ELSEVIER

CrossMark

Urologic Oncology: Seminars and Original Investigations 33 (2015) 330.e1–330.e7

UROLOGIC ONCOLOGY

Original article

Influence of pathological factors on oncological outcomes after robot-assisted radical prostatectomy for localized prostate cancer: Results of a prospective study

Sébastien Kozal, M.D.[a], Benoit Peyronnet, M.D.[a,b], Susanna Cattarino, M.D.[a], Thomas Seisen, M.D.[a], Eva Comperat, M.D., Ph.D.[c], Christophe Vaessen, M.D.[a], Pierre Mozer, M.D., Ph.D.[a], Raphaële Renard-Penna, M.D.[d], Olivier Cussenot, M.D., Ph.D.[a,e], Morgan Rouprêt, M.D., Ph.D.[a,e,*], Sarah J. Drouin, M.D.[a]

[a] *Service d'Urologie, AP-HP, Hopital Pitié-Salpétrière, Paris, France*
[b] *Service d'Urologie, CHU Rennes, Rennes, France*
[c] *Service d'Anatomopathologie, AP-HP, Hopital Pitié-Salpétrière, Paris, France*
[d] *Service de Radiologie, AP-HP, Hopital Pitié-Salpétrière, Paris, France*
[e] *UPMC Univ Paris 06, GRC5, ONCOTYPE-Uro, Institut Universitaire de Cancérologie, Paris, France*

Received 2 February 2015; received in revised form 26 March 2015; accepted 27 March 2015

Abstract

Purpose: To assess the prognostic significance of lymphovascular invasion (LVI), maximum tumor diameter (MTD), high-grade prostatic intraepithelial neoplasia, perineural invasion, and length of positive surgical margins after robot-assisted radical prostatectomy (RARP).

Methods: A single-institution prospective analysis of all patients who underwent RARP for localized prostate cancer was performed between January 2005 and June 2013. The primary end point was biochemical recurrence-free survival (BRFS). BRFS was estimated using the Kaplan-Meier method and compared to that from the log-rank test. Cox's proportional hazards regression univariate and multivariate analyses were performed to define the prognostic factors.

Results: Overall, 742 men were included. After a median follow-up of 31.4 months, biochemical recurrence occurred in 80 patients (10.8%). BRFS was 93%, 87%, and 80.7% at 1, 3, and 5 years, respectively. Progression to local recurrence occurred in 49 patients (6.6%). During the follow-up period, 3 patients experienced progression to metastatic disease and were treated with hormonotherapy. No patient died of disease during the study period. In multivariate analyses, Gleason score was the strongest predictor of BRFS (hazard ratio [HR] = 3.4; $P < 0.001$). There were 3 other predictive factors of BRFS were LVI (HR = 7.64; $P = 0.005$), MTD (HR = 4.04; $P = 0.009$), and margin length ≥ 3 mm (HR = 1.25; $P = 0.04$).

Conclusion: In the era of serum prostate-specific antigen testing maturity in conjunction with a single approach to extirpation of the prostate gland by RARP, LVI, MTD, and positive surgical margins ≥ 3 mm are prognostic factors associated with BRFS after RARP. Consideration could be given to incorporate them in the pathology report of the radical prostatectomy specimens and they could assist physicians in clinical decision making.

Keywords: Adenocarcinoma; Prostate; Tumor volume; Positive surgical margin; Lymphovascular invasion

1. Introduction

Prostate cancer (PCa) is the most commonly diagnosed male cancer and the second leading cause of death from cancer in male patients in the United States and Europe [1]. Radical prostatectomy (RP) is the only treatment of localized PCa that provides improved overall survival and cancer-specific survival compared with conservative management [2]. RP is therefore considered as the gold-standard treatment for low-risk and intermediate-risk PCa, and as an option in selected patients with high-risk PCa [3]. However,

* Corresponding author.
E-mail address: mroupret@gmail.com (M. Rouprêt).

http://dx.doi.org/10.1016/j.urolonc.2015.03.020

after RP, up to 40% of patients have been reported to experience biochemical recurrence (BCR) in long-term follow-ups, and death from PCa has been observed in up to 15% of men by 15 years after RP surgery [4]. Therefore, it has been hypothesized that adjuvant treatments could optimize oncological outcomes of RP. However, despite several randomized controlled trials, the benefits of adjuvant radiotherapy and hormonal therapy remain controversial [5,6], and current guidelines recommending their usage is limited to patients with a high risk of disease recurrence, i.e., in case of adverse pathological findings [3,7].

