Review Article on Current and Future Topics on Prostate Cancer

Narrative review of management strategies and outcomes in node-positive prostate cancer

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Abstract: Pelvic nodal involvement is present in 13% of new prostate cancer diagnoses each year and is associated with a poor prognosis compared to localized disease. Grouped as stage IV along with distant metastatic disease, node-positive nonmetastatic patients historically received systemic therapy alone as primary treatment. This treatment paradigm has shifted as data have demonstrated that these patients may benefit from aggressive locoregional therapy and are potentially curable. There is currently a lack of randomized evidence to define the optimal management for node-positive patients. While a few trials have included node-positive patients, the majority of data are derived from large multi-institutional series or population-based series. This narrative review summarizes the current literature supporting curative-intent management strategies for patients diagnosed with nonmetastatic clinically node-positive prostate cancer (cN1M0), as well as patients found to have pathologic nodal disease at the time of surgery (pN1M0). Treatment of both scenarios requires multimodality considerations including surgery, radiation therapy (RT) and systemic therapy to minimize the risks of both locoregional and distant recurrence. Future considerations include developments in enhanced imaging and systemic therapy. Inclusion of node-positive patients on prospective, randomized trials such as NRG GU 008 is needed to enhance our understanding of optimal management strategies.

Keywords: Lymph node metastasis; prostate cancer; radiation; prostatectomy

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Introduction

Approximately 13% of the 191,930 patients newly diagnosed with prostate cancer in the United States in 2020 will present with metastasis to the regional lymph nodes (N1M0) (1). In the current American Joint Committee on Cancer (AJCC) 8th edition staging manual, metastasis to pelvic lymph nodes (pelvic, hypogastric, obturator, iliac, sacral) are classified as N1, and are group stage IV-A (2). Historically, clinicians have grouped prostate cancer that have metastasized to lymph nodes together with distant metastasis in the same category of advanced prostate cancer. However, evolving data now support the management of N1M0 patients akin to locally advanced prostate cancer, including the use of multimodality therapy to reduce recurrence, improve survival, and potentially cure a portion of patients. Due to a paucity of randomized evidence in this area, the management of this patient population varies

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Table 1 Studies evaluating ADT and systemic treatments for node-positive prostate cancer

Study	Study design	N	Treatment	Median follow-up (yr)	Study outcomes
EORTC 30846 (3)	Randomized trial	234	Immediate *vs.* delayed ADT	13.0	Median OS 6.1 yr (delayed) *vs.* 7.6 yr; NS
					10-yr CSS 44.4% (delayed) *vs.* 47.9%; NS
STAMPEDE[†], James *et al.* 2017 (4)	Randomized trial	1,917 (N1M0 n=369)	ADT ± abiraterone/ prednisolone	3.3	Favors ADT + abiraterone
					3-yr OS 76% *vs.* 83%; P<0.001
					3-yr FFS 45% *vs.* 75%; P<0.001
GETUG-12[‡] (5)	Randomized trial	413 (N1M0 n=119)	ADT ± docetaxel and estramustine	8.8	Favors ADT + docetaxel/estramustine
					8-yr RFS 50% *vs.* 62%; P=0.017
STAMPEDE[†], James *et al.* 2016 (6)	Randomized trial	2,962 (N1M0 15%)	ADT ± docetaxel ± zoledronic acid	3.6	Favors ADT + docetaxel
					Median OS 40 mo (ADT alone) *vs.* 60 mo; P=0.005
					Mean FFS 35 mo (ADT alone) *vs.* 44 mo; P<0.001

[†], Study included M1, N1M0, and N0M0 patients with two or more high-risk features (T3–4, Gleason score ≥8, PSA ≥40 ng/mL). [‡], Study included N1M0 and N0M0 patients with one or more high-risk feature (T3–4, Gleason score ≥8, PSA ≥20 ng/mL). ADT, androgen deprivation therapy; EORTC, European Organization for Research and Treatment of Cancer; OS, overall survival; CSS, cancer-specific survival; NS, not significant; FFS, failure-free survival; N/A, not available; ng/mL, nanogram per milliliter; RFS, relapse-free survival; PSA, prostate-specific antigen.

widely in clinical practice. This article reviews the relevant studies that have shaped the modern management of node-positive prostate cancer patients and summarizes their associated outcomes. We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/tau-20-1031).

