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Survival Outcomes of Men with Lymph Node-positive Prostate Cancer After Radical Prostatectomy: A Comparative Analysis of Different Postoperative Management Strategies

Karim A. Touijer[a,*], *Robert Jeffery Karnes*[b], *Niccolo Passoni*[c], *Daniel D. Sjoberg*[c], *Melissa Assel*[c], *Nicola Fossati*[d], *Giorgio Gandaglia*[d], *James A. Eastham*[a], *Peter T. Scardino*[a], *Andrew Vickers*[c], *Cesare Cozzarini*[e], *Francesco Montorsi*[d], *Alberto Briganti*[d]

[a] *Urology Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA;* [b] *Department of Urology, Mayo Clinic Rochester, Rochester, MN, USA;* [c] *Department of Epidemiology & Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY, USA;* [d] *Division of Oncology, Unit of Urology, IRCCS Ospedale San Raffaele, Vita-Salute San Raffaele University, Milan, Italy;* [e] *Department of Radiotherapy, IRCCS Ospedale San Raffaele, Vita-Salute San Raffaele University, Milan, Italy*

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Abstract

Background: Optimal management of patients with lymph node metastasis (LNM) after radical prostatectomy (RP) remains undefined.
Objective: We evaluated the association between three different management strategies and survival in prostate cancer with LNM after RP.
Design, setting, and participants: We analyzed data of 1338 patients with LNM after RP from three tertiary care centers. Three hundred and eighty-seven patients (28%) were observed, 676 (49%) received lifelong adjuvant androgen deprivation therapy (ADT), and 325 (23%) received adjuvant external beam radiation therapy (EBRT) and ADT. Three hundred and sixty-eight men were followed for more than 10 yr.
Outcome measurements and statistical analysis: Primary outcome measure was overall survival (OS). Secondary outcomes were cancer-specific survival (CSS) and other-cause mortality. Kaplan-Meier methods were used to visualize OS for the three treatment groups. Cox proportional hazards regression was utilized to compare OS and CSS among the three groups.
Results and limitations: ADT + EBRT was associated with better OS than ADT alone (hazard ratio [HR]: 0.46, 95% confidence interval [CI]: 0.32–0.66, $p < 0.0001$) or observation (HR: 0.41, 95% CI: 0.27–0.64, $p < 0.0001$). Higher-risk patients benefited more from ADT + EBRT than lower-risk patients. Ten-year mortality risk difference between ADT + EBRT, observation, or ADT alone ranged from 5% in low-risk patients to 40% in high-risk patients. Adjuvant ADT + EBRT was also associated with better CSS than observation or ADT alone ($p < 0.0001$), ADT had better CSS compared to observation (HR: 0.64, 95% CI: 0.43–0.95, $p = 0.027$). However, ADT was associated with an increased risk of other-cause mortality (HR: 3.05, 95% CI: 1.45–6.40, $p = 0.003$) compared with observation, resulting in similar OS between ADT and observation (HR: 0.90, 95% CI: 0.65–1.25, $p = 0.5$). While selection bias might remain, its effect would operate in the opposite direction to our findings.
Conclusions: In men with LNM after RP, ADT + EBRT improved survival over either observation or adjuvant ADT alone. This survival benefit increases with higher-risk disease.
Patient summary: Lymph node metastasis following radical prostatectomy is associated with poor survival outcomes. However, we found that adjuvant androgen deprivation therapy with external beam radiation therapy improved survival in these patients.

* Corresponding author. Urology Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, USA. Tel. +1 646 422 4486; Fax: +1 212 988 0768.
E-mail address: touijerk@mskcc.org (K.A. Touijer).

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1. Introduction

The presence of lymph node metastasis (LNM) after radical prostatectomy (RP) is a poor prognostic sign. The long-term risk of death from prostate cancer is substantially increased, and is estimated to range between 20% and 42% [1,2]. However, the optimal management of patients diagnosed with LNM at the time of RP is not clearly established. The debate centers on the question of appropriate timing and type of secondary therapy.

Results from the Eastern Cooperative Oncology Group randomized clinical trial (ECOG 3886) comparing immediate lifelong androgen deprivation therapy (ADT) to observation, made a strong argument in favor of early initiation of ADT [3]. However, concerns about the trial design and disease characteristics of the enrolled patients limit the applicability of this trial's findings to contemporary prostate cancer patients.

Therapeutic decisions in the management of patients with LNM after RP are driven by physicians' preference or dictated by institutional standards. This heterogeneity results in various therapeutic strategies including observation followed by treatment only if biochemical recurrence develops [4], adjuvant long-term ADT [5], or a combination of adjuvant ADT and external beam radiation therapy (EBRT) [6]. It is currently unknown what benefit either of these adjuvant treatments provide compared to observation, particularly, given the known morbidity associated with ADT and EBRT [7–11].

We analyzed data from three centers in the USA and Europe to quantify differences in survival in patients with LNM after RP managed with observation, lifelong adjuvant ADT, or a combination of adjuvant ADT + EBRT.

