LAPAROSCOPIC RADICAL PROSTATECTOMY IN PATIENTS WITH HIGH-RISK PROSTATE CANCER: FEASIBILITY AND SAFETY. RESULTS OF A MULTICENTRIC STUDY.

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Running title: Laparoscopy for high risk prostate cancer

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ABSTRACT

Introduction

In Western countries about 25% of prostate cancer (PCa) are high risk tumors at presentation and its treatment is still a matter of debate among urologists. When the surgical treatment is chosen the proposal of a mini-invasive approach in still a dilemma due to the lack of data in literature. The aim of this study is to evaluate feasibility and safety of laparoscopic radical prostatectomy for high-risk prostate cancer.

Material and methods

The study included 1114 patients with high-riskPCa submitted to LRP between 1998 and 2014. High-risk patients were defined according to D'Amico classification. We collected functional and oncological long terms outcomes and evaluated with univariate and multivariate analyses the role of predictive factors for survival and biochemical recurrence (BR).

Results

Mean age at the treatment was 62 ± 8 years; mean follow-up was 74 ± 50 months.

We obtained an OS at a mean follow-up of 74 months of 96.6% (1076 patients) and a DFS of 66.2% (737 patients). Age (P= 0.0006), pT (P< 0.0001), pN (P= 0.0018) and surgical margins (P= 0.0076) resulted as independent predictors for BR in multivariate analysis. pN (P=0.0025) and Gs (P= 0.0003) are independent predictors for OS and CSS in a univariate analysis; just the Gs results significant in the multivariate model.

Conslusion

According to our encouraging data about oncological and functional outcomes we believe that radical prostatectomy represents an effective treatment for patients with high-risk prostate cancer and that laparoscopy is a safe approach offering a mini-invasive alternative to open surgery.

INTRODUCTION

Despite the introduction of aggressive screening policies in Western countries, about 25% of prostate cancers (PCa) are high risk tumors at presentation, [1] according to the D'Amico classification (stage > cT2c and/or PSA > 20 ng/ml and/or Gleason score > 7) [1, 2, 3, 4, 5]. The management of patients is complex, since no randomized studies have directly compared the oncological efficacy of surgery, radiation therapy and hormonal therapy. [6]. Moreover, when the surgical approach is chosen,

surgeons have to face another dilemma: is a mininvasive technique such as laparoscopy or robotic surgery comparable to traditional open surgery? [7,8,9].

Laparoscopic radical prostatectomy (LRP) was introduced in the late nineties, but to date only few series have shown long-term oncological results of this surgical approach and, moreover, this information is lacking especially in patients with high-risk disease. The importance of pure laparoscopic procedures is nowadays to underline in literature in order to encourage the use of mininvasive procedures in hospital that cannot afford a robot.

The aim of our study is to evaluate the feasibility and safety of laparoscopic radical prostatectomy in terms of intra- and postoperative complications and long term oncological and functional results.

MATERIAL AND METHODS

Patient population

The study included 1114 consecutive patients with high-riskPCa who underwent LRP between May 1998 and May 2014 in three European Institutions: Henri Mondor University Hospital, Creteil, France (428 patients), SLK Clinic, Heilbronn, Germany (421 patients) and L. Sacco Hospital, Milan, Italy (265 patients). High-risk patients were defined according to D'Amico classification: PSA > 20 ng/ml and/or Gleason Score ≥ 8 and/or clinical stage > T2c.

PSA value was always measured before the prostate biopsy. Clinical stage was assigned before surgery. Pathologic grading was assessed according to the Gleason system and clinical stage was assigned according to the 2002 TNM system [1]. Patients with clinical souspicious of metastatic disease were staged with computed tomography (CT) or magnetic resonance (MRI). Bone scan was performed according to the EAU guidelines [1].

Surgical procedure

All the procedures were performed transperitoneally by expert surgeons who already accomplished their learning curve in laparoscopic radical prostatectomy.

Lymphadenectomy was performed according to the EAU guidelines indications at the moment of surgery; in most recent cases extended pelvic limphnode dissection (ePLND) was performed if the estimated risk for positive LNs exceeded 5% [1].

