# Lymph Node-Positive Prostate Cancer after Radical Prostatectomy

Subjects: Oncology

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Pathological lymph node involvement (pN1) after a pelvic lymph node dissection represents one of the most unfavorable prognostic factors for disease recurrence and cancer-specific mortality in prostate cancer. However, optimal management for pN1 patients remains unclear. Thus, the guideline from the European Association of Urology recommends discussing three following management options with pN1 patients after an extended pelvic lymph node dissection, based on nodal involvement characteristics: (i) offer adjuvant androgen-deprivation therapy, (ii) offer adjuvant androgen-deprivation therapy with additional radiotherapy and (iii) offer observation (expectant management) to a patient with ≤2 nodes and a prostate-specific antigen <0.1 ng/mL. Treatment intensification may reduce risks of recurrence and cancer-specific mortality, but it may increase adverse events and impair quality of life. Few randomized control trials for pN1 are under investigation. In addition, there are limited reports on the quality of life and patient-reported outcomes in patients with pN1. Therefore, more research is needed to establish an optimal therapeutic strategy for patients with pN1.

androgen deprivation therapy | lymph node involvement | pelvic lymph node dissection | radiotherapy | radical prostatectomy

## 1. Introduction

Pelvic lymph node dissection (PLND) is recommended during radical prostatectomy (RP) for prostate cancer in clinical practice, depending on risk classification [1]. PLND is the gold standard procedure for the diagnosis of lymph node involvement (LNI), although so far, its therapeutic value has not been proven [2][3]. Pathological LNI (pN1) rates after RP with PLND vary between 0% and 37% depending on risk classification and the areas removed in PLND [4]. LNI represents one of the most unfavorable prognostic factors for recurrence and cancer-specific mortality [5].

So far, the only randomized clinical trial (RCT) performed for patients solely with pN1 prostate cancer showed that immediate androgen deprivation therapy (ADT) was associated with better overall survival (OS) than deferred ADT in patients with distant metastases or symptomatic recurrences [6]. However, this finding cannot be generalized to all patients with pN1. First, this study started in the pre-prostate specific antigen (PSA) era, and limited PLND was performed, which is no longer a standard practice [1]. Nevertheless, the median number of positive lymph nodes removed was higher than in recent studies [6]. Second, the initiation of deferred ADT may be delayed too long, as early ADT should be reserved for those men at the highest risk of disease progression and a long-life expectancy

[1]. Therefore, it remains an open question whether the prognosis of early salvage ADT can be equivalent to immediate ADT. It has been shown that the survival between observation and adjuvant ADT was comparable using the Surveillance, Epidemiology, and End Results database [7]. In addition, several retrospective studies have suggested that the long-term prognosis in pN1 patients is heterogeneous and varies according to disease characteristics, such as the number of positive nodes, disease extension, margin status in RP, and PSA kinetics [8] [9]. Meanwhile, favorable disease control and better survival by the addition of radiation therapy (RT) to immediate ADT have been reported by retrospective studies. Thus, RT plus ADT appeared to be a promising approach to improve the prognosis among men with pN1 prostate cancer. However, given the lack of level-1 evidence applicable to contemporary patients, the European Association of Urology (EAU) has recommended practitioners to discuss with pN1 patients three management options after an extended PLND, based on nodal involvement characteristics: (i) offer adjuvant ADT, (ii) offer adjuvant ADT with additional RT and (iii) offer observation (expectant management) to a patient with ≤2 nodes and a PSA < 0.1 ng/mL after extended PLND [1].

## 2. The Prognosis in pN1 Prostate Cancer by Treatments

Several retrospective studies reported the prognosis in pN1 prostate cancer (**Table 1**). Since the standard treatment for pN1 has not been established, management strategies differed among studies. Biochemical recurrence (BCR)-free survival rate is affected by adjuvant therapy and varies from 28% to 61% at five years. Recurrence-free survival (RFS), determined basically by radiological recurrence, and metastasis-free survival (MFS) was 55–84% and 65–80% at 10 years, respectively. Cancer-specific survival (CSS) and OS were ~80% and ~70% at 10 years, respectively. Although survival in patients with pathological negative LNI (pN0) or unknown LNI (pNx) after RP is generally excellent, the prognosis in pN1 prostate cancer is inferior, making the improvement of treatment outcomes an unmet need, where treatment intensification is an attractive approach.

**Table 1.** Prognosis among men with pN1.

| Authors | *n* | Groups | Median Follow-Up | Time (year) | BCR-Free Survival (%) | Reference |
|---|---|---|---|---|---|---|
| Tilki et al. | 773 | All | 33.8 (month) | 4 | 43.3 | [10] |
| | | Matched pair cohorts | – | – | – | |
| | 192 | Observation | | 4 | 43 | |
| | 192 | aRT | | 4 | 57 | |
| Fleischmann et al. | 102 | Observation | 7.7 (year) | 5 | 28 | [11][12] |
| Touijer et al. | 369 | Observation | 4 (year) | 10 | 28 | [8] |
| Dorin et al. | 150 | All | 10.4 (year) | 10 | 57 | [13] |

