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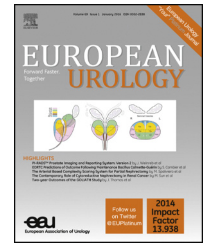

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Platinum Priority – Prostate Cancer
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Patterns of Lymph Node Failure after Dose-escalated Radiotherapy: Implications for Extended Pelvic Lymph Node Coverage

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Abstract

Background: Clinical trials evaluating the benefit of pelvic radiotherapy (PRT) in the radiotherapeutic management of patients with higher-risk prostate cancer have limited the superior field border to the S1/S2 or L5/S1 interspace. However, imaging and surgical series have demonstrated a high frequency of prostatic lymph node (LN) drainage beyond these landmarks.
Objective: To determine the patterns of radiographically defined abdominopelvic LN failures and their potential implications for PRT field design.
Design, setting, and participants: During 1992–2008, 2694 patients with localized prostate cancer were treated with prostate/seminal vesicle–only radiotherapy without PRT. Some 156 patients had their first failure within the abdominopelvic LNs, of whom 60 had isolated failures within the pelvic LNs.
Outcome measurements and statistical analysis: A radiologist reviewed all imaging and mapped each LN failure to a template consisting of 34 abdominopelvic LN stations.
Results and limitations: The median follow-up was 8.9 yr. Of patients who experienced first recurrence in the pelvic LNs ($n = 60$), the common iliac station was involved in 55% ($n = 33$) of patients, including 10% ($n = 6$) who had isolated common iliac failures. Use of a PRT field superior border of L5/S1 would fully cover only 42% of the first recurrences among these patients. Extending the field to cover the common iliac stations would increase coverage to 93% of recurrences. The presence of T3/T4 disease and omission of androgen-deprivation therapy both independently conferred an approximate fivefold increase in the likelihood of having a common iliac LN failure. Use of imaging as a surrogate for LN involvement is the primary study limitation.
Conclusions: Pelvic LN failures frequently occur superior to the commonly used L5/S1 landmark for PRT coverage, and use of ADT may be protective of more superior LN failures. The current RTOG 0924 trial is evaluating the benefit of PRT with extended superior coverage to L4/5 when possible, which, according to our data, should significantly improve the coverage of potential sites of failure.
Patient summary: We looked at lymph node recurrence patterns after external beam radiotherapy of the prostate in men who did not have their lymph nodes treated. We found that there was a high incidence of pelvic lymph node recurrences above the internal and external iliac lymph node regions. Therefore, the current field recommendation for pelvic lymph nodes that stops at the superior border of the internal and external iliac vessels provides inadequate coverage of common sites of cancer recurrence, namely the common iliac lymph nodes.
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1. Introduction

The use of whole pelvic radiotherapy (WPRT) has not been associated with improvement in outcomes in randomized trials [1–3]. Multiple retrospective series have demonstrated the benefit of WPRT, and the rationale for sterilizing micrometastatic disease and/or altering the microenvironment by prophylactically destroying potential lymph nodes (LNs) that may be routes of tumor spread is sound [4,5]. Proponents of WPRT argue that the lack of benefit demonstrated by the GETUG-01 and RTOG 9413 trials may be due in part to inadequate coverage of the pelvic LNs, given that the respective superior field borders of S1/2 and L5/S1 would not provide full dose coverage to the entire superior pelvic LN basins [6].

There are extensive data from the surgical literature regarding a similar controversy for the extent and use of extended pelvic LN dissection (PLND) [7]. Mattei et al [8] assessed abdominopelvic LN drainage patterns using intraprostatic injection of ^{99m}Tc nanocolloid, single-photon emission computed tomography (SPECT)/CT or SPECT/magnetic resonance imaging (MRI), and a superextended PLND. They noted that only 63% of LNs draining the prostate were located in regions surgically evaluated in a traditional extended PLND. Furthermore, 18% (50/277) of pelvic LNs mapped to the common iliac region. Importantly, common iliac LNs are not routinely covered by WPRT.

Although understanding the LN drainage patterns for prostate cancer is important, identifying where patients actually experience recurrence within the pelvis following prostate/seminal vesicle–only radiotherapy is ultimately what should guide our pelvic radiotherapy treatment fields. To investigate this, we analyzed the patterns of radiographically defined abdominopelvic LN failures in a large series of patients treated with definitive dose-escalated radiotherapy without pelvic nodal radiotherapy.