Data on limphadenectomy are available for 1022 patients (91.7%) due to the retrospective nature of the study; most of the pNx patients underwent surgery in the late 90's when guidelines were still evolving about thisprocedure. Lymphadenectomy is performed before or after the prostatectomy depending on surgeon habits. If performed after it, lymphadenectomy is always performed before the vescico-urethral anastomosis in order to allow a better mobilization of the bladder without damaging the anastomosis. We always use a transperitoneal approach to minimize the risk of postoperative lymphocele formation.

Tamplates for standard dissection was the same in all the centers including obturator and external iliac nodes.

Due to the retrospective nature of the study and the variable definition of ePLND in literature the exact borders of the dissection is not always standardized in all the centers; all the procedures included obturator, external iliac and internal iliac nodes but not clear data are available about presacral, common iliac and presciatic nodes.

Post-operative evaluation

The Clavien-Dindo complications grading system was used to evaluate intra- and perioperative complications. Postoperative follow-up included digital rectal examination (DRE) and serum PSA and was scheduled according to the scheme proposed by EAU PCa guidelines [1]. A telephonic update was realized in September 2014 for all patients. Biochemical recurrence (BCR) was defined as two consecutive PSA values > 0.2 ng/ml.

Overall Survival (OS) was defined as the number of alive patients at last follow-up. Cancer Specific Survival (CSS) was defined as the number of patients alive after excluding deaths for other causes. Disease Free Survival (DFS) was defined as no evidence of BCR at last follow-up.

Urinary incontinence was evaluated in all patients and continence was defined as the use of 0 pads. We didn't evaluate the potency due to the risk characteristics of our population that exclude a nerve sparing approach according to the EAU guidelines; this decision was in 1998 and is still adherent to the guidelines where no specific recommendations for high risk tumor is made [1].

Statistical analysis

Categorical variables are reported as count (percentage), continuous variables are reported as mean (± standard deviation) or median (range), as appropriate.

Kaplan-Meier analyses were used for the estimation of survival curves, considering BCR, cancer-specific and all cause mortality as the events of interest respectively. The log-rank test was used for comparison of survival curves between groups of patients.

Subsequently, univariate and multivariate Cox regression analyses were performed to establish the predictors of outcomes. Covariates were age, preoperative PSA, pathological Gleason score, surgical margins status, the use of lymphadenectomy, pT and pN. Only those predictors which resulted

significant in univariate analysis were introduced in the multivariate model. Thereafter, a backward elimination procedure was used to find the optimal predictive models. This set of analyses was performed for both BCR and cancer-specific mortality. For all the fitted Cox models, the proportional hazard assumption was checked. Hazard ratios (HR), with their 95% confidence intervals (CI), were derived from the Cox models.

P values < 0.05, two sided, were considered statistically significant. All the statistical analyses were performed with SAS statistical software (release 9.4; SAS Institute Inc., Cary, NC).

RESULTS

Patients characteristics, preoperative PSA, clinical stage and bioptic Gleason score are reported in Table 1.

Complications

Table 2 reports all the complications classified according to Clavien Dindo and respective treatments [7].

Overall 180 patients (16.2%) presented a total of 186 complications. Blood transfusions represented the most common postoperative complication, a total of 132 cases (11.8%). Excluding transfusions, number of patients with perioperative complications decreases to 54 patients (4.8%).

The 11 patients presenting symptomatic lymphocele underwent percutaneous drainage.

Ten patients presented urethral stenosis at different point of follow-up; 6 of them underwent adjuvant radiotherapy.

The overall complication rates were similar in patients undergoing e-PLND, st-PLND, and noPLND (15.8% vs.17.2% vs. 16.1. P = 0.412).

Oncological and functional outcomes

Mean follow-up time was 74 ± 50 months.

