The Role of Radiotherapy in Node-Positive Prostate Cancer

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This article summarizes the existing literature on use of radiotherapy for node-positive prostate cancer, as well as the associated outcomes.

Introduction

Among the 230,000 patients diagnosed with prostate cancer each year in the United States, 81% have localized cancer, 12% have node-positive disease, and 4% have distant metastatic disease (with the remainder unstaged).[1] While there are numerous randomized trials to guide the management of patients with localized and metastatic cancers, few trials have specifically addressed node-positive patients—or even included any of these patients at all. As a result, there is uncertainty regarding the optimal treatment in this setting. Node-positive prostate cancer is categorized as “stage IV,” but patient management likely needs to be different from that for distant metastatic disease, and a portion of node-positive patients are likely curable with aggressive multimodality therapy.

This article summarizes the existing literature on use of radiotherapy for node-positive prostate cancer, as well as the associated outcomes. Studies that examined the use of radiotherapy as definitive treatment (discussed below and outlined in Table 1) and as adjuvant therapy after radical prostatectomy (discussed below and outlined in Table 2) are reviewed separately.

Use of Radiotherapy as Definitive Treatment

Efficacy of androgen deprivation therapy (ADT) alone as treatment for node-positive prostate cancer

ADT alone is one treatment option for patients with node-positive prostate cancer.[2] In the European Organisation for Research and Treatment of Cancer (EORTC) 30846 trial, 234 men with node-positive (pN1-3) prostate cancer were randomized from 1986 to 1998 to receive either immediate ADT or delayed ADT (given at time of clinical progression).[3,4] Patients were confirmed to be node-positive after lymphadenectomy, but no prostatectomy or other local treatment was performed. ADT consisted of either orchiectomy or treatment with gonadotropin-releasing hormone (GnRH) analog plus anti-androgen.

After a median follow-up of 13 years, the median overall survival (OS; 6.1 years with delayed ADT vs 7.6 years with immediate ADT) and 10-year prostate cancer–specific survival (44.4% for delayed ADT vs 47.9% for immediate ADT) were not statistically significantly different between the two arms. (P values were not reported.) Given these results, it is not clear if immediate ADT is better than a watch-and-wait approach for these patients.

Addition of definitive radiotherapy to immediate ADT

Definitive radiotherapy significantly improves OS over ADT alone for patients with locally advanced prostate cancer, as demonstrated by two randomized trials that compared ADT with ADT plus radiotherapy. The absolute survival benefit from radiotherapy in these trials was 8% to 10%.[5,6] Whether such benefit extends to patients with even more aggressive disease—node-positive prostate cancer—has not been definitively demonstrated. However, several retrospective studies provide support for a benefit from radiotherapy in these patients.[7-9]

In an analysis of patients treated at The University of Texas MD Anderson Cancer Center, Zagars et al compared the outcomes of 255 patients with staging lymphadenectomy-proven pathologically node-positive (pN+) disease who were treated with indefinite ADT alone (n = 183) vs ADT plus radiotherapy to a median dose of 68 Gy (n = 72).[7] None of the patients had a prostatectomy. ADT consisted of either orchietomy (58%) or medical castration (42%, using either a GnRH agonist or
Patients who received ADT plus radiotherapy had better 10-year OS (46% for ADT alone vs 67% for ADT plus radiotherapy; \( P = .008 \)), local control (49% vs 89%; \( P < .001 \)), freedom from metastasis (56% vs 85%; \( P = .006 \)), and freedom from recurrence (25% vs 80%; \( P < .001 \)); however, patients treated with ADT alone had more aggressive cancers. On multivariate analysis, which adjusted for Gleason score, T stage, and pretreatment prostate-specific antigen (PSA) level, the addition of radiotherapy increased freedom from relapse or rising PSA (hazard ratio [HR] = 6.0; 95% confidence interval [CI], 3.1–11.5), freedom from distant metastasis (HR = 2.7; 95% CI, 1.3–5.6), and OS (HR = 2.1; 95% CI, 1.2–3.9).

