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Prostate Cancer

Long-term Outcomes of Salvage Lymph Node Dissection for Clinically Recurrent Prostate Cancer: Results of a Single-institution Series with a Minimum Follow-up of 5 Years

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Abstract

Background: Prostate cancer (PCa) patients with lymph node recurrence after radical prostatectomy (RP) are usually managed with androgen-deprivation therapy. Despite the absence of prospective randomized studies, salvage lymph node dissection (LND) has been proposed as an alternative treatment option.
Objective: To examine long-term outcomes of salvage LND in patients with nodal recurrent PCa documented by 11C-choline positron emission tomography/computed tomography (PET/CT) scan.
Design, setting, and participants: Overall, 59 patients affected by biochemical recurrence (BCR) with 11C-choline PET/CT scan with pathologic activity treated between 2002 and 2008 were included.
Intervention: Pelvic and/or retroperitoneal salvage LND.
Outcome measurements and statistical analyses: Biochemical response (BR) was defined as prostate-specific antigen (PSA) <0.2 ng/ml at 40 d after surgery. BCR for those who achieved BR was defined as a PSA >0.2 ng/ml. Clinical recurrence (CR) was defined as a positive PET/CT scan after salvage LND in the presence of a rising PSA. Kaplan-Meier curves assessed time to BCR, CR, and cancer-specific mortality (CSM). Cox regression analyses were fitted to assess predictors of CR.
Results and limitations: Median follow-up after salvage LND was 81.1 mo. Overall, 35 patients (59.3%) achieved BR. The 8-yr BCR-free survival rate in patients with complete BR was 23%. Overall, the 8-yr CR- and CSM-free survival rates were 38% and 81%, respectively. In multivariable analyses evaluating preoperative variables, PSA at salvage LND represented the only predictor of CR ($p = 0.03$). When postoperative variables were considered, BR and the presence of retroperitoneal lymph node metastases were significantly associated with the risk of CR (all $p \leq 0.04$). Our study is limited by the lack of a control group.
Conclusions: Salvage LND may represent a therapeutic option for patients with BCR after RP and nodal pathologic uptake at 11C-choline PET/CT scan. Although most patients progressed to BCR after salvage LND, roughly 40% of them experienced CR-free survival.
Patient summary: Salvage lymph node dissection may represent a therapeutic option for selected patients with nodal recurrence after radical prostatectomy. Roughly 40% of men did not show any further clinical recurrence at long-term follow-up after surgery.

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1. Introduction

Radical prostatectomy (RP) represents a first-line treatment modality for patients with localized prostate cancer (PCa) and a life expectancy of at least 10 yr [1]. Although this approach is associated with excellent cancer control rates [2,3], a non-negligible proportion of patients still experiences biochemical recurrence (BCR) and clinical progression after surgery [4,5]. Of note, these individuals represent subjects at a higher risk of dying from cancer-specific mortality (CSM) [6,7]. In these patients, pelvic and/or distant lymph nodes may represent the site of recurrent disease [8]. Men experiencing nodal recurrence after surgery are currently considered as affected by systemic disease, and they are thus managed with medical treatments such as androgen-deprivation therapy (ADT) [9]. However, evidence exists supporting heterogeneous survival among clinically recurrent patients [10,11]. In particular, patients with nodal recurrence showed more favorable outcomes compared with patients with bone or visceral metastases after primary treatment [10]. In addition, ADT does not represent a potential curative treatment, and many of these men ultimately develop castration-resistant disease [12,13]. Moreover, ADT is associated with significant toxicity at long term [14–16]. On the basis of these considerations, imaging-guided therapies such as salvage lymph node dissection (LND) have been proposed for lymph node recurrent patients [17–22].

