Radiotherapy Boost for the Dominant Intraprostatic Cancer Lesion—A Systematic Review and Meta-Analysis

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Abstract

External beam radiotherapy (EBRT) for prostate cancer can be performed with a high dose of 86 Gy; however, one-tenth or more of the patients will develop recurrence. Prostate cancer is mainly multifocal, but a dominant intraprostatic lesion (DIL) is often the site of local recurrence after EBRT. We undertook a systematic review and meta-analysis to clarify whether functional imaging might identify the DIL and whether a RT boost to the DIL might be increased to an ultrahigh dose level of $\geq$ 90 Gy without increased toxicity. Of 62 selected studies, 13 reported the size of the DIL. The mean of the median DIL volumes was 2.4 cm^3 (95% confidence interval, 0.9-4.4 cm^3). Eighteen diagnostic studies with 1205 patients evaluated the diagnostic accuracy using multiparametric magnetic resonance imaging for intraprostatic cancer lesions. Evaluating 14,654 prostate segments, the diagnostic accuracy was 77%. Eleven therapeutic studies with 988 patients reported a RT boost for the DIL. The summary boost dose for the DIL was a mean of 89 Gy in 5 studies using intensity modulated RT (calculated as the equivalent dose in 2-Gy fractions) and a mean of 141 Gy in 4 studies using a combination of EBRT and brachytherapy ($P = .018$, t test). In 1 therapeutic study, 239 patients had a 98% 10-year disease-free survival rate. Many of our therapeutic studies used a boost dose to the DIL of $>$ 90 Gy. The reported boost for DIL is effective and safe.

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Introduction

Prostate cancer (PC) is the most common non-skin cancer for elderly men. In Western societies, PC has a high cure rate, but it is also the second leading cause of cancer deaths for men. The National Comprehensive Cancer Network has grouped localized prostate cancer as low risk, intermediate risk, and high risk. Randomized trials have shown that adding definitive radiotherapy (RT) to androgen deprivation therapy (ADT) for patients with intermediate- and high-risk PC improved survival.[1] Most radiation oncologists perform definitive RT to the whole prostate, because the primary PC is often multifocal. The RT technique is usually external beam RT (EBRT) or brachytherapy. Other randomized trials have shown that it is best to add neoadjuvant, concomitant, and adjuvant ADT to RT.[2,3] Patients tolerated definitive EBRT with a high radiation dose $\leq$ 86 Gy given with conventional fractionation.[4] Improved local tumor control leads to improved serum prostate-specific antigen (PSA) recurrence-free survival, disease-free survival, and overall survival.[5] Rectal toxicity was related to the dosimetric variables, such as a dose given to $>$ 15% of the rectal volume.[6]

For most patients, a dominant intraprostatic lesion (DIL) will determine the clinical course.[7] Up to one third of patients undergoing definitive EBRT will develop recurrence after treatment. Patients with recurrence after RT often develop local recurrence, and the DIL was often the site of the local recurrence.[8] Accordingly, a team at the University of California, San Francisco, in 1999, incorporated multiparametric (mp)-magnetic resonance imaging (MRI) in the planning of RT and gave 90 Gy to the DIL and 70 Gy to the rest of the prostate.[9] Since 1999, urologists have used functional imaging studies, such as single photon emission computed tomography, positron emission tomography/computed

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tomography, and mp-MRI, to delineate the DIL. Dose-escalation studies have also suggested that an ultrahigh radiation boost dose to the DIL of $\geq$ 90 Gy might improve local tumor control. Therefore, some urologists and radiation oncologists have used an ultrahigh boost dose for the DIL.

Our systematic review and meta-analysis assessed whether functional imaging might identify the DIL for a RT boost to the DIL and whether an ultrahigh boost dose might improve local tumor control without causing excess toxicity.

