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Impact of Adjuvant Radiation Therapy on Urinary Continence Recovery After Radical Prostatectomy

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Abstract

Background: Little is known about the impact of adjuvant radiation therapy (aRT) after radical prostatectomy (RP) on urinary continence (UC).
Objective: To evaluate the impact of aRT on UC recovery in patients with unfavourable pathologic characteristics.
Design, setting, and participants: The study included 361 patients with either pT2 with positive surgical margin(s) or pT3a/pT3b node-negative disease treated with RP at a tertiary care referral centre.
Intervention: Patients were stratified according to the administration of aRT into two groups: group 1 (no aRT; $n = 208$; 57.8%) and group 2 (aRT; $n = 153$; 42.2%).
Outcome measurements and statistical analysis: Continence was defined as no use of protective pads. Log-rank test was used to compare the rate of UC recovery according to aRT status. The association between aRT and UC was also tested in Cox regression models after accounting for age, Cancer of the Prostate Risk Assessment (CAPRA) score, nerve-sparing (NS) status, Charlson Comorbidity Index, body mass index, and year of surgery.
Results and limitations: At a mean follow-up of 30 mo, 254 patients (70.4%) recovered complete UC. The 1- and 3-yr UC recovery was 51% and 59% for patients submitted to aRT versus 81% and 87% for patients not receiving aRT, respectively ($p < 0.001$). At univariable analysis, older age ($p < 0.001$), presence of non–organ-confined disease ($p < 0.001$), non-NS procedure ($p < 0.001$), and delivery of aRT ($p < 0.001$) were significantly associated with lower UC. At multivariable analysis, the delivery of aRT remained an independent predictor of worse UC recovery (hazard ratio: 0.57; $p = 0.001$). Patients treated with aRT had a 1.6-fold higher risk of incontinence. Younger age ($p = 0.02$), lower CAPRA score ($p = 0.03$), and NS approach ($p < 0.001$) also represented independent predictors of UC recovery. The main limitations of the study are related to the lack of validated questionnaires in the evaluation of UC and in the lack of information regarding UC status at aRT.
Conclusions: The delivery of aRT has a detrimental effect on UC. The oncologic benefits must be balanced with an impaired UC recovery. Patients should be informed of such impairment before adjuvant treatments are planned.

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1. Introduction

Radical prostatectomy (RP) represents an effective treatment for patients with organ-confined prostate cancer (PCa), associated with excellent long-term cancer control and acceptable morbidity [1]. However, up to 30% of patients undergoing RP are diagnosed with locally advanced disease (≥pT3a) with or without positive surgical margins at final pathology [2]. The presence of positive surgical margins, extracapsular extension, and/or seminal vesicle invasion is associated with higher rates of biochemical recurrence as well as of metastatic progression after RP [3,4]. Three prospective randomised trials reported improved cancer recurrence–free rates in patients affected by PCa with poor pathologic characteristics receiving adjuvant radiotherapy (aRT), although in those studies salvage radiation therapy (RT) was delivered at high prostate-specific antigen (PSA) levels in most of the patients not receiving immediate aRT. However, little is known concerning the potential urologic side effects of aRT, namely erectile dysfunction (ED) and the recovery of urinary continence (UC). Although the effect of aRT on ED might be of relative interest for patients with locally advanced disease, the potential detrimental effect of aRT on UC recovery represents a major issue. Nevertheless, only a few studies addressed the association between aRT and UC recovery, reporting controversial results [5–7]. All these studies originated from small series, mainly based on noncontemporary patients. None of these studies extensively accounted for all parameters associated with postoperative UC recovery, such as cancer stage and grade, patient comorbidity [8], and surgical technique (namely, nerve sparing [NS] vs non-NS) [9]. This is key because UC recovery after RP represents a multifactorial time-dependent phenomenon.

To address this issue, we evaluated the impact of aRT on UC recovery in a series of contemporary patients with unfavourable PCa characteristics treated with RP.

2. Materials and methods

Since September 2002, data from patients treated with RP at our centre were collected in a prospective institutional review board database. All patients were asked to provide informed consent to be included anonymously in the database. Among all patients treated with RP at our institution, we analysed data from 361 men diagnosed with either pT2 disease and positive surgical margin(s) or pT3a/pT3b node-negative disease between January 2006 and October 2011 treated with open RP. The pathologic inclusion criteria had been previously adopted by a prospective randomised trial testing the role of aRT after RP.