Management of clinically node-positive, nonmetastatic (cN1M0) prostate cancer

Androgen deprivation therapy (ADT) without local therapy

ADT historically was an accepted treatment for patient with cN1M0 prostate cancer. This follows the paradigm for patients with metastatic prostate cancer (M1) where ADT is the long-established standard of care. ADT in node-positive patients is generally initiated at the time of diagnosis rather than delayed. The randomized EORTC 30846 trial evaluated the non-inferiority of delayed ADT compared to immediate ADT in 234 patients diagnosed with nodal disease by biopsy or staging lymphadenectomy (*Table 1*) (3).

No local treatment was offered to the primary tumor. The intent-to-treat analysis showed a 22% [hazard ratio (HR): 1.22; 95% CI: 0.92–1.62] increase in the hazard of death with delayed ADT, though this did not reach statistical significance. Median overall survival (OS; 7.6 *vs.* 6.1 years) and 10-year cancer-specific survival (CSS; 47.9% *vs.* 44.4%) were not statistically significantly different between the immediate and delayed ADT arms. This trial was unable to demonstrate non-inferiority of delayed ADT, thus starting ADT at the time of diagnosis remains the standard of care.

Intermittent ADT has not specifically been studied in cN1M0 patients, so its use is not recommended. The SWOG 9346 trial randomized newly diagnosed M1 patients to continuous versus intermittent ADT (7), and was unable to conclude non-inferiority of intermittent ADT by excluding 20% increased risk of death with intermittent ADT. However, the applicability of results from this trial to patients with cN1M0 disease is unclear.

For M1 patients, several large randomized trials demonstrated improvement in OS with the addition of advanced hormonal therapy (e.g., abiraterone, enzalutamide, apalutamide) to ADT in hormone sensitive metastatic prostate cancer (8-10). However, none of these trials specifically studied cN1M0 patients. The STAMPEDE trial investigated the addition of abiraterone to ADT in a heterogenous population of men with M1 (53%), N1M0 (20%), or localized high risk prostate cancer (27%) (4). Local therapy with radiotherapy was optional for N1M0 patients. Abiraterone improved failure-free

survival (FFS) in the overall study population (HR: 0.29; P<0.001) with similar effect on the N1 (HR: 0.29) and M0 (HR: 0.21) patient subsets. However, N1M0 patients were not specifically analyzed. Abiraterone was also associated with improved OS for the overall study population (HR: 0.63; 95% CI: 0.5–0.76; P<0.001) and on subset analysis for patients with any nodal dissemination (HR: 0.61; 95% CI: 0.48–0.77). Again, data for N1M0 patients were not separately analyzed. This study suggests but does not clearly demonstrate that the addition of abiraterone to standard ADT improves cancer control or survival outcomes in N1M0 patients.

ADT + radiation therapy (RT)

Definitive RT for cN1M0 prostate cancer most commonly covers the pelvic nodal regions, prostate and seminal vesicles. In randomized clinical trials, adding RT to ADT has demonstrated an improvement in survival in patients with high-risk localized disease (less advanced than N1M0 disease) and also in hormone sensitive M1 disease (more advanced than N1M0). Two large randomized trials compared indefinite ADT alone *vs.* ADT + RT in patients with high risk localized prostate cancer. The SPCG-7 reported a dramatic reduction in prostate-specific antigen (PSA) recurrence (HR: 0.16; 95% CI: 0.12–0.20; P<0.0001) and improved prostate CSS (HR: 0.44; 95% CI: 0.30–0.66; P<0.001) (11) from the addition of RT. NCIC PR.3 reported similar improvement in prostate CSS (HR: 0.46; 95% CI: 0.34–0.66; P<0.001) (12). In hormone sensitive M1 prostate cancer, the H-arm of the STAMPEDE trial compared ADT + prostate RT to ADT alone (13). In a pre-specified subset analysis of patients with low metastatic burden, the addition of prostate RT improved both FFS (HR: 0.59; 95% CI: 0.49–0.72; P<0.001) and OS (HR: 0.65; 95% CI: 0.47–0.90; P=0.01). Of note, node-positive prostate cancer is a disease state between localized and metastatic prostate cancers. Extrapolation of improved survival from these randomized trials in patients with less advanced (high risk localized) and more advanced (low volume M1) prostate cancer provides a rationale for the potential benefit of adding RT to ADT for N1M0 positive cancer.