During the last decades, efforts have been made to identify the pathological features associated with adverse oncological outcomes after RP [8]. Gleason score (GS), extraprostatic extension (EPE), positive surgical margins (PSM), and seminal-vesicle invasion (SVI) are well-established adverse prognostic factors for prostate carcinoma [8]. Conversely, conflicting results have been reported regarding the prognostic significance of lymphovascular invasion (LVI), perineural invasion (PNI), high-grade prostatic intraepithelial neoplasia (HGPIN), length of PSM, and maximum tumor diameter (MTD) [8]: these are not included within current postoperative nomograms [9].

Robot-assisted RP (RARP) has increased significantly over the past few years [10]. In recent years, a reverse shift has been observed with increased rates of high-risk PCa among patients who undergo RP [11]. This escalating risk in men undergoing RP, the maturity of serum prostate-specific antigen (PSA) testing, the improvement of PCa imaging (magnetic resonance imaging), and the increasing use of targeted biopsies in conjunction with a single approach to extirpation of the prostate gland by RARP could affect the oncological outcomes obtained after RP. Very few studies have sought to assess the prognostic value of LVI, PNI, HGPIN, length of PSM, and MTD in the contemporary robotic era.

In the present study, our aim was to evaluate the effect of LVI, PNI, HGPIN, length of PSM, and MTD on biochemical recurrence-free survival (BRFS) after RARP.

2. Materials and methods

2.1. Population

After institutional review-board approval, we prospectively collected the data of all patients who underwent RARP for localized PCa at our institution between January 2005 and June 2013. Collected data included the patients' characteristics (age and body-mass index), clinical presentation, cT stage, preoperative PSA level, pathological findings from the biopsy cores and from the surgical specimens (discussed later), perioperative parameters (e.g., operative time and estimated blood loss), oncological outcomes (BCR, clinical recurrence, date of recurrence, death, causes of death, etc.), and the use of adjuvant treatments. Patients were categorized preoperatively, according to the European Association of Urology guidelines, as low risk (Gleason 6, PSA $<$ 10 ng/ml and cT1c-cT2a), intermediate risk (Gleason 7 or PSA $=$ 10–20 ng/ml or cT2b–cT2c) or high risk (Gleason $\geq$ 8 or PSA $>$ 20 ng/ml or $\geq$cT3a) [3]. Patients with neoadjuvant hormonal therapy, neoadjuvant radiotherapy, or adjuvant radiotherapy before PSA relapse were excluded from the study ($n = 29$).

The primary end point was BRFS. BCR was defined according to current guidelines by 2 consecutive PSA values of $>$0.2 ng/ml postoperatively [12]. Oncological follow-up involved a digital rectal examination and PSA measurement at 3 and 6 months after surgery, and then annually. In cases of biochemical failure, patients underwent salvage radiotherapy.

2.2. Surgical technique

A total of 2 senior surgeons experienced in robotic surgery performed all the surgical procedures using a transperitoneal approach. An extended pelvic lymph-node dissection was performed in intermediate- and high-risk patients. A nerve-sparing approach was used in men with low- or intermediate-risk disease who were preoperatively potent and who were interested in preserving sexual function. Adjuvant radiotherapy was used only in patients with persistently elevated PSA levels at 3 months after the RARP (PSA-free patients did not undergo adjuvant radiotherapy even in case of adverse pathological factors). Adjuvant androgen deprivation therapy was used in patients with positive lymph nodes and when $>$2 nodes were involved. Hence, these patients were excluded from the study.

2.3. RP pathology

All pathological specimens were reviewed by a single senior uropathologist. The RP specimens were fixed intact in 10% neutral-buffered formalin. The prostate surface was painted to allow accurate assessment of surgical-margin (SM) status. Whole-mount specimens were then sectioned transversally at regular intervals. GSs were graded according to the 2005 International Society of Urological Pathology (ISUP) consensus conference [13]. PCa was considered multifocal when cancer foci were discontinuous. PNI was defined as a tumor tracking along or around the nerve fiber. In accordance with the 2009 ISUP consensus conference [14], LVI was defined as the presence of tumor emboli in small intraprostatic vessels, i.e., as the presence of tumor cells in the endothelium space. If LVI was equivocal or tumor cells merely encroached on a vascular space, the finding was considered negative for LVI. An abnormal proliferation and cellular dysplasia of prostate epithelium within the prostatic ducts without stromal invasion was reported as HGPIN. GS was analyzed in primary tumors and independently in SMs.