2. Patient and methods

2.1. Study design

The study was approved by the Institutional Review Board from the three participating institutions: Memorial Sloan Kettering Cancer Center (MSK), New York, NY, Mayo Clinic, Rochester, MN, and San Raffaele Hospital, Milan, Italy. This was a retrospective analysis comparing survival outcomes of node-positive patients after RP performed between 1988 and 2010 at one of three institutions, according to whether they were managed by observation, received lifelong adjuvant ADT, or adjuvant ADT + EBRT. The choice of treatment was primarily driven by practice patterns or standard of care at each institution. Overall, 84% of the patients managed by observation after RP were treated at MSK, while 73% of those managed by lifelong adjuvant ADT were treated at the Mayo Clinic, and 83% of the patients who received adjuvant ADT + EBRT were treated at San Raffaele Hospital.

Observation consisted of no treatment until patients experienced biochemical recurrence (prostate specific antigen [PSA] $\geq$ 0.1 ng/ml with subsequent confirmatory rise, PSA $\geq$ 0.2 ng/ml for the Milan patients, and PSA $\geq$ 0.4 ng/ml for the Mayo clinic patients) at which point patients were treated. ADT alone was the most commonly used (72%), followed by salvage EBRT (13%), ADT plus EBRT (8.9%), and ADT plus chemotherapy (2.1%). The remaining 4.7% were enrolled in clinical trials. Only 24.52% of patients in the observation group had a detectable PSA between 42 d and 100 d after RP.

Adjuvant ADT consisted of either bilateral orchiectomy or luteinizing hormone releasing hormone agonist. ADT was generally intended to be life-long. When combined with EBRT, the median duration of ADT was 5.9 yr (interquartile range [IQR]: 3.55–8.91), 10% of the patients received ADT for less than 1 yr, 15% for 1–3 yr, and 75% for more than 3 yr.

Adjuvant radiation therapy consisted of local radiation to the prostatic $\pm$ seminal vesicle bed and pelvic lymph nodes area (whole-pelvis radiotherapy [WPRT]). All patients were treated with high-energy photon beams (6–18 mV) at conventional fractionation (1.8–2 Gy/fraction), at a median dose of 68 Gy (IQR: 66, 70). A three-dimensional conformal (3D-CRT) approach was always used up to 2002. Intensity-modulated radiation therapy (IMRT) was gradually introduced since 2003.

The clinical target volumes (CTVs) were drawn on computed tomography images and always included the prostatic bed (CTV1). In case of seminal vesicle invasion (pT3b), the seminal vesicle bed was also identified (CTV2).

The corresponding planned target volumes (PTVs) were defined as CTVs plus a 0.8-cm margin, with the exception of the cranio-caudal direction where a 1 cm margin was applied. The lymph-nodal area was contoured only in patients treated with IMRT and included obturator, hypogastric, internal and external iliac, as well as presacral lymph-nodes. The corresponding PTV lymph node was generated by isotropic expansion of the lymph-nodal area of 7 mm.

In patients treated with 3D-CRT, adjuvant radiation therapy consisted of a four-field (anteroposterior [AP]-posteroanterior plus latero-lateral [LL]) WPRT at a median dose of 50 Gy (IQR: 45–50 Gy), followed by a three-field (AP plus LL) boost to PTV1 at a median dose of 68 Gy (IQR: 56–72 Gy). The median dose to PTV2, if present, was 60 Gy. WPRT was irradiated by means of static 6-MeV 5–7 field IMRT (always 50.4 Gy), but the consequential boost to prostatic bed was always delivered with 3D-CRT (AP + LL) up to a median dose of 70 Gy (IQR: 68–72).

From the respective institutional databases, 1471 patients with LNM after RP and extended pelvic lymph node dissection for prostate cancer were identified. The extended pelvic lymph node dissection included the external iliac, hypogastric, and obturator fossa nodes. None of the patients received preoperative ADT, EBRT, or chemotherapy. Treatment was considered adjuvant if it was administered within 6 mo of surgery. A total of 33 patients were treated more than 6 mo after RP and thus were excluded from the analysis. In addition, 50 patients with missing information on the type of adjuvant therapy were also excluded, leaving 1388 men eligible for analysis.

2.2. Study end points

The primary outcome measure was overall mortality. Secondary outcomes were cancer-specific mortality. Information about date of death was obtained from the Social Security Death Index notification for MSK and Mayo Clinic. Data on the date and cause of death for patients treated in Milan were obtained from the Italian National Civil Registry. Data on development of metastasis were only available from two of the three sites.

2.3. Statistical analysis

Our primary goal was to assess differences in overall and cancer-specific mortality among patients receiving observation, adjuvant ADT, and adjuvant ADT + EBRT following RP. Kaplan-Meier methods were used to visualize overall survival for the three treatment groups. Cox proportional hazards regression was utilized to compare overall and cancer-specific survival (CSS) among the three groups. The Cox models were adjusted for pathologic Gleason score (6 vs 7 vs 8–10), tumor stage (pT2–pT3a, pT3b, pT4), surgical margin status, number of positive nodes removed (1 vs 2 vs 3+), and age. As sensitivity analysis, we repeated the cancer-specific mortality model utilizing a competing risk regression model with death from other causes as the competing risk. To assess

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