In Table 2 are reported pathological results after LRP. There were 296 patients (26.6%) with pT2 tumor, 769 (69%) with pT3 tumor including 348 (31.2%) cases of seminal vescicle invasion (pT3b); pT4 stage is reported in 49 cases (4.4%). 118 patients (10.6%) presented positive nodes and 383 (34.4%) positive surgical margins. Most of the tumors (61.6%) resulted with a Gleason score ≤ 7. We obtained an OS at a mean follow-up of 74 months of 96.6% (1076 patients) and a DFS of 66.2% (737 patients).

The mean (SD) overall lymph node yield was 18.5 (5.7).

781 patients (76.4%) underwent ePLND with a node yield of 19.1; 241 patients (23.6%) underwent stPLND with a node yield of 15.6. In Table 2 are shown pathologic data according to standard and extended procedures.

In Table 3 are reported survival results stratified for stage, relaps and adjuvant treatment.

75 patients (6.7%) presented disease persistence after surgery and are now alive and free of disease. Most of these patients (54) had a pT3 tumor; 17 a pT2 and just 4 a pT4. 536 patients (48.1%) had a biochemical recurrence followed by adjuvant therapy; 527 (98.3%) are still alive; 6 (1.1%) died due to the tumor and 3 (0.6%) for other causes. 500 patients (44.9%) didn't receive any adjuvant treatment; most of them had a pT3 tumor (327), 155 had a pT2 and 18 a pT4. 472 (94.4%) are still alive; 14 (2.8%) died due to the tumor and 14 (2.8%) due to other causes. As reported in Table 4 age

(P= 0.0006), pT (P< 0.0001), pN (P= 0.0018) and surgical margins (P= 0.0076) resulted as independent predictors for BR in multivariate analysis.

Figures 1, 2, 3, 4 and 5 show survival curves with Kaplan-Meier model for DFS. Table 5 identifies pN (P=0.0025) and Gs (P= 0.0003) as independent predictors for OS and CSS in a univariate analysis; just the Gs results significant in the multivariate model.

At a mean follow-up of 74 months 911 patients (81.8%) were continent.

Pathological results

In Table 6 are reported clinical stagings and our final pathological results. 237 patients were cT1; 64 (27%) pT2 and 173 (73%) pT3. All the cT4 tumors were confirmed by final pathological examination.

DISCUSSION

Prostate cancer is characterized by heterogeneus presentation, extension and progression. The D'Amico classification allows a risk stratification helping the urologist to suggest the patient the best therapeutic opportunity. However it remains impossible to surely predict the behavior of the disease, its progression, treatment success and the risk of biochemical recurrence [9]. If it's generally not easy to choose the best approach it is even more difficult when we have to face an high risk tumor [10]. The surgical approach remains nowadays a matter of debate; radical prostatectomy plays an important role and it still very controversial if a mininvasive technique should be the standard of care [4, 5, 11].

The safety of the procedure and its feasibility is strongly related to the complications. Gontero et al described radical prostatectomy for high risk patients as an acceptable procedure in terms of morbidity; with increasing in surgery time, transfusion rate, and lymphoceles [12]. Recently Soares et al described a large population of 1138 patients treated with LRP [13]. More than 80% were low-

intermediate risk patients according to D'Amico classification. The overall complication rate was 5.2% (59 patients); which is lower than our 16.2% (180 patients); this group becomes significantly smaller if we exclude patients who needed blood transfusions, remains than 54 patients (4.8%). Encouraging data emerge analyzing grade III complications; the author describes complication rate of 3.3%, higher than our 1.4%. Our results seems encouraging also compared with those presented by Di Benedetto et al: 446 patients with high risk tumor undergoing LRP; the author describes an overall complication rate of 7.6% and a grade III rate of 6.5% [14].

Certainly we report a significant transfusion rate (11%); however this value is not so far from many results described in literature for LRP: Artibani et al describe a TR of 11% in a series of 71 patients, in a series of 219 patients the TR for Rassweiler et al is 9.6% and 9.8 % for Rozet et al after 133 LRP [15,16,17].

We can assume thatcomplications are relatively rare and most of them are not severe and also easy to treat.

The mean (SD) overall lymph node yield was 18.5 (5.7) which is comparable to data described in literature for open and robotic surgery [18].

