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Oncological results at 2 years after robotic radical prostatectomy – the Romanian experience

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Introduction To assess the oncological outcomes of robotic radical prostatectomy in a country where there are no on-going national screening programs for prostate cancer.

Material and methods Between November 2009 and November 2014, 220 robotic radical prostatectomies were performed at our Robotic Surgery Center. We already have the complete data for the 2-year follow-up of the first 105 patients, who were therefore included in the study group. Pre-operative (age, prostate-specific antigen, body-mass index, prostate volume, clinical staging, biopsy characteristics), post-operative (surgical technique, surgical margin status, lymph node status, pathological stage, Gleason score) and follow-up parameters (biochemical recurrence) were assessed.

Results The global rate of positive surgical margins was 34.3%, with rates of 17.2% in stage pT2 and 55.3% in stage pT3. The most frequent localization for positive surgical margins was at the base and apex of the prostate. The positive surgical margins rate was correlated with the pre-operative prostate-specific antigen, clinical and pathological Gleason score, lymph node status and the number of positive biopsy cores. The rate of biochemical recurrence at the 2-year follow-up was 11.8%. The most important predictors for the biochemical recurrence were the positive surgical margins, pathological staging and Gleason score on the prostatectomy specimen.

Conclusions Robotic surgery is validated by the oncological results at medium follow-up (2 years) for localized and locally advanced prostate cancer, even in countries where there is no on-going national screening program.

Key Words: prostatic neoplasms ‹› robotic surgical procedures ‹› radical prostatectomy

INTRODUCTION

Prostate cancer is the most frequently diagnosed cancer in the male population in developed countries. Given the aging of the global population, an increase in the number of newly diagnosed prostate cancer patients is expected. The screening allows early diagnosis of clinically localized tumors, with the possibility of curative treatment – radical prostatectomy. The screening programs for prostate cancer are not routinely performed in Eastern European countries, where the mortality rate of this disease is still rising [1]. Meanwhile, the robotic approach is tending towards becoming the new gold standard for radical prostatectomy, ensuring, at least, the same oncological outcome as the other two types of approach (open and laparoscopic) [2].

Our study aims to evaluate the postoperative oncological results (the pathological stage, Gleason score, pathological characteristics of the prostatectomy specimen, surgical margin status on the prostatectomy specimen and lymph node status) and the 2-year

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follow-up (the biochemical recurrence rate) after robotic radical prostatectomy performed at our Robotic Surgery Center, in a country where screening programs are not yet routinely carried out.

MATERIAL AND METHODS

Between November 2009 and November 2014, 220 robotic radical prostatectomies were performed for localized and locally advanced prostate cancer at our Robotic Surgery Center. Of these, 105 patients were monitored and evaluated 2 years after robotic radical prostatectomy for oncological outcomes. The collected data were entered into an electronic database.

The study group was formed of patients diagnosed with prostate cancer by ultrasound-guided transrectal prostate biopsy. The clinical staging was established using digital rectal examination or prostate magnetic resonance imaging – when available (42 cases). The recommendation for surgical treatment was made by the uro-oncological committee, after discussing all therapeutic alternatives. Before surgery, all the patients were briefed on possible intra- and postoperative complications, and all signed the informed consent. The surgical procedure was performed using the da Vinci SI system, employing all 4 robotic arms. The robotic radical prostatectomy followed the technique described by Patel [3], with bilateral/ unilateral/ non-nerve-sparing according to the staging of prostate cancer (no nerve-sparing in cases of suspected extracapsular extension) and presence of sexual activity before surgery. We also performed the sphincter reconstruction in the manner described by Rocco et al. [4, 5].

The oncological results assessed were the presence of positive surgical margins and the biochemical recurrence at the 2-year follow-up, considering the pathological staging, Gleason score, characteristics of the prostatectomy specimen (pathological subtype, perineural invasion, lymphovascular invasion) and the lymph node status (presence of positive lymph nodes). After the surgery, the robotic radical prostatectomy specimen was processed by a pathologist. Positive surgical margins were defined as the presence of malignant tissue at the surface of the specimen.

The patients were monitored, from an oncological point of view, by repeated determinations of the prostate-specific antigen: 1 month after surgery, then every 3 months during the first year, and every 6 months during the second year. The biochemical recurrence was defined as a prostate-specific antigen value above 0.2 ng/ml.

RESULTS

General results – characteristics of the study group

The study group consisted of 105 patients who underwent robotic radical prostatectomy and had complete follow-up data 2 years after surgery. The patients' characteristics were as follows: mean age 62 years, mean body mass index 27.1 kg/m^2, median prostate-specific antigen 8.7 ng/ml and median prostate volume 36 g. The clinical and pathological staging of patients having undergone robotic radical prostatectomy are summarized in Table 1. The staging performed by the pathologist, based on the robotic radical prostatectomy specimens, showed extracapsular extension in almost half of the patients.

The preoperative staging of prostate cancer was based in the majority of cases only on digital rectal examination and was accurate in about a third of the patients – 29.5%. We observed an important rate of understaging of the disease – 63.8% of the patients. In 6.7% of the cases the staging was downgraded after the pathological examination.