Retrospective series also provide evidence for the role of RT in cN1M0 prostate cancer. With caveats of potential uncontrolled confounders and selection bias, these studies have consistently demonstrated improvements in both cancer control and survival outcomes (*Table 2*). One prospective randomized trial, RTOG 9608, attempted to compare RT and ADT versus ADT alone in node-positive patients but it was terminated early due to poor accrual.

The largest single institution series from the MD Anderson Cancer Center retrospectively evaluated 255 men with pelvic nodal metastases identified on staging pelvic lymphadenectomy treated with either ADT alone or ADT + RT (14). ADT consisted of orchiectomy or medical castration. External beam radiotherapy (EBRT) was delivered to the prostate in 72 patients, with doses ranging from 60–78 (median 68) Gy. After a median follow-up of 6.2 (ADT + RT) to 9.4 (ADT alone) years, patients who received ADT + RT demonstrated superior 10-year OS (46% *vs.* 67%; P=0.008), local control (LC) (49% *vs.* 89%; P<0.001), freedom from biochemical relapse (25% *vs.* 80%; P<0.001), and freedom from distant metastasis (FFDM) (56% *vs.* 85%; P=0.006).

An unplanned analysis of N1M0 patients from the control arm of the STAMPEDE trial also support the addition of RT (18). All patients received ADT on the control arm of the trial, and RT was optional for N1M0 patients. Of the 157 patients included in the analysis, 45% (n=71) received RT to doses at discretion of the treating physician. The addition of RT to ADT was associated with higher 2-year FFS (89% *vs.* 64%; HR: 0.35; 95% CI: 0.19–0.65) after adjusting for Gleason score, PSA, age and performance status. OS data have not yet been presented.

Population and hospital-based studies have also reported improvement in OS with the use of RT in patients with N1M0 prostate cancer. Tward *et al.* used the Surveillance Epidemiology & End Results (SEER) database to compare outcomes in node-positive patients diagnosed from 1988–2006 who received RT versus no local therapy. On multivariable analysis, RT was associated with an improvement in CSS (HR: 0.67; 95% CI: 0.54–0.84; P<0.01); 10-year CSS results were 50.3% *vs.* 62.7% (15). Similar results were noted by Rusthoven *et al.* in a separate SEER study of local therapy for node-positive cancer (16). Of note, the use of ADT was not recorded in the SEER and is a major limitation to these analyses. An analysis of the National Cancer Database (NCDB) compared OS in a propensity matched cohort of 636 node-positive patients receiving ADT alone (n=318) or ADT + RT (n=318) (17). Of those receiving RT, 97% received RT with median doses of 50.4 Gy to the pelvis and 75.6 Gy total. The use of combined ADT + RT was associated with an approximately 50% reduction in all-cause mortality at 5 years compared to ADT alone (HR: 0.50; 95% CI: 0.37–0.67; P<0.001).

Overall, the published evidence including clinical trials

Table 2 Studies evaluating definitive radiotherapy for node-positive prostate cancer