Materials and Methods

Search Strategy

In January 2015, the first search in PubMed used the Medical Subject Headings terms or text words: ("prostatic neoplasms" OR "prostate cancer") AND ("index lesion*" OR ("intraprostatic lesion*" OR "dominant lesion*" OR "DIL" OR "IPL") AND ("imaging" OR "magnetic resonance imaging" OR "positron emission tomography" OR "MRI" OR "PET"). The second search used the search words ("prostatic neoplasms" OR "prostate cancer") AND ("index lesion*" OR "intraprostatic lesion*" OR "dominant lesion*" OR "DIL" OR "IPL") AND ("radiotherapy" OR "brachytherapy" OR "boost"). In addition, we undertook a similar search in Embase and a manual search of the reference lists and review studies. The 3 searches found 201 studies. We also searched for ongoing trials in the ClinicalTrials database (available at: www.clinicaltrials.gov).

Inclusion and Exclusion Criteria

Our review included original research studies of patients with localized PC. We selected diagnostic studies that had used histopathologic examination of whole mount specimens after radical prostatectomy as the reference test. Histopathologic examination of surgical specimens is the reference standard for diagnostic accuracy. We excluded reports with < 20 patients because studies with a small sample size might give imprecise estimates of the effect size. We also excluded reports published before 2006 because the International Society of Urologic Pathology revised the classification of the Gleason score in 2005.[10] We excluded studies that were reported only as conference abstracts and duplicates. For diagnostic studies, we excluded those that did not report sufficient data to construct 2 × 2 tables and those that had defined the DIL from biopsy examinations. Finally, we excluded therapeutic studies that had planned a boost to the DIL but had not executed it, and those that gave a boost to the whole prostate or to all intraprostatic lesions detected using functional imaging.

Data Collection

One of us (F.E.v.E.) read the full text of 99 studies and included 62 in our systematic review. For these studies, the baseline clinical characteristics, imaging findings of the prostate, and imaging and histopathologic findings of the DIL were collected. Furthermore, data on the RT doses, schedules, and outcomes after a boost to the DIL such as PSA recurrence-free survival, disease-free survival, and overall survival, and gastrointestinal and genitourinary toxicities were collected.

Definitions

In 2010, the European Society of Urologic Radiology defined and standardized mp-MRI as a combination of T_2-weighted MRI, dynamic contrast enhanced, and diffusion weighted imaging MRI.[11] The European Symposium on Urogenital Radiology has defined a standard for reporting mp-MRI findings. For multifocal PC without extracapsular extension, the DIL is the cancer lesion with highest Gleason score and the largest tumor volume. For multifocal PC with extracapsular extension, the DIL is the cancer lesion that also has extracapsular extension. We considered a prostate segment examined with mp-MRI as positive if both the imaging and histopathologic findings after radical prostatectomy showed PC. PC has a low α/β ratio of 1.3 to 1.8 Gy.[12] Thus, we defined and calculated the equivalent dose in 2-Gy fractions (EQD_2), for an α/β ratio of 1.5 Gy. The Radiation Therapy Oncology Group and the National Cancer Institute Common Terminology Criteria for Adverse Events have defined the grades of RT toxicity, and the Phoenix criteria have defined PSA recurrence after RT.

Table 1 Items in Quality Assessment of Diagnostic Accuracy Studies-2

Item	Description
Patient selection	Was the spectrum of patients representative of the patients who will receive the test in practice?
	Was a consecutive or random sample of patients enrolled?
	Did the study avoid inappropriate exclusions?
Index test	Was the index test sufficiently described to permit its replication?
	If a threshold was used, was it prespecified?
	Was the index test interpreted without knowledge of the reference standard?
	Was observer variation likely to have affected the index test performance?
Reference standard	Did the reference standard correctly classify the target condition?
	Did all patients receive the same reference standard?
	Was the reference standard sufficiently described to permits its replication?
	Was the reference standard interpreted without knowledge of the index?
Flow and timing	Was the interval appropriate between the index test and the reference standard?
	Were uninterpreted test results reported?
	Were withdrawals from the study explained?

Assessment of Quality and Strength of Evidence

We assessed the quality of the studies of diagnostic accuracy included in the present meta-analysis using the revised Quality Assessment of Diagnostic Accuracy Studies system[13] (Table 1). We assessed the evidence and strength of a recommendation for the