The majority of the patients had a low or intermediate aggressiveness Gleason score on the prostate biopsy specimens: Gleason score 6 (3+3) – 45.7%, Gleason score 7 (3+4) or (4+3) – 46.7%, Gleason score 8 (4+4) – 4.8% and Gleason score 9 (4+5) – 2.9%. On the prostatectomy specimen, the reported Gleason scores were: 6 (3+3) – 31.7% and 7 (3+4) or (4+3) in 68.3% of cases.

Table 1. *The characteristics of the patients in the study group*

Age at diagnosis, mean (range)	62 years (46-74)
Body-mass index, kg/m^2, mean (range)	27.1 (19.0-36.3)
Prostate-specific antigen, ng/ml, median (range)	8.7 (3.2-34.0)
Prostate volume, g, median (range)	36 (10.6-163.6)
American Joint Committee on Cancer Clinical T Stage, percentage	
T1c	21%
T2a	21.9%
T2b	18.1%
T2c	14.3%
T3a	21%
T3b	3.8%
American Joint Committee on Cancer Pathological T Stage, percentage	
T2a	14.3%
T2b	4.8%
T2c	36.2%
T3a	30.5%
T3b	14.3%

Surgical technique

Of the 105 patients in our study group, 47.9% had bilateral nerve-sparing, 25.5% unilateral and 26.6% no nerve-sparing. Most of the cases with bilateral nerve-sparing (29 out of 45) were stages cT1c and cT2a.
Pelvic lymphadenectomy was indicated when the risk for positive lymph nodes was higher than 4% on the Memorial Sloan Kettering Center nomograms. Pelvic lymphadenectomy was performed in 45.8% of cases and in 5 patients the presence of lymph node metastases was identified. The median number of excised lymph nodes was 8 (minimum 5 – maximum 21 lymph nodes).

Pathological characteristics

In 98% of the cases, the pathologist identified the presence of acinar adenocarcinoma, while the remaining 2% presented ductal carcinoma. Other pathological characteristics of the patients in our study group were: intraductal carcinoma in 5.8%, perineural invasion in 54.4% and lymphatic or vascular invasion in 3.9% of patients.
The number of positive biopsy cores was associated with the presence of perineural or lympho-vascular invasion on the prostatectomy specimen (p = 0.001 for both), but not with the presence of intraductal carcinoma.

Oncological outcomes

The global rate of positive surgical margins was 34.3%. The overall positive surgical margins rate according to the pathological staging was as follows: 17.2% in clinically localized prostate cancer (all in pT2c; no positive surgical margins in pT2a or b) and 55.3% in locally advanced disease. We observed a statistically significant association between the pathological staging and the positive surgical margins (p = 0.0001). The majority of the positive surgical margins were located at the base or apex of the prostate – we identified positive surgical margins at the base of the prostate in 61.1% of cases, in the anterior part in 13.9%, at the apex of the prostate in 61.1% and in the posterolateral area in 41.7% of patients. Multiple positive surgical margins were found in half of the patients with positive surgical margins (52.8%).
In this setting, we evaluated the degree to which the nerve-sparing technique might lead to positive surgical margins. Thus, we analyzed the presence of positive surgical margins in patients with unilateral, bilateral or no nerve-sparing. We found no statistically significant correlation between the type of nerve-sparing and the overall positive surgical margins rate (p = 0.06), or with the positive surgical margins rate in stage pT2 (p = 0.4).
The evaluation of the oncological outcomes assumed the identification of the correlation between the positive surgical margins and other perioperative parameters. We observed that the positive surgical margins were correlated with the preoperative prostate-specific antigen (p = 0.002), the Gleason score on the prostate biopsy cores (p = 0.02), the Gleason score on the prostatectomy specimen (p = 0.008) and the lymph node status (p = 0.005).
There was no statistically significant correlation between the positive surgical margins and the clinical stage of prostate cancer (p = 0.23), prostate volume (p = 0.193) or body-mass index (p = 0.49). The presence of intraductal carcinoma, perineural invasion and lymphatic and vascular invasion was not correlated with the overall rate of positive surgical margins, or with their localization. We found no correlation between the localization of the positive surgical margins and the perioperative parameters.
When performing univariate and multivariate analyses, of all the preoperative parameters, only prostate-specific antigen (OR 1.13) and the number of positive biopsy cores (OR 1.54) showed a significant association with positive surgical margins (Table 2). The age of the patient, the body-mass index and prostate volume had a moderate influence on the positive surgical margins rate, when taken into consideration separately. However, associating all of these parameters with the preoperative prostate-specific antigen and the number of positive biopsy cores, yielded a sensitivity of 77.8% and a specificity of 84.5% in predicting the presence of positive surgical margins (AUROC = 0.84).