Study	Study design	N	Treatment	Median follow-up (yr)	Study outcomes
RT versus no local therapy					
Zagars *et al.* (14)	Retrospective, single institution	255	ADT ± RT	9.4 (ADT), 6.2 (ADT + RT)	Favors ADT + RT
					10-yr OS 46% *vs.* 67%; P=0.008
					10-yr FFS 20% *vs.* 80%; P<0.001
					10-yr LC 49% *vs.* 89%; P<0.001
					10-yr FFDM 56% *vs.* 85%; P=0.006
Tward *et al.* (15)	Retrospective, SEER	1,100	RT *vs.* no local therapy: ADT use not reported	7.5	Favors RT
					10-yr OS 29% *vs.* 44%; P<0.01
					10-yr CSS 50% *vs.* 63%; P<0.01
Rusthoven *et al.* (16)	Retrospective, SEER	796	RT *vs.* no local therapy: ADT use not reported	5.2	Favors RT
					10-yr OS 29% *vs.* 45%; P<0.001
					10-yr CSS 53% *vs.* 67%; P<0.001
Lin *et al.* (17)	Retrospective, NCDB	636	ADT ± RT	2.7	Favors ADT + RT
					5-yr OS 53% *vs.* 72%; P<0.001
James *et al.* (18)	Secondary analysis of a randomized trial	157	ADT ± RT	1.4	Favors ADT + RT
					2-yr FFS 64% *vs.* 89%; P not reported
RT alone versus RT + ADT					
RTOG 85-31 (19)	Secondary analysis of a randomized trial	173	RT ± ADT	6.5	Favors RT + ADT
					OS; multivariable P=0.03
					CSS; multivariable P=0.014
					Metastatic failure; P=0.0005
					Biochemical control; P<0.0001
Granfors *et al.* (20)	Secondary analysis of a randomized trial	91	RT ± ADT	9.7	Favors RT + ADT
					OS; P=0.005

ADT, androgen deprivation therapy; RT, radiotherapy; CSS, cancer-specific survival; OS, overall survival; LC, local control; FFDM, freedom from distant metastasis; FFS, failure-free survival; Gy, Gray; SEER, Surveillance Epidemiology & End Results; NCDB, National Cancer Database.

and retrospective studies support the addition of prostate RT to ADT for the treatment of cN1M0 patients.

ADT + radical prostatectomy (RP) with extended pelvic lymph node dissection (ePLND)

The evidence for definitive surgery for patients with known nodal disease is limited. RP with or without PLND is one standard of care in patients with localized prostate cancer. However, for clinically node-positive disease, the use of RP remains controversial. The EAU-ESTRO-SIOG allows for RP with ePLND in very selected patients, whereas this is not a recommendation in the NCCN guidelines (*Table 3*).

Historically, planned prostatectomies have been abandoned for futility upon finding of lymph node metastasis during the lymph node dissection (24). This perspective has been challenged with multiple retrospective series which have reported improvement in survival with RP in node-positive prostate cancer (see section "Management for pathologically node-positive prostate cancer"). It is

Table 3 Current guidelines on the management of N1M0 prostate cancer

Guideline	cN1M0 diagnosis	pN1 diagnosis
EAU-ESTRO-SIOG (21)	1. Pelvic EBRT + immediate long-term ADT (grade B)	1. Adjuvant ADT (grade A)
	2. Offer RP + eLND in a multimodality setting to highly selected patients (grade C)	2. Discuss EBRT + ADT (grade A)
		3. Observation after eLND if < 2 nodes with microscopic involvement and PSA <0.1 ng/mL and absence of extranodal extension (grade B)
FROGG (22)	1. Pelvic and prostate EBRT + long-term ADT (grade B)	1. Individualized discussion of observation, ADT, or RT + ADT (grade A)
		2. Patients should be referred to a radiation oncologist to discuss RT + ADT (grade B)
NCCN (23)	1. EBRT + ADT (preferred)	1. ADT (category 1)
	2. EBRT + ADT + abiraterone	2. EBRT + ADT (category 2B)
	3. ADT ± abiraterone	3. Observation
	4. If <5 year expected survival and asymptomatic: observation or ADT	

EBRT, external beam radiotherapy; ADT, androgen deprivation therapy; RP, radical prostatectomy; eLND, extended lymph node dissection; PSA, prostate-specific antigen; EUA, European Association of Urology; ESTRO, European Society for Radiotherapy and Oncology; SIOP, International Society of Pediatric Oncology; FROGG, Faculty of Radiation Oncology Genitourinary Group (Australia); NCCN, National Comprehensive Cancer Network.

important to note a distinction between clinical node-positive (cN+) and pathologic node-positive (pN+) prostate cancer. Many of the patients with pathologically detected lymph node metastasis after PLND had clinically negative nodes (cN0) pre-operatively.

Data on the role of prostatectomy in cN+ patients are limited. Seisen *et al.* used the NCDB to compare outcomes in cN1M0 patients treated with ADT versus RP + ADT, and reported an improvement in 5-year OS from 49.2% to 78.8% (HR: 0.31; 95% CI: 0.13–0.74; P=0.007) (25). This study also compared outcomes of ADT + RT, and found ADT + either RP or RT had similar improvements compared to ADT alone. These data suggest that local therapy, regardless of modality, may confer a survival improvement compared to ADT alone.