Although clinical guidelines do not currently recommend this approach, salvage LND might have two main aims: to delay further cancer recurrence and to postpone the use of systemic treatments [21]. Previous studies showed that approximately 70% of individuals treated with imaging-guided salvage LND were free from further clinical recurrence (CR) at 5-yr follow-up [17,18]. Although these results are promising, their applicability in clinical practice is still limited by the lack of data with adequate follow-up supporting the oncologic safety and rationale of salvage LND. We aimed at examining the long-term BCR-, CR-, and CSM-free survival rates in a cohort of patients treated with salvage LND for nodal recurrence documented by 11C-choline positron emission tomography/computed tomography (PET/CT) scan after RP. In particular, we present an update of our previous study with mature data from patients with at least a 5-yr follow-up [17].

2. Materials and methods

2.1. Study population

The current study included 59 patients who experienced postoperative BCR after RP. Postoperative BCR was defined as two consecutive prostate-specific antigen (PSA) values >0.2 ng/ml. All patients included in the study had pathologic lymph nodal uptake at 11C-choline PET/CT scan, suggesting the presence of nodal recurrence. All patients also underwent conventional imaging such as abdominal CT scan and bone scan using technetium Tc 99m methylene diphosphonate (MDP) to exclude any other sites of disease recurrence. All patients fulfilled previously reported inclusion criteria [17].

2.2. Intervention and follow-up

Patients were treated with imaging-guided salvage LND between January 2002 and December 2008 at a single tertiary referral center. After approval by the ethical committee of our institution, all patients signed an informed consent highlighting the absence of guideline recommendations regarding this surgical approach. Preoperative imaging modalities, surgical technique, and histologic evaluation were previously described [17]. All patients included in our cohort had negative biopsies of the prostatic fossa before salvage LND, as previously reported [17]. Use of any therapy after surgery was decided following discussion between the surgeon and the patient about possible treatment options. All patients with an incomplete biochemical response (BR) to surgery were treated with a minimum of 2 yr of adjuvant ADT, whereas in patients with a complete BR to surgery, the decision was left to the treating physician regardless of the extent of nodal involvement. Follow-up consisted of PSA testing 40 d after surgery, as well as at 3, 6, 9, and 12 mo after salvage LND, and biannually thereafter. Postoperative 11C-choline PET/CT scan and eventual bone scan using Tc 99m MDP were performed in the presence of BCR after salvage LND (defined as 0.2 ng/ml and rising).

2.3. Covariates and end points

All patients had available data on pathologic disease characteristics at RP, age at salvage LND, PSA at salvage LND, time to BCR after RP, use of adjuvant and/or salvage therapies after RP, and site and number of the positive 11C-choline PET/CT spots. BR was defined as a PSA <0.2 ng/ml at 40 d after salvage LND. The primary end point of our analyses was represented by clinical recurrence (CR), defined as a positive 11C-choline PET/CT scan in the presence of a rising PSA. Vital status and cause of death were identified from death certificates and physician correspondence. On death certificates, PCa was considered the cause of death when it was mentioned as the first cause on the list.

2.4. Statistical analyses

Means, medians, and interquartile ranges were reported for continuous variables. Frequencies and proportions were reported for categorical variables.

Our statistical approach consisted of different steps. First, Kaplan-Meier analyses were performed to evaluate the BCR-free survival rates in patients who experienced BR ($n = 35$). Second, Kaplan-Meier analyses were used to evaluate the rates of CR and cancer-specific mortality (CSM) in the overall population ($n = 59$). Finally, to identify patients who might benefit from surgery, both pre- and postoperative uni- and multivariable Cox regression models predicting CR after salvage LND were fitted. Multivariable pre- and postoperative Cox regression models including only significant predictors in univariable analyses were then generated.

All statistical analyses were performed using the R statistical package system v.3.0.2 (R Foundation for Statistical Computing, Vienna, Austria). All tests were two sided with a significance level set at 0.05.

3. Results

3.1. Baseline characteristics

Table 1 depicts the baseline characteristics of all patients included in the study. Mean age at salvage LND was 66.6 yr (median: 64). Overall, 41 patients and 18 patients had one and two positive spots, respectively, at 11C-choline PET/CT scan, and 36 patients (61.0%), 10 patients (16.9%), and 13 patients (22.0%) had pelvic, retroperitoneal, and pelvic plus retroperitoneal positive spots, respectively, at