Table 2. *Association between preoperative parameters and surgical margin status: univariate analysis*

Preoperative parameters	Surgical margin status		p
	Negative	Positive	
Age, mean ± standard deviation	61.8 ±6.05	62.4 ±5.6	0.62
Body-mass index, mean ± standard deviation	26.97 ±3.54	27.45 ±3.05	0.5
Preoperative prostate-specific antigen, median (95% confidence interval)	7.3 (6.86–8.28)	10.8 (8.9–13.6)	0.001
Prostate volume, median (95% confidence interval)	41 (33.88–44.68)	33.75 (28.8–37.89)	0.181
Number of positive biopsy cores, median (95% confidence interval)	2 (2–3)	6 (5–7)	<0.0001

The evaluation of the oncological outcomes also included the lymph node status assessment. We observed a statistically significant association between the lymph node status and the clinical and pathological staging ($p < 0.0001$ for both), the preoperative Gleason score ($p = 0.0004$), the number of positive biopsy cores ($p = 0.0002$), the presence of intraductal carcinoma ($p = 0.003$), perineural invasion ($p = 0.001$) and the lymphatic or vascular invasion ($p = 0.0001$) on the prostatectomy specimen. Furthermore, the intraductal carcinoma and the lympho-vascular invasion were associated with the number of positive lymph nodes ($p < 0.001$ for both).

Another marker of the oncological outcome is prostate-specific antigen dynamics after surgery. The overall rate of biochemical recurrence at 24 months after robotic radical prostatectomy was 11.8% (7.5% in stage pT2 and 18.8% in stage pT3). The presence of positive surgical margins, the pathological staging and the Gleason score on the prostatectomy specimen were the main factors associated with biochemical recurrence ($p = 0.01$, $p = 0.01$ and $p = 0.03$, respectively). The biochemical recurrence was not correlated with the presence of intraductal carcinoma, perineural invasion or lympho-vascular invasion. At the 2-year follow-up, only one patient had died following myocardial infarction.

The 5 patients with positive lymph nodes in our study group had detectable prostate-specific antigen levels 1 month after surgery; as such, they were considered to harbor residual disease and underwent adjuvant treatment.

DISCUSSION

Worldwide, due to the increasing use of prostate-specific antigen and screening programs, more than 90% of diagnosed prostate cancer is organ-confined [6], therefore being suitable for curative treatment. At present in Romania, there is no ongoing national screening program for prostate cancer. Up until now, only one screening program, based on digital rectal examination and prostate-specific antigen, has been attempted in Cluj-Napoca in 2005, which identified 45% of prostate cancer in localized stage [7]. Nowadays, a large percent of prostate cancer cases identified in Romania are still locally advanced or metastatic at diagnosis.

In this setting, robotic surgery has emerged as a new and very precise tool, tending toward a gold standard [8] in the treatment of localized and locally advanced prostate cancer: in 2011 almost 90% of the radical prostatectomies in the United States were performed robotically [9, 10].

When performing oncologic procedures, the main goal is to ensure cancer control. After radical prostatectomy, cancer control can be validated by the biochemical recurrence and cancer-free survival rates. A more accessible method for evaluating the procedure is the assessment of positive surgical margins and prostate-specific antigen dynamics after surgery.

The overall rate of positive surgical margins reported in the literature ranges between 6.5% and 32% [11], in comparison to 34.3% in our study group, but none of the cited studies reports such a high percentage of locally advanced disease as the one at present. When stratifying by pathological staging, the reported mean positive surgical margin rates are as follows: 9% in pT2 and 37–50% in pT3 [11]. In our study group, the rates of positive surgical margins, dependent on pathological staging, were 17.2% in pT2 and 55.3% in pT3. The relatively high rates of positive surgical margins could be explained by the fact that the preoperative staging of prostate cancer and the surgical planning were based, in the majority of cases, only on digital rectal examination and a high percentage of patients (63.8%) were understaged preoperatively.

Among the predictive factors for positive surgical margins cited in the literature we identified: preoperative prostate-specific antigen above 10 ng/ml, stage T3-T4 [12] and tumor volume. Also, the patient's body-mass index was shown to be an independent predictive factor of apical positive surgical margins, even in high-volume centers [13]. Regarding the positive surgical margins in organ-confined disease, only perineural invasion was shown to be an independent predictor [14]. In our study group, we identified preoperative prostate-specific antigen and the number of positive biopsy cores as being significantly predictive for overall positive surgical margins. Furthermore, the association of the age of the patient, the body mass index and prostate volume led to an increase in the predictive value of these parameters for positive surgical margins. In our study group, we found no correlation between the most frequent localization of the positive surgical margins (base and apex) or the positive surgical margins rate in organ-confined disease and the perioperative parameters.

The biochemical recurrence rate is a parameter that assesses the oncological control of prostate cancer, after a certain follow-up period. Independent predictors for the biochemical recurrence are: prostate-specific antigen density above 0.4, pathological T stage >T3a, Gleason score >8 and positive surgical margins [15]. In our study, we observed that the biochemical recurrence at the 2-year follow-up

was significantly associated with the positive surgical margins, pathological staging and Gleason score of the prostatectomy specimen.

CONCLUSIONS

Robotic radical prostatectomy is feasible, having been validated by the oncological results at medium-term follow-up (2 years), and must be considered an option for the treatment of localized and locally advanced prostate cancer, even in countries where screening programs are not yet a routine procedure.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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