RT ± ADT

Randomized data suggest that local therapy alone is not sufficient for patients with node-positive cancer. Multiple randomized studies have demonstrated improvements in OS, biochemical control, and distant failure when ADT is added to RT for localized and locally advanced prostate cancers (19,20,26-28). Two smaller trials specifically provide data related to RT *vs.* RT + ADT in node-positive disease (*Table 2*). The RTOG 8531 trial randomized 977 patients with either nodal metastasis or clinical T3 prostate cancer to RT + ADT versus RT alone. Post-prostatectomy patients were allowed if they contained pT3 disease or involved margins. A subgroup analysis of patients with node-positive prostate cancer (n=173) showed that combination RT + ADT was associated with improved absolute survival (P=0.03), cause-specific failure (P=0.014), metastatic failure (P=0.0005), and biochemical control (P<0.0001) compared to RT alone (19). A Swedish trial randomized node-positive patients to RT or RT plus orchiectomy (20). Initially planned for 400 patients, the study closed early after 91 patients when interim analysis showed significant rates of disease progression in the RT alone arm. Combined modality therapy showed a significant OS benefit (P=0.005) at a median follow-up of 9.7 years. These data established the need to add ADT to RT for this patient population.

The optimal duration of ADT with definitive RT in the cN1M0 setting is not established. Clinicians have commonly extrapolated from trials of locally advanced prostate cancer to offer 2–3 years of ADT (29,30).

Chemotherapy

The role of chemotherapy in the primary management of

node-positive prostate cancer is controversial. The addition of chemotherapy improves survival in patients with castrate-sensitive M1 prostate cancer, a disease state that is more advanced than N1M0 prostate cancer, though this benefit may be limited to patients with high volume disease (31). Data for chemotherapy in patients with N1M0 cancer are limited. Patients with node-positive cancer have been included in two randomized trials evaluating the addition of chemotherapy (*Table 1*). GETUG AFU-12 randomized 413 patients with N1M0 (29%) or high-risk N0M0 prostate cancer (71%) to receive either 3 years of ADT plus four cycles of docetaxel and estramustine, or ADT alone (5). Almost all patients also received local therapy. The primary endpoint of relapse-free survival (RFS) at 8 years was improved with ADT plus chemotherapy compared to ADT alone (62% *vs.* 50%; adjusted HR: 0.71; 95% CI: 0.54–0.94; P=0.017). OS at 8 years was 83% for both arms combined; however, there were too few events to analyze the N1M0 and N0M0 groups separately. No subgroup analysis was reported for patients with N1M0 disease.

The STAMPEDE trial randomized 2,962 prostate cancer patients to ADT alone, ADT plus six cycles of docetaxel, ADT plus zoledronic acid, or ADT plus docetaxel and zoledronic acid (6). Eligible patients were diagnosed with either M1 (61%), N1M0 (15%), or localized prostate cancer with at least two high-risk features (24%). Radiotherapy was optional for N1M0 patients. OS (median 60 *vs.* 45 months; HR: 0.78; 95% CI: 0.66–0.93; P=0.005) and FFS (median 44 *vs.* 35 months; 95% CI: 0.53–0.70; P<0.001) were improved with the addition of docetaxel to ADT. On subset analyses of patients with M0 disease, docetaxel was associated with an improvement in FFS but not OS. A subset analysis of N1M0 only patients was not performed.

Based on these results, there is currently no clear role for chemotherapy for N1M0 prostate cancer.

Management for pathologically node-positive prostate cancer

RP and lymph node dissection

Retrospective surgical series with long-term follow-up suggest a beneficial impact of RP compared to no local therapy on both overall and CSS for patients with node-positive prostate cancer (24,32,33). One large German cohort compared outcomes of patients with intraoperative finding of lymph node metastasis where the prostatectomy was abandoned versus completed (24). Completion prostatectomy was associated with an improvement in 5-year OS from 60% to 84% (HR: 2.04; 95% CI: 1.59–2.63; P<0.0001). In multiple series, the reported 10-year outcomes of pN+ patients after RP and PLND without further adjuvant local therapy are approximately 60–66% OS and 70–85% CSS; however, only a third of patients remained free of biochemical progression (24,32-37).