2. Patients and methods

2.1. Patient selection

This study was conducted after approval by the institutional review board. From 1992 to 2008, 2694 consecutive patients with prostate cancer were treated with dose-escalated radiotherapy (75.6–86.4 Gy) at our institution. All patients had pathologic confirmation of prostate cancer and Gleason score by an expert urologic pathologist. All patients had localized prostate cancer as defined by negative pelvic LN imaging with either CT or MRI. Of these patients, 188 experienced a radiographic pelvic or abdominal LN failure as their first site of relapse in the context of biochemical failure. Patients with complete abdominal and pelvic imaging with MRI, CT, and/or fluorodeoxyglucose (FDG) positron emission tomograpy (PET)/CT imaging were included to determine patterns of nodal relapse; 156 men met the inclusion criteria and formed the study cohort.

2.2. Treatment

The radiotherapy techniques utilized have been described previously [9,10]. In brief, radiotherapy was delivered daily, using 42–48 fractions at 1.8 Gy/fraction with 15-MV photons to a total dose of 75.6–86.4 Gy. All patients underwent CT-based simulation with custom immobilization. The entire prostate and seminal vesicles were routinely treated. No patients received elective pelvic LN radiation, as per our institutional policy during this study. Androgen deprivation therapy (ADT) was prescribed at the discretion of the treating radiation oncologist [11]. The median ADT duration was 6 mo (range 3–36 mo), and all patient had neoadjuvant ADT and 80% received additional adjuvant ADT.

2.3. Radiographic LN mapping

A custom nodal location template consisting of 34 abdominal and pelvic LN stations with anatomic boundaries was generated as previously described (Supplementary material) [12]. Multiple adjacent LN stations in the abdomen were combined (pericolic, right colic, middle colic, and left colic were combined as "pericolic/colic"), and for bilateral abdominal LN stations they were merged to one station. In addition, the internal iliac, obturator, and hypogastric LNs were grouped together. Lymph node stations in the chest and inguinal regions were excluded from analysis and were not reviewed by the radiologist (since a previous study revealed that 0.05% of men had isolated thoracic failures, and none had inguinal failures [13]).

The date of abdominal or pelvic failure was recorded according to institutional radiology reporting, and the CT, MR, and/or PET scan(s) corresponding to this time ($\pm$3 mo) were re-reviewed by an oncologic radiologist blinded to the clinical details and outcomes at the time of image interpretation. LNs were considered suspicious on imaging if they had a short axis measurement >8 mm in the pelvis or >10 mm in the abdomen (except in the periportal/hepatoduodenal station, for which a threshold of >15 mm was used). Regardless of their size, nodes were also considered suspicious if they had a rounded shape, an irregular outline, a replaced fatty hilum (fat content in the LN hilum is a typical characteristic of benign nodes), or had uptake above background blood-pool activity on FDG-PET/CT. CT imaging of the pelvis and/or abdomen was performed routinely for patients who experienced biochemical failure (prostate-specific antigen [PSA] nadir plus 2 ng/ml), and were ordered thereafter at the discretion of the treating oncologist (usually every 4–6 mo).

The images were reviewed on a picture archiving and communications system (PACS; GE, Waukesha, WI, USA), and the involvement of each LN station was mapped to the custom template. A binary method was used to identify involvement of an LN station (involved or uninvolved) rather than documenting the number of involved LNs within each station.

2.4. Patterns of failure analyses

The location of abdominal and pelvic failures was categorized as three distinct subgroups and a composite total cohort: (1) first failure was limited to the pelvic LNs without bone, visceral, or abdominal LN metastases ($n = 60$); (2) first failure included the abdominal LNs with or without synchronous pelvic LN involvement, but without bone or visceral metastases ($n = 31$); (3) abdominal and/or pelvic LN involvement with synchronous bone metastases at the time of first failure ($n = 65$); and (4) all patients in groups 1–3 whose first site of failure was in the abdomen and/or pelvis.

Coverage of involved LN stations was compared with recommended pelvic LN fields from historical clinical trials and the RTOG consensus contouring atlas based on the superior field border for WPRT [2,1,14]. The superior field border definitions used were S1/S2 for the GETUG trial [8], L5/S1 for RTOG 9413 [1] and the RTOG contouring atlas, and L4/L5 for the ongoing RTOG 0924 trial (NCT01368588).

2.5. Statistical methods

Data are reported as frequency and percentage for categorical variables, and as median with range or interquartile range (IQR) for continuous

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