781 patients (76.4%) underwent ePLND with a node yield of 19.1; 241 patients (23.6%) underwent stPLND with a node yield of 15.6. In Table 2 are shown pathologic data according to standard and extended procedures.

Our results are encouraging about the node yield if compared to literature; for an adeguate detection is described as necessary a node yield of at least 13 nodes removed during PLND of high risk PCa patients for robotic surgery by Sagalovich et al [19] and for retropubic prostatectomy by Briganti et al [20].

We obtained an overall survival of 96.6% (1076) and a disease free survival of 66.2% (737 patients) at a mean follow up of 74 ± 50 months which is acceptable if compared with results by Rassweiler et al. that described an OS of 94.9 % and a DFS fo 78.2 % in patients laparoscopically treated with organ confined tumors. Our OS and DFS are also comparable with those recently described by Borjian et al. [21] and Di Benedetto et al [14] for patients with high risk tumors treated with open and laparoscopic approach respectively. The last author presents a population of 446 patients and find out that the minimally invasive approach doesn't hide worse oncological and functional outcome if compared with an open approach. Probably the most important comparison should be made against radiotherapy that is described by randomized studies as the best approach for these tumors; our results are encouraging and seem comparable to the serie presented by Bolla et al. of RT and 3 years of androgen deprivation therapy [22]. Table 3 shows how an adjuvant therapy plays a positive role in survival rate in proportion to the higher T stage. The disease persistence occurred in 75 patients after surgery; they all received an adjuvant treatment and 74 of them were alive with no BR at the follow up. 500 patients didn't receive any adjuvant therapy after surgery; 438 of them result alive and free of disease at the follow up. We think our data we describe an encouraging outcome for patients recieveing adjuvant therapy; however it's not easy to state the best timing like Zwergel et al try to do; they describe a 5 year PSA progression-free survival rate of 76% in patients with immediate hormonal treatment an of 53% in patients with surveillance and delayed hormonal therapy [23].

Our uni- and multivariate analysis show that pT and pN are directly proportional to the probability of BR. Positive surgical margins are also a positive predictor for BR. The age at the surgery is inversely proportional; younger patients are more likely to present BR after surgery. These correlations are well described in Kaplan-Mayer courves. On the contrary, in Zwergel's analysis none of the investigated parameters was demonstrated to be of independent prognostic significance for tumor-specific survival but in an importantly smaller population. The data regarding pN confirms the importance of lymphadenectomy in these patients as described by Briganti et al. developing the well known

nomogram and by Bader who analyzed the survival of patients with positive nodes [24,25]. Our data seems in line with the growing evidence that ePLND plays not only a prognostic role but also a therapeutic one in high risk patients, there is now level 1 evidence as reported in literature [26].

Just pN and pGS resulted as predictors for overall- and cancer specific survival; they are obviously inversely proportional.

The comparison of clinical and pathological stage brought interesting results. We reported a clinical understaging in about 30% of cT2 and in 100% of cT1. That means that patients clinically considered as low or intermediate risk could reveal an high risk tumor, it plays a foundamental role in defining the disease and approach it with the best treatment.

CONCLUSIONS

Our work brings encouraging data about the oncological and functional safety of laparoscopic radical prostatectomy even in high-risk patients. We believe that radical prostatectomy represents an effective treatment for patients with high risk prostate cancer and that laparoscopy is a safe approach offering a mini-invasive alternative to open surgery. It permits also to a better identification and characterization of the disease leading to a more accurate evaluation of the prognosis and planning of the follow-up. We therefore propose a more comprehensive use of this technology in all patients who are candidates for surgery.

Author Disclosure Statement

All the authors of the manuscript disclose any commercial associations that might create a conflict of interest in connection with the submitted manuscript.