Two studies analyzing data from SEER (Surveillance, Epidemiology and End Results) also suggest a survival benefit from radiotherapy. In a study from Tward et al,[8] a total of 1,100 patients with node-positive disease diagnosed from 1988 to 2006 were included. The authors grouped both external beam radiation therapy (EBRT) and brachytherapy patients together, and compared them with a group that received no radiotherapy. After a median follow-up of 7.5 years, men who received radiotherapy had greater 5-year OS (56.2% for no radiotherapy vs 67.8% for radiotherapy; multivariate HR = 0.68; \( P < .01 \)) and prostate cancer–specific survival (71.1% for no radiotherapy vs 78.1% for radiotherapy; multivariate HR = 0.67; \( P < .01 \)). Another SEER analysis from Rusthoven et al showed improved 10-year OS and prostate cancer–specific survival in patients treated with radiotherapy vs no local therapy.[9] It is important to note that SEER data do not definitively distinguish patients with clinical (radiographic) or pathologic (from biopsy or nodal dissection) node-positive disease, and no information on ADT is available. Taken together, these retrospective studies have consistently demonstrated a survival benefit from radiotherapy compared with conservative management for node-positive prostate cancer, and suggest that definitive therapy with radiation is reasonable to consider. However, these studies are limited by their retrospective nature and patient selection factors that can potentially confound the comparisons. It is important to note, however, that patients with node-positive cancer, while stage IV, can achieve long-term survival; these retrospective studies strongly suggest that a proportion of patients are curable with aggressive therapy. Future prospective, randomized studies are needed to more definitively demonstrate the potential benefit of radiotherapy in node-positive disease. Current guidelines recommend either radiotherapy plus long-term ADT (2 to 3 years) or long-term ADT alone as treatment options.[2]

Radiotherapy with or without ADT

For patients with high-risk and locally advanced prostate cancer, multiple randomized trials have demonstrated improved OS from adding ADT to definitive radiotherapy,[10-13] establishing this combination as a standard of care.[2] Two of these trials included patients with node-positive disease, and subgroup analyses of these patients provide support for adding ADT to radiotherapy in this setting.

The Radiation Therapy Oncology Group (RTOG) 85-31 trial randomized 977 men with either T3 or node-positive disease to EBRT alone vs EBRT plus ADT.[13] The ADT regimen was goserelin indefinitely or until progression, and radiotherapy was 65–70 Gy as definitive treatment or 60–65 Gy in the post-prostatectomy setting. In a subgroup analysis of the 173 patients with pathologic node-positive disease,[14] the combined-therapy group had significantly better 5-year biochemical control (54% combined vs 10% for radiotherapy alone; \( P < .0001 \)) and distant metastasis–free survival (\( P = .026 \); no percentages reported). OS was 72% for combined therapy vs 62% for radiotherapy alone (\( P = .23 \)), but this subgroup analysis was not adequately powered to detect a survival difference. On multivariate analysis, radiotherapy alone compared with combined therapy was associated with increased overall mortality (HR = 1.62; \( P = .03 \)), disease-specific failure (HR = 2.12; \( P = .014 \)), metastatic failure (HR = 2.54; \( P = .0005 \)), and biochemical failure (HR = 3.82; \( P < .0001 \)).

Granfors et al randomized 91 patients to either EBRT alone or radiotherapy plus ADT.[15] All patients underwent surgical lymph node staging (but not prostatectomy) prior to randomization, and 43% (\( n = 39 \)) of patients were pathologic node-positive. The radiation dose delivered was 65 Gy, and androgen deprivation was achieved by bilateral orchiectomy. In a subgroup analysis of pathologically node-positive patients, after a median follow-up of 9.7 years, patients who received combined therapy had better OS compared with patients who received radiotherapy alone (log rank \( P = .005 \); percentages not reported).

With numerous randomized trials demonstrating a survival benefit from adding ADT to radiotherapy for patients with intermediate-risk,[16,17] high-risk, and locally advanced prostate
cancers,[11-13,18-20] the results from these subgroup analyses of trials suggest that the benefit of adding ADT to definitive radiotherapy likely applies to patients with node-positive prostate cancer.

**Use of Radiotherapy as Adjuvant Treatment After Prostatectomy**

For patients who undergo a radical prostatectomy and are found to have pathologically node-positive disease, the optimal strategy for adjuvant management is unclear. Current guidelines include a broad array of options, ranging from observation to ADT with and without radiotherapy,[2] but definitive data are lacking to further guide treatment decisions.