In highly selected pN+ patients with favorable disease characteristics, outcomes after surgery alone may be more favorable. A series from Mayo Clinic reported 10-year CSS as high as 94% for patients with only one positive lymph node (35). Another series reported that patients with fewer than three positive nodes and Gleason grade group 1–3 had less than a 10% risk of clinical recurrence at 8 years (38). However, it should be noted a majority of patients included in these studies received adjuvant therapies in addition to surgery. A series from Memorial Sloan Kettering Cancer Center reported 5- and 10-year freedom from biochemical recurrence of 35% and 28% following prostatectomy alone without adjuvant therapy (37). Gleason score of 8–10, multiple positive nodes, positive surgical margins, and a low total number of lymph nodes removed have been identified as predictors of higher post-prostatectomy recurrence and cancer-specific mortality (CSM) for patients with pN+ disease (36,37,39,40).

While selected pN+ patients with favorable disease can achieve long term biochemical control with surgery alone, the addition of adjuvant therapy with ADT or ADT + RT can improve survival and is generally recommended. The following sections will review the data for these approaches.

Adjuvant ADT

The role of adjuvant ADT after RP and PLND for node-positive patients was established by the ECOG 3886 trial (41). Messing *et al.* randomized 98 patients found to have pathologic node-positive cancer after RP to immediate continuous ADT (n=47) or deferred ADT (n=51) until the development of metastasis or symptomatic recurrence. Immediate ADT was initiated within 12 weeks of surgery. Compared to delayed ADT, immediate adjuvant ADT was associated with superior OS (median OS 11.3 *vs.* 13.9 years; P=0.04) and CSS (median CSS 12.3 years *vs.* not reached for immediate ADT; P=0.0004) after 11.9 years of median follow-up. Despite its small sample size, ECOG 3886 provides the only level 1 evidence to date to guide adjuvant treatment for pN+ disease.

Retrospective data have been mixed. Results from a SEER-Medicare analysis of 731 men did not show a survival improvement with adjuvant ADT within 120 days of surgery compared to observation (42). After propensity score matching, there was no difference in OS (HR: 0.95; 95% CI: 0.71–1.27) or CSM (HR: 0.97; 95% CI: 0.56–1.68) from adjuvant ADT compared to no immediate treatment. A multi-institutional comparative analysis demonstrated improved CSM with adjuvant ADT compared to surgery alone (HR: 3.05; 95% CI: 1.45–6.40; P=0.003), but OS was not improved (43). Nonetheless, based the randomized Messing data, adjuvant ADT remains a standard of care. While the ECOG 3886 trial was designed for lifelong ADT, in actual clinical practice, stopping ADT at 2 years is common. The optimal duration of adjuvant ADT in pN+ patients has not been studied prospectively.

Adjuvant ADT + RT

Many patients found to have pN+ prostate cancer experience disease progression despite RP and adjuvant ADT (34,39). Isolated locoregional recurrences after RP were observed in 31% of patients experiencing clinical progression in one series (44). No randomized trial has assessed the use of adjuvant RT for pN+ patients. There are several retrospective studies which have demonstrated improved OS, CSS, and biochemical relapse-free survival (BCRFS) with the addition of adjuvant RT (*Table 4*).

A single institution series of 250 patients found that adjuvant RT was independently associated with improved CSS and BCRFS compared to adjuvant ADT alone for patients with pN+ disease (45). A matched retrospective analysis contained 364 pN1 patients who received either adjuvant ADT (n=247) or adjuvant RT + ADT (n=171) after surgery (46). The addition of adjuvant RT improved both CSS (10-yr CSS: 86% *vs.* 70%; P=0.004) and OS (10-yr OS: 74% *vs.* 55%; P<0.001) after matching for patient age, Gleason score, pathologic T stage, extent of nodal dissection, and follow-up length. Touijer *et al.* published the largest multi-institutional series to date comparing of outcomes from 1,338 pN+ patients managed with observation after RP (n=387), RP plus ADT (n=676), or RP plus ADT + RT (n=325) (43). The adjuvant ADT + RT group contained patients with higher pathologic stages and Gleason scores. Despite this, combined adjuvant ADT + RT was associated with a lower risk of all-cause mortality (HR: 0.46; 95% CI: 0.32–0.66; P<0.0001) and CSM (HR: 0.41; 95% CI: 0.27–0.64; P<0.0001) compared to adjuvant ADT. Similarly, adjuvant ADT + RT was associated with improved survival compared to observation after surgery.