All patients had complete preoperative clinical data including age at surgery, PSA at diagnosis, clinical stage, biopsy Gleason sum, percentage of positive cores at biopsy, comorbidity profile assessed by the Charlson Comorbidity Index (CCI; stratified into 1 and ≥2) [10], and body mass index (BMI). All patients were treated with RP performed by seven high-volume surgeons. An NS approach, when indicated, was performed with a previously described technique [11]. NS status at surgery was defined by each operating surgeon at the end of the procedure and reported in our prospectively collected database. No patient received neoadjuvant, adjuvant, or salvage hormonal therapy during the study period. No patient in the non-aRT group received salvage RT within the study period. Patients previously submitted to surgery for benign prostatic enlargement were excluded from the analyses, as well as patients reporting the use of any pad before surgery [12].

UC recovery was defined as the use of no pads [13]. Patients were followed up at 1, 3, 6, and 12 mo postoperatively and every 6 mo thereafter. At each visit postoperative UC recovery was assessed.

Patients were stratified according to the administration of aRT into two groups: group 1 (no aRT; $n = 208$; 57.8%) and group 2 (aRT; $n = 153$; 42.2%). Administration of aRT was based on the indication given by each treating physician and followed extensive discussion with patients about treatment options and expectations. In patients treated with aRT, it was delivered within a period of 1–6 mo after surgery. The details of the RT techniques used in the treatment of these patients were previously published [14]. In this context, it should only be emphasised that all patients received a three-dimensional conformal approach: the clinical target volume (CTV) was drawn on computed tomography (CT) images by the physicians and included the prostatic fossa and periprostatic tissue: clinical findings, presurgery CT scan, and surgical clips guided the clinicians in defining the CTV. The planned target volume (PTV) was defined as the CTV plus a 1-cm margin (to account for organ motion and set-up error). A small margin around the PTV (ie, 0.8–1 cm) was retained only for the posterior orientation (ie, at the interface between PTV and rectum), resulting in a more rectum-sparing technique when compared with our conventional treatment. All patients received irradiation of the prostatic bed only to a median dose of 70.2 Gy (interquartile range [IQR]: 65.8–72.0). With respect to the volumes irradiated, the seminal vesicles bed was always irradiated regardless of the pathologic stage (pT2, pT3a, or pT3b) with a median dose delivered to the seminal vesicles bed of 60–61 Gy. All treatments were delivered at conventional fractionation (1.8 Gy per fraction).

2.1. Statistical analyses

Descriptive statistics were performed with the independent t test for continuous variables and with the Pearson chi-square test for categorical variables, respectively. Kaplan-Meier univariable analyses targeted time to UC recovery after surgery according to the delivery of aRT in the overall population as well as in the population of patients treated with a bilateral NS approach. The log-rank test was used to compare the rate of UC recovery over time according to aRT status. Second, the association between aRT and UC recovery was tested in univariable and multivariable Cox regression models. Covariates consisted of patient age at surgery, Cancer of the Prostate Risk Assessment (CAPRA) score (used as a proxy for disease severity) [15], NS technique, categorised CCI, and preoperative BMI. Multivariable analyses were also adjusted for the year of surgery to minimise the impact of different RT schedules and of surgical skills over time. Finally, univariable and multivariable Cox regression analyses were performed in patients submitted to aRT only to identify predictors of delayed continence recovery including as covariates time from RP to aRT delivery and total radiation dose. Statistical analyses were performed using SPSS v.17 (IBM Corp., Armonk, NY, USA), with a two-sided significance level set at $p < 0.05$.

3. Results

Table 1 shows the preoperative clinical characteristics of the 361 patients included in the study. Several statistically significant differences were noted between the two groups of patients (namely aRT vs no aRT; Table 1). Men treated with aRT were older ($p = 0.01$), had a higher clinical and pathologic stage ($p = 0.01$ and $p < 0.001$, respectively) distribution as well as Gleason score ($p < 0.001$) as