**Radical prostatectomy with immediate vs delayed ADT**

Between 1988 and 1993, the Eastern Cooperative Oncology Group (ECOG) 3886 trial randomized 98 men found to be node-positive following radical prostatectomy and lymphadenectomy to either immediate (and lifelong) or delayed ADT.[21,22] In the delayed-ADT arm, treatment was initiated on detection of metastatic disease or symptomatic local recurrence. Therapy consisted of a GnRH agonist or orchiectomy, as chosen by the patient. Of note, 80 of the 98 patients enrolled had preoperative CT scans, and none had radiographic evidence of nodal metastasis. After 11.9 years median follow-up, patients in the immediate-ADT arm had improved OS (64% vs 45% delayed ADT; \( P = .04 \)) and progression-free survival (53% vs 14% delayed ADT; \( P < .0001 \)), as well as reduced prostate cancer–specific mortality (15% vs 49% delayed ADT; \( P = .0004 \)). To date, this trial provides the only available level 1 evidence to guide adjuvant treatment decisions for pathologically node-positive disease after radical prostatectomy.

**Radical prostatectomy with immediate adjuvant radiotherapy**

Adjuvant radiotherapy vs observation following radical prostatectomy improves biochemical recurrence–free survival,[23,24] metastasis-free survival,[24,25] and possibly OS,[25] as demonstrated by three randomized trials that included patients with locally advanced prostate cancer (pT3 disease or positive margins). None of these trials included sufficient numbers of node-positive patients to determine whether the benefit of adjuvant radiotherapy extended to these patients. However, multiple retrospective studies have compared adjuvant radiotherapy with conservative management.[26-28]

Briganti et al performed a retrospective analysis of 364 pathologically node-positive patients who underwent radical prostatectomy, pelvic lymphadenectomy, and adjuvant ADT alone (N = 247) vs with adjuvant radiotherapy (N = 117), between 1988 and 2003.[27] The two groups were matched for pathologic T stage, age at surgery, pathologic Gleason score, surgical margins, number of nodes removed, and length of follow-up. ADT used was orchiectomy (44% of patients) or GnRH agonist for a median of 38 months.

After a median follow-up of 7.9 years, patients who received adjuvant ADT plus radiotherapy had higher 10-year OS compared with patients who received only adjuvant ADT (55% for adjuvant ADT only vs 74% for adjuvant ADT and radiotherapy; \( P < .001 \)). Patients with combined adjuvant treatment also had better 10-year cancer-specific survival (70% for adjuvant ADT alone vs 86% for combined treatment; \( P = .004 \)).

The magnitudes of benefit from radiotherapy to cancer-specific survival and OS were similar, suggesting that treatment benefit is likely attributable to a reduction in cancer mortality. In subgroup analysis, radiotherapy was associated with an OS benefit for patients with two or fewer positive nodes (10-year survival of 54% for those treated with ADT only vs 69% for ADT and radiotherapy), as well as for patients with more than two positive nodes (survival of 56% for ADT only vs 87% for ADT and radiotherapy).

A more recent publication from similar authors included a retrospective analysis of 1,107 patients with pathologically node-positive disease treated with radical prostatectomy and lymphadenectomy, followed by adjuvant ADT; 35% also received adjuvant radiation therapy.[28] After a median follow-up of 7.1 years, adjuvant radiation was associated with improved 8-year OS (75.1% no radiation vs 87.6% radiation; \( P < .001 \)). The authors performed further hypothesis-generating analyses to discern whether certain patient subgroups benefited from adjuvant radiotherapy more than others. This demonstrated a cause-specific mortality benefit in two groups: (1) patients with 3–4 positive lymph nodes (multivariate HR = 0.21; \( P = .02 \)), and (2) patients with 1–2 positive nodes and Gleason score ≥ 7, plus either pT3b/T4 stage or positive surgical margins (HR = 0.30; \( P = .002 \)). In contrast, Kaplan et al performed a SEER-Medicare analysis that did not demonstrate a benefit from adjuvant radiotherapy. This study included 577 patients with pathologically node-positive
disease after radical prostatectomy,[29] and compared outcomes of patients who received no adjuvant radiotherapy vs those who received radiotherapy within 12 months of surgery. Patients in the two groups were propensity score–matched by age, comorbidities, Gleason score, pathologic T stage, PSA level, number of positive nodes, and receipt of adjuvant ADT (about one-third of patients in both comparison groups). There was no statistically significant difference between the two groups in terms of overall mortality (3.77 deaths per 100 person-years for no radiotherapy vs 5.09 deaths per 100 person-years for adjuvant radiotherapy; \( P = .153 \)) or prostate cancer–specific mortality (1.31 deaths per 100 person-years for no radiotherapy vs 2.89 deaths per 100 person-years for adjuvant radiotherapy; \( P = .09 \)).