| | | | | | | |
|---|---|---|---|---|---|---|
| | 49 | Observation | 11.4 (year) | 10 | 59 | |
| Hofer et al. | 201 | aADT | 41 (month) | 5 | 61 | [14] |
| Abdollah et al. | 1107 | aADT/aRT | 7.1 (year) | 10 | 56 | [15][16] |
| **Authors** | ***n*** | **Groups** | **Median follow-up** | **Time (year)** | **RFS (%)** | **Reference** |
| Hussain et al. | | | 11.2 (year) | – | – | [17] |
| | 79 | aADT | | 10 | 55 | |
| | 83 | aADT + mitoxantrone and prednisone | | 10 | 66 | |
| Bravi et al. | | | 77(month) | 10 | | [18] |
| | 100 | aRT | – | | 92 | |
| | 272 | aADT + aRT | – | | 70 | |
| Dorin et al. | 150 | All | 10.4 (year) | 10 | 84 | [13] |
| | 49 | Observation | 11.4 (year) | 10 | 80 | |
| Shiota et al. | 561 | All | 4.8 (year) | 510 | 8775 | [19] |
| **Authors** | ***n*** | **Groups** | **Median follow-up** | **Time (year)** | **MFS (%)** | **Reference** |
| Tilki et al. | 773 | All | 33.8 (month) | 4 | 86.6 | [10] |
| | | Matched pair cohorts | – | | | |
| | 192 | Observation | | 4 | 82.5 | |
| | 192 | aRT | | | 91.8 | |
| Touijer et al. | 369 | Observation | 4 (year) | 10 | 65 | [8] |
| Shiota et al. | 561 | All | 4.8 (year) | 510 | 9080 | [19] |
| **Authors** | ***n*** | **Groups** | **Median follow-up** | **Time (year)** | **CSS (%)** | **Reference** |
| Bravi et al. | | | 77 (month) | 10 | – | [18] |
| | 100 | aRT | | | 98 | |
| | 272 | aADT + aRT | | | 92 | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Mandel et al. | 209 | Observation | 60.2 (month) | | | [20] |
| Fleischmann et al. | 102 | Observation | 7.7 (year) | 5 | 78 | [11][12] |
| Touijer et al. | 369 | Observation | 4 (year) | 10 | 72 | [8] |
| Abdollah et al. | 1107 | aADT/aRT | 7.1 (year) | 10 | 83.6 | [15][16] |
| Bianchi et al. | 518 | aADT/aRT | 52 (month) | 8 | 71.2 | [21] |
| Shiota et al. | 561 | All | 4.8 (year) | 510 | 9891 | [19] |
| **Authors** | ***n*** | **Groups** | **Median follow-up** | **Time (year)** | **OS (%)** | **Reference** |
| Hussain et al. | | | 11.2 (year) | – | – | [17] |
| | 79 | aADT | | 10 | 81 | |
| | 83 | aADT + mitoxantrone and prednisone | | 10 | 81 | |
| Bravi et al. | | | 77 (month) | 10 | | [18] |
| | 100 | aRT | | | 81 | |
| | 272 | aADT + aRT | | | 85 | |
| Fleischmann et al. | 102 | Observation | 7.7 (year) | 5 | 75 | [11][12] |
| Touijer et al. | 369 | Observation | 4 (year) | 10 | 60 | [8] |
| Dorin et al. | 150 | All | 10.4 (year) | 10 | 74 | [13] |
| | 49 | Observation | 11.4 (year) | 10 | 81 | |
| Abdollah et al. | 1107 | aADT/aRT | 7.1 (year) | 8 | 78.1 | [15][16] |
| Shiota et al. | 561 | All | 4.8 (year) | 510 | 9789 | [19] |

sfunction,
or Cancer
the most
significant negative effect on urinary continence and sexual function in those patients undergoing RP [22]. Similarly, a prospective trial showed that patients who underwent RP had worse urinary incontinence and a worse sexual domain score compared with patients with RT or active surveillance [23]. Thus, additional treatment after RP may lead to further deterioration in QoL.

aADT, adjuvant androgen deprivation therapy; aRT, adjuvant radiotherapy; BCR, biochemical recurrence; CSS, cancer-specific survival; OS, overall survival; RFS, recurrence-free survival; MFS, metastasis-free survival.

Additionally, ADT can cause several adverse effects (AEs) including sexual dysfunction, hot flushes, bone fractures, metabolic effects, cardiovascular morbidity, fatigue, and neurological disorders [24]. A prospective observational study that included patients with locally advanced prostate cancer or PSA relapse after local therapy found that immediate ADT was associated with a lower overall QoL than in those with deferred treatment [25]. Consistently, in another prospective observational study, patients undergoing ADT, after RP or RT, showed higher levels of depression, worse self-body image perception, worse sleep quality, and worse QoL than controls [26].

Similarly, salvage RT is also associated with toxicity. A prospective study evaluating salvage RT plus ADT after RP showed increased bowel dysfunction and urinary dysfunction by the end of RT. These rates improved after RT completion, but not completely. Meanwhile, erectile function presented no change during RT but showed an abrupt decline after RP [27]. Similarly, in an observational study from the Martini-Klinik Prostate Cancer Center, patients who received RT after RP had a higher incontinence rate and lower potency rate than matched RP-only patients. Both rates increased further with the addition of ADT [28]. Thus, currently available data on toxicity demonstrate an increased incidence of acute and long-term grade 2 AEs and transient decline in QoL outcomes, but no significant increase in long-term grade 3–4 AEs with the use of RT after RP [29].

Based on this evidence, treatment addition after RP may lead to increased toxicity and reduced QoL. Meanwhile, treatment addition may reduce or delay recurrence, which may lead to a recovery of QoL by avoiding continuous ADT. However, there is little data on QoL and outcomes reported by patients with pN1. Thus, a prospective study on treatment strategies would be necessary.

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