Patient selection may be important when considering adjuvant radiation. Abdollah *et al.* compared outcomes of adjuvant ADT versus ADT + RT stratified by clinical risk factors: number of lymph nodes, Gleason score, and pathologic local extension (47). These risk features were used to stratify pN+ patients in to five risk groups. In this analysis, only two of the five risk group subsets benefitted from the addition of RT in terms of 8-year prostate CSS: (I) patients with 3–4 positive lymph nodes; and (II) patients with 1–2 positive lymph nodes and Gleason score ≥7, plus either stage pT3b-T4 or positive surgical margins. Patients with more positive nodes or lower risk disease did not demonstrate a survival benefit in this retrospective analysis. A separate study used data from the NCDB to confirm the external validity of the Abdollah *et al.* study, and replicated the observation that adjuvant RT only benefitted patients with 3–4 positive nodes or patients with 1–2 positive nodes plus additional adverse pathological features (52). Another analysis of the NCDB data demonstrated that the survival benefit of adjuvant RT was only apparent for patients with at least one adverse pathological feature: ≥3 positive nodes, stage pT3b-4 disease, Gleason score ≥9, or positive margins (51).

Overall, existing studies suggest that for patients with pN+ disease, adding RT to adjuvant ADT likely improves long-term outcomes including survival, at least for some subgroups of pN+ patients with certain characteristics. Accordingly, the EAU guidelines (grade A) and NCCN guidelines (category 2B) recommend adjuvant RT plus ADT for pN+ patients (*Table 3*).

Timing of post-prostatectomy therapy

In general, the timing of post-prostatectomy therapy for pN+ patients has been guided by the ECOG 3886 trial, which initiated ADT within 12 weeks of prostatectomy.

In select patients with pN+ cancer after RP and undetectable post-operative PSA, observation without immediate adjuvant therapy is a potential option as described in the EAU guidelines (Grade B) and NCCN guidelines (no category recommendation) (*Table 3*). In these patients, whether initial observation followed by treatment at the time of biochemical recurrence ("early salvage") may be equally effective compared to immediate

Table 4 Studies evaluating RP and adjuvant therapies for pathologically node-positive prostate cancer

Study	Study design	N	Treatment	Median follow-up (yr)	Study outcomes
RP ± adjuvant ADT					
ECOG 3886 (41)	Randomized trial	98	RP ± immediate ADT	11.9	Favors RP + immediate ADT Median OS 11.3 *vs.* 13.9 yr; P=0.04 Median CSS 12.3 yr *vs.* not reached; P=0.0004 Median PFS 2.4 *vs.* 13.9 yr, P<0.0001
RP ± adjuvant RT					
Da Pozzo *et al.* (45)	Retrospective, single institution	250	RP + adjuvant ADT ± RT	7.6	Favors adjuvant RT HR 0.49 for BCRFS; P=0.002 HR 0.38 for CSS; P=0.009
Briganti *et al.* (46)	Retrospective, two institutions	364	RP + adjuvant ADT ± RT	8.4	Favors adjuvant RT 10-yr OS 55% *vs.* 74%; P<0.001 10-yr CSS 70% *vs.* 86%, P=0.004
Abdollah *et al.* (47)	Retrospective, two institutions	1,107	RP + adjuvant ADT ± RT	7.1	Favors adjuvant RT for specific risk groups[†] 8-yr OS 75% *vs.* 88%; P<0.001 8-yr CSS 86% *vs.* 92%; P=0.08
Touijer *et al.* (43)	Retrospective, three institutions	1,338	RP ± adjuvant ADT ± RT	5.8	Favors adjuvant ADT + RT over adjuvant ADT HR 0.46 for OS; P<0.0001 HR 0.41 for CSS; P<0.0001 Favors adjuvant ADT + RT over RP alone HR 0.41 for OS; P<0.0001 HR 0.26 for CSS, P<0.0001
Kaplan *et al.* (48)	Retrospective, SEER	577	RP ± adjuvant RT	NR	No benefit of adjuvant RT OM 3.8 *vs.* 5.1 deaths/100 person-yr; P=0.153 CSM 1.3 *vs.* 2.9 deaths/100 person-yr; P=0.09
Wong *et al.* (49)	Retrospective, NCDB	7,225	RP ± adjuvant ADT ± RT	3.8	Favors adjuvant RT 5-yr OS 85% (RP alone), 83% (adjuvant ADT), 88% (adjuvant RT), 89% (adjuvant ADT + RT); P<0.001[‡]
Jegadeesh *et al.* (50)	Retrospective, NCDB	1,652	RP + adjuvant ADT ± RT	4.4	Favors adjuvant RT 5-yr OS 81% *vs.* 88%; P=0.004
Gupta *et al.* (51)	Retrospective, NCDB	8,074	RP ± adjuvant ADT ± RT	4.0	Favors adjuvant ADT + RT over adjuvant ADT HR 0.76 for OS; P=0.007 Favors adjuvant ADT + RT over RP alone HR 0.77 for OS; P=0.008