No competing financial interests exist

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Figure 1: pathological T

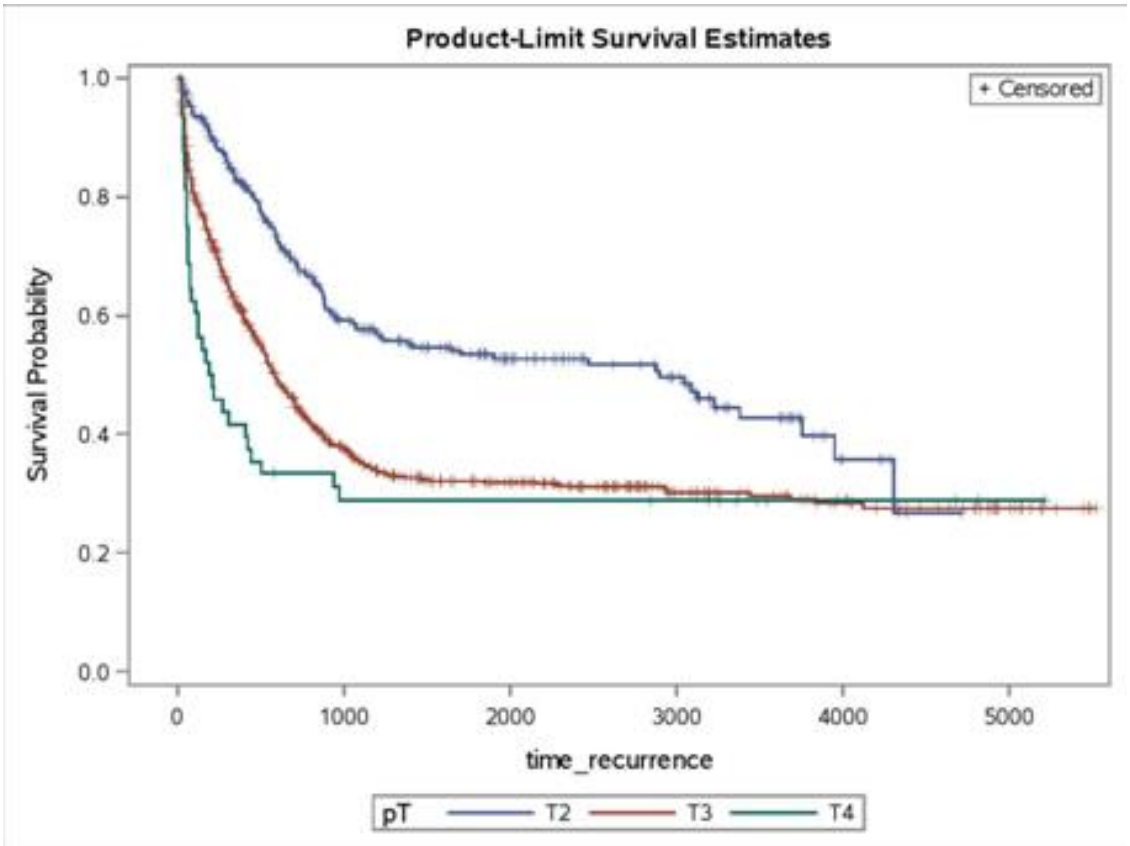


Figure 2: pathological N

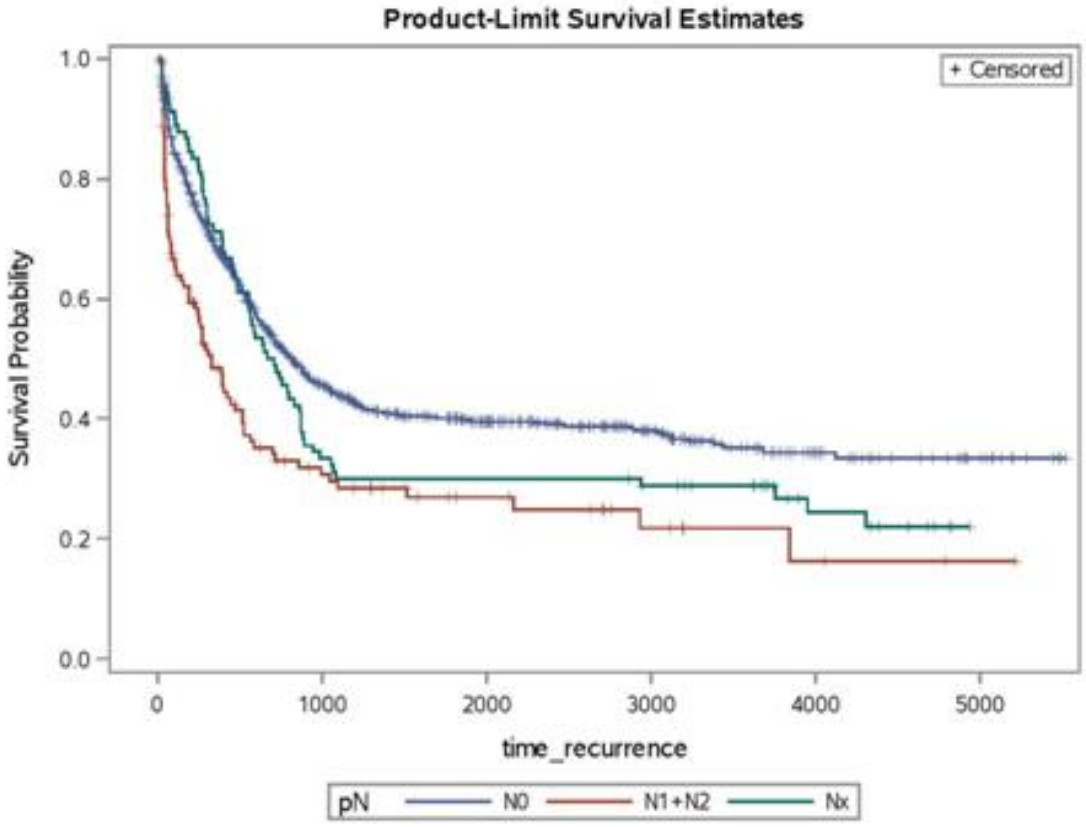


Figure 3: pathological Gleason Score