These studies provide conflicting results, with institutional retrospective analyses demonstrating a sizable survival benefit from adjuvant radiotherapy, but a population-based analysis showing no benefit. Clinical trials are needed to clarify whether adjuvant radiotherapy improves survival in these patients.

**Adjuvant radiotherapy with vs without ADT**

No randomized trial or retrospective study has compared adjuvant radiotherapy alone with adjuvant radiotherapy plus ADT for node-positive patients. However, two retrospective studies of node-negative patients suggest that adjuvant radiotherapy plus ADT may be superior to radiotherapy alone. Ost et al analyzed 225 patients referred for adjuvant radiotherapy because of seminal vesicle invasion, extracapsular extension, or positive margins.[30] The decision of whether to administer ADT was left to the treating physician. On multivariate analysis, the addition of ADT to radiotherapy was associated with improved biochemical relapse–free survival (HR = 0.4; 95% CI, 0.1–0.9; \( P = .02 \)) and clinical relapse–free survival (HR = 0.1; 95% CI, 0.02–0.5; \( P = .004 \)).

Another study examined the outcomes of 199 node-negative patients after prostatectomy by the adjuvant treatment strategy: observation, radiotherapy alone, ADT alone, or radiotherapy plus ADT.[31] Biochemical no evidence of disease was the primary endpoint, defined as PSA ≤ 0.2 ng/mL. After a mean follow-up of 60.3 months, with observation as the reference group, radiotherapy plus ADT was associated with improved biochemical no evidence of disease (HR = 0.15; 95% CI, 0.07–0.34; \( P = .001 \)), but radiotherapy alone was not (HR = 0.64; 95% CI, 0.36–1.15; \( P = .13 \)).

While these studies suggest a benefit from adding ADT to adjuvant radiotherapy for patients with high-risk node-negative disease, further study is required to determine whether this benefit applies to patients with node-positive prostate cancer.

**Does the extent of lymph node dissection matter?**

Along with a prostatectomy and standard pelvic lymphadenectomy, an extended dissection reaches from the bifurcation of the common iliac artery superiorly to the femoral canal inferiorly. Posteriorly, nodes are resected around the obturator nerve, obturator vessels, and internal iliac artery. The potential benefits of an extended pelvic lymphadenectomy include more accurate staging and increased resection of pelvic disease. In a retrospective study by Yuh et al of 406 patients with either intermediate- or high-risk prostate cancer,[32] extended pelvic lymph node dissection (ePLND) compared with limited PLND increased median lymph node yield (21.5 vs 7; \( P < .0001 \)) and percent node positivity (11.9% vs 3.9%; \( P = .003 \)). However, there is controversy over whether the more aggressive dissection leads to improved clinical outcomes.

Two retrospective studies suggest that there may be a benefit to ePLND. Bivalacqua et al analyzed 4,265 patients who underwent radical prostatectomy by two surgeons, one of whom performed routine ePLND while the other performed routine limited PLND.[33] Patients who received neoadjuvant or immediate adjuvant treatments were excluded. After a median follow-up of 10.5 years, ePLND was associated with improved 5-year biochemical recurrence–free survival (7.1% with limited PLND vs 30.1% with ePLND; \( P = .018 \)) and 10-year metastasis-free survival (22.2% with limited PLND vs 62.2% with ePLND; \( P = .035 \)). Another study by Allaf et al was of similar design, comparing patient outcomes for ePLND (2,135 cases, performed by one surgeon) with those of limited PLND (1,865 cases, performed by another surgeon).[34] This study showed that ePLND was borderline-associated with improved biochemical recurrence–free survival (\( P = .07 \)).

Further research is needed to more definitively address this issue. Currently, ePLND is recommended as standard practice by the European Association of Urology and the National Comprehensive Cancer Network.[2,35] The American Urological Association recommends that PLND be performed in patients with a high risk of nodal involvement, and does not take a position on limited PLND vs ePLND.[36]
Chemotherapy in Node-Positive Prostate Cancer

Chemotherapy is a common treatment for metastatic prostate cancer.[2] However, the potential benefit of adding chemotherapy to the treatment regimen for patients with nonmetastatic, node-positive disease is unclear. The French Genitourinary Tumor Group (Groupe d’Etude des Tumeurs Urogénitales [GETUG])-12 trial randomized 413 patients with high-risk or node-positive (29%) prostate cancer (proven by staging pelvic lymph node dissection) to neoadjuvant ADT alone vs ADT plus docetaxel and estramustine. In both arms of the study, patients received local treatment (either prostatectomy or EBRT, decided prior to randomization) after systemic therapy. Results at a median follow-up of 7.6 years have been presented in abstract form.[37] Chemotherapy was associated with increased progression-free survival that was of borderline statistical significance (62% vs 53%; \(P = .06\)). However, it is unclear if the subgroup of patients with node-positive disease benefited more or less than the overall group. OS has not yet been reported.