[†], Risk groups benefitting from adjuvant RT: (I) 3–4 positive lymph nodes; (II) 1–2 positive lymph nodes + Gleason score ≥7 + stage pT3b/T4 or positive surgical margins. [‡], Pairwise analyses showed that combined adjuvant ADT + RT was superior to RP alone (P=0.007) and adjuvant ADT (P<0.001), but not superior to adjuvant RT (P=0.44). RP, radical prostatectomy; ADT, androgen deprivation therapy; RT, radiotherapy; BCRFS, biochemical relapse-free survival; CSM, cancer-specific mortality; CSS, cancer-specific survival; HR, hazard ratio; NCDB, National Cancer Database; NR, not reported; OM, overall mortality; OS, overall survival; PFS, progression-free survival; SEER, Surveillance Epidemiology & End Results.

adjuvant therapy is unknown. In one large retrospective study in pN+ patients, the use of adjuvant ADT + RT was associated with an improvement in OS (HR: 0.41; P<0.001) compared observation and salvage therapy at recurrence (43). The recently reported results from the RAVES (53) and RADICALS (54) randomized trials—which found equivalent control between adjuvant RT and early salvage RT in mainly early-stage prostate cancer patients after RP—should not be extrapolated to pN+ patients who constitute a much higher risk population than those studied in the trials.

Conclusions

There is currently limited randomized evidence to define the optimal treatment strategy for men with node-positive prostate cancer. The studies reviewed in this article provide a rationale for a multimodality treatment approach. For patients with cN1M0 prostate cancer, one standard option is definitive RT with long-term ADT, and another option is RP. For patients with pN+ disease after RP, adjuvant ADT is supported by the ECOG 3886 trial. Adjuvant ADT + RT is another option supported by retrospective studies suggesting that it may improve survival compared to adjuvant ADT alone. For select pN+ patients, observation could also be considered. Current international guideline recommendations for both cN1M0 and pN+ diagnoses are summarized in *Table 3*.

The outcomes summarized here are reflective of a heterogenous population contained in mostly retrospective studies which have methodological limitations. More clinical trials are needed for this understudied patient population to provide high-quality evidence to guide treatment decision-making. One such trial is NRG GU008 (NCT 04134260), which for patients with pN+ disease after RP is comparing salvage RT + ADT *vs.* RT + ADT + abiraterone and apalutamide. Intensifying treatment for this group of patients with stage IV disease is likely needed to maximize long-term survival and the potential for cure. Of note, the incidence of node-positive prostate cancer at diagnosis is currently increasing, coincident with decreased PSA screening and enhanced ability to detect occult nodal metastases with new imaging modalities such as the FACBC, choline and prostate-specific membrane antigen PET scans (55). This increase may provide an opportunity for improved participation in prospective randomized trials designed to test the optimal management of node-positive prostate cancer.

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Footnote

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