date, four consensus articles have been published to address the need for standardization of postoperative radiotherapy target delineation in prostate cancer (15–18). These guidelines were developed employing various methodologies, including imaging and surgical/pathological reports, and are based on the natural history of spread of prostate cancer and patterns of recurrence. Although the four guidelines have many similarities, important differences exist between the CTV definitions. One common theme in all definitions is that the current consensus articles discuss the significance of covering the entire preoperative prostate bed and planes of surgical dissection. According to previous studies, these are the areas considered to have the greatest risk of possessing microscopic disease (19–21). To our knowledge, the extent to which the current consensus guidelines adequately cover these high-risk areas has not been ascertained. A volumetric comparison between the guidelines and an evaluation of target coverage based on four CTV definitions would allow for a better understanding of the relative strengths of the guidelines, while highlighting the potential areas of concern associated with their use.

In this study, the treatment volumes derived from the four CTV consensus guidelines were compared in a cohort of 20 patients treated with postoperative radiotherapy to evaluate volumetric differences in prostate bed CTV delineation. The possibility that inadequate CTV coverage maybe an important cause of local failure was then explored by evaluating the extent of geographic miss in each patient according to the guideline used, by comparing the prostate bed CTVs with the preoperative magnetic resonance imaging (MRI)-defined prostate and tumor volumes. Secondly, the study investigators evaluate the utility of preoperative MRI in defining prostate bed CTV.

Methods and Materials

Patient selection

The clinical study was approved by the Research Ethics Board of The Ottawa Hospital. A list of prostate cancer patients who underwent radical prostatectomy and adjuvant or salvage radiotherapy was compiled from The Ottawa Hospital between May 2007 and January 2010. Using this list, the first 20 patients (chosen alphabetically) who had also undergone a preoperative staging pelvic MRI were chosen as the study group. The decision for preoperative MRI staging in the study group had been at the discretion of the treating Urologist performing surgery. Patients were excluded if they had an endorectal coil placed during the preoperative MRI because the probe can result in compression and shift of the prostate.

Computed tomography simulation and treatment

Radiotherapy treatment planning computed tomography (CT) scans were performed on all 20 patients. Patients were scanned in a supine position with a full bladder and empty rectum (achieved via a fleet enema prior to CT simulation). Immobilization consisted of a rubber