Prognostic Factors in Node-Positive Patients

Several retrospective studies have examined clinical factors associated with survival outcomes in patients with node-positive prostate cancer. In a study by Abdollah et al that included 1,107 patients who received a radical prostatectomy and extended pelvic nodal dissection at two institutions, patients were grouped into five prognostic groups using a regression tree approach.[28] These groups (and associated 8-year cancer-specific mortality–free survival) were as follows:

- 1 to 2 positive nodes and Gleason score 2 to 6: 98.6% (95% CI, 95.8–100);
- 1 to 2 positive nodes, Gleason score 7 to 10, pT2/T3a, and negative surgical margins: 96.6% (95% CI, 93.4–99.9);
- 1 to 2 positive nodes and Gleason score 7 to 10, plus either pT3b/T4 or positive margins: 86.7% (95% CI, 83.0–90.6);
- 3 to 4 positive nodes: 85.3% (95% CI, 78.9–92.1); and
- > 4 positive nodes: 72.2% (95% CI, 62.7–83.1).

Multiple other studies have also found pathologic Gleason score,[38-40] positive surgical margins,[38,39] number of positive nodes,[38,39] lack of adjuvant radiotherapy,[39] and pathologic T stage[39,40] to be prognostic of cancer-specific survival in node-positive patients following prostatectomy. A nomogram to predict 10-year cancer-specific mortality has also been developed for node-positive patients following prostatectomy, using a Cox regression coefficient-based method from the variables described in an analysis by Abdollah et al.[41]

Conclusion

Patients with node-positive prostate cancer represent 12% of all newly diagnosed prostate cancers in the United States each year, and this proportion is likely to increase in the future with less use of screening for this disease. However, this is currently an understudied patient population.

As definitive treatment, retrospective institutional and population-based analyses suggest that ADT plus radiotherapy improves OS compared with ADT alone. In addition, secondary analyses of prospective trial data have shown that adding ADT to definitive radiotherapy further improved survival outcomes. These studies also consistently demonstrated that many patients with node-positive disease can achieve long-term survival—and are likely curable—with aggressive therapy. Given the available published evidence, current guidelines recommend either radiotherapy with 2 to 3 years of ADT or long-term ADT alone.[2]

ECOG 3886 provides level 1 evidence to support the use of adjuvant ADT in patients who have undergone a radical prostatectomy and lymph node dissection, and been found to have pathologically node-positive disease. Institutional retrospective studies have demonstrated that adding radiotherapy to ADT is associated with a sizable OS benefit, but an analysis of the population-based SEER-Medicare data showed no significant difference in overall mortality or cancer-specific mortality between patients who received adjuvant radiotherapy vs no radiotherapy. No study has yet directly compared patient outcomes of adjuvant radiotherapy with vs without ADT in these patients. Given an overall lack of relevant data addressing this question, and the sometimes conflicting results, current guidelines recommend either observation after prostatectomy, adjuvant ADT alone, or ADT with radiotherapy in this group of patients.[2]

At our institution, definitive radiotherapy with ADT is offered to patients with clinically node-positive prostate cancer, and adjuvant radiotherapy with ADT after prostatectomy is offered to patients with pathologic node-positive disease. However, discussion with patients includes acknowledging the lack
of definitive clinical data and the uncertainty regarding optimal management of this aggressive disease. There is a significant need for continued research to further examine the potential role of radiotherapy as either definitive treatment, or as adjuvant treatment, for patients with node-positive prostate cancer. Specifically, a randomized trial comparing the currently recommended treatment options (ADT alone vs ADT plus radiotherapy) is needed, to confirm the possible survival benefit of definitive and adjuvant radiotherapy seen in retrospective analyses. Such a trial would provide the necessary data to guide appropriate treatment decisions for patients with this disease.

Financial Disclosure: The authors have no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

Table 1: Studies Comparing Primary Treatment Options for Node-Positive Prostate Cancer

Table 2: Studies Comparing Adjuvant Treatment Options for Node-Positive Prostate Cancer

References:


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