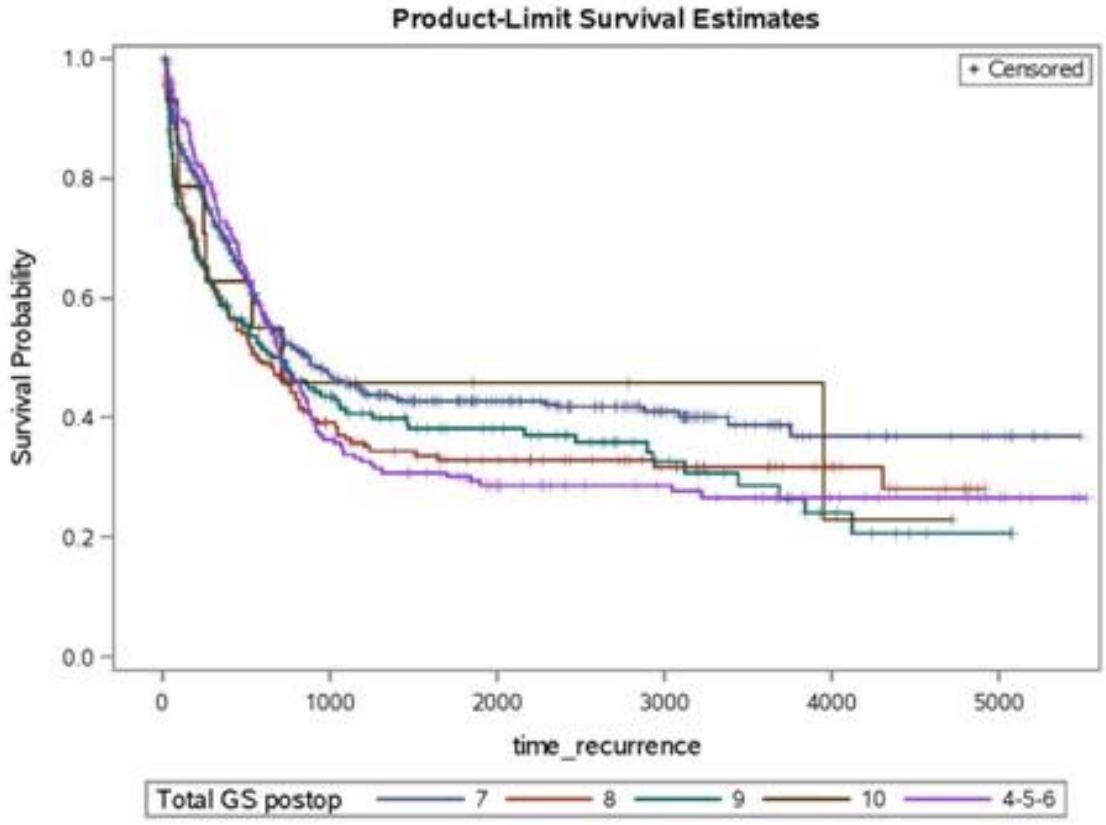


Figure 4: surgical margins

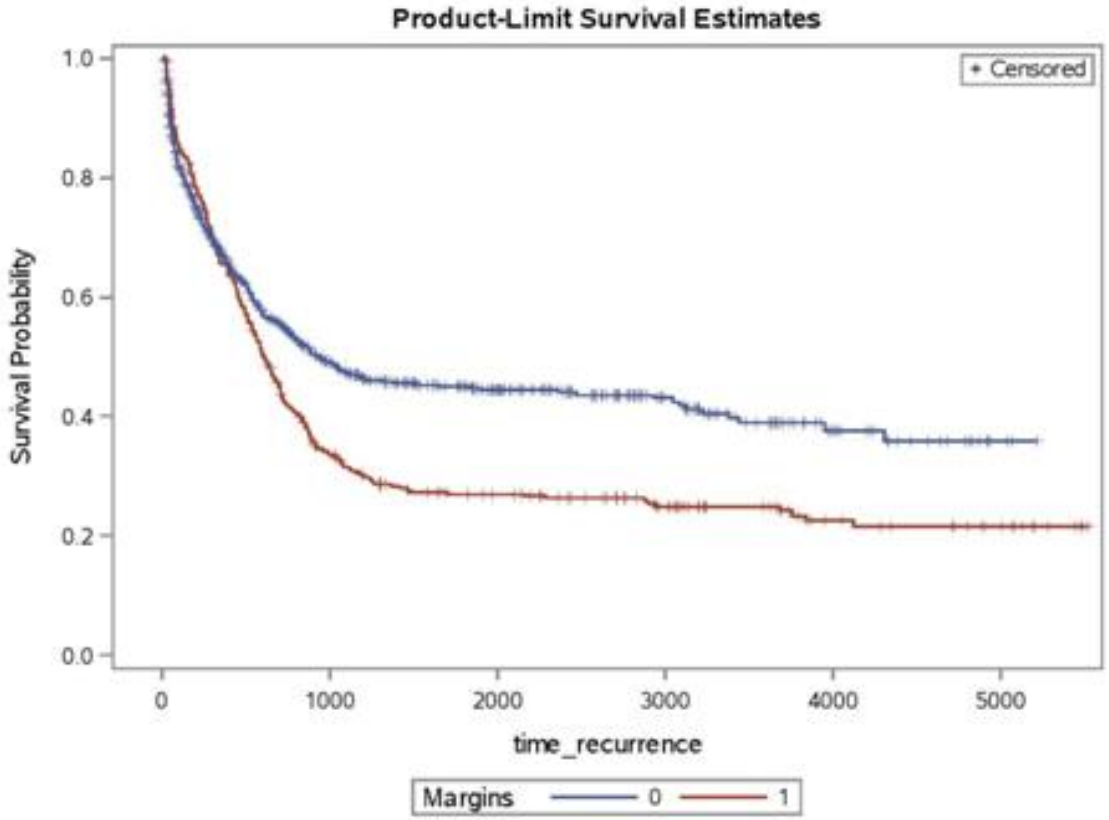
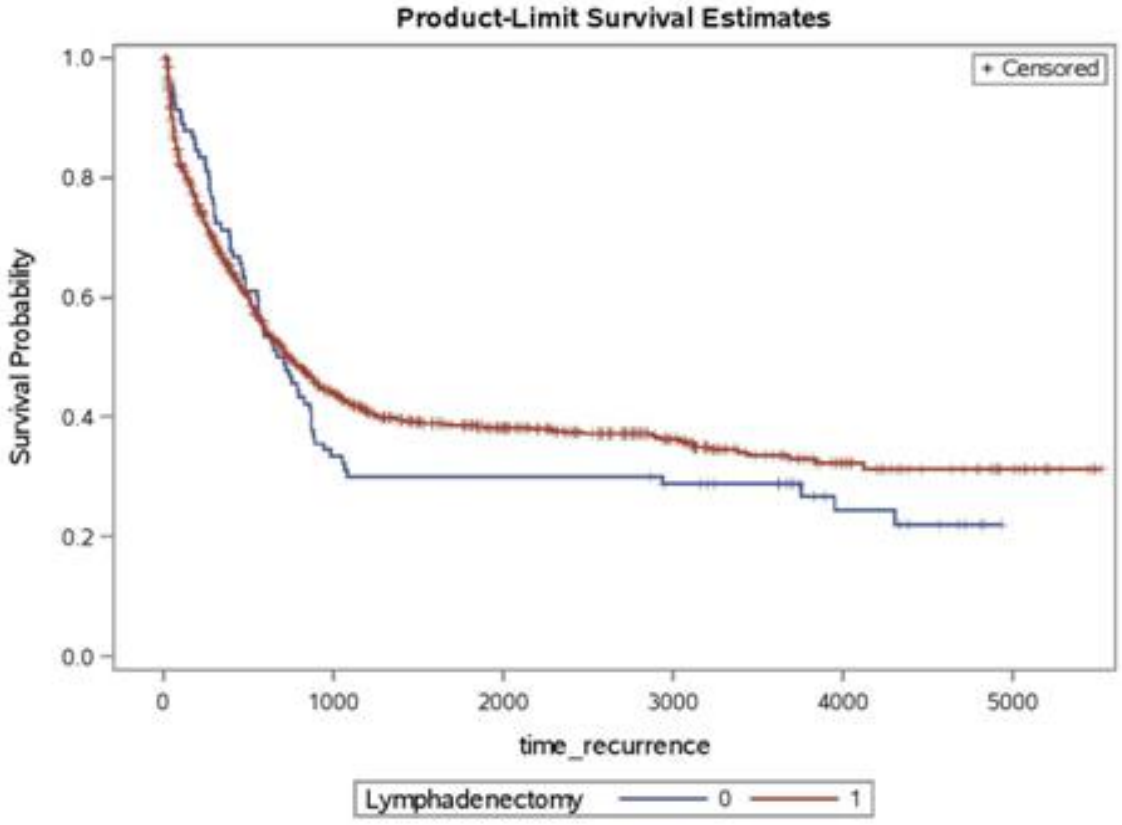


Figure 5: lymphadenectomy



TABLES

Table 1: preoperative characteristics

General preoperative characteristics	
Total population	1114
Mean Age (± SD; range)	62.0 ± 8 (32 – 79)
PSA	
≥ 100	13 (1.2%)
50 – 99.9	64 (5.8 %)
20 – 49.9	299 (26.8 %)
10 – 19.9	280 (25.1 %)
< 10	458 (41.1 %)
cT	
cT1b	2 (0.2 %)
cT1c	235 (21.2 %)
cT2a	101 (9.1 %)
cT2b	15 (1.3 %)
cT2c	218 (19.7 %)
cT3a	294 (26.5 %)
cT3b	196 (17.7 %)
T4	48 (4.3 %)
Gleason Score	
10	23 (2.2 %)
9	99 (9.3 %)
8	304 (28.7 %)
7	371 (34.9 %)
≤ 6	264 (24.9 %)

Table 2: postoperative data

Post-operative data		
pT		
· pT2a	21 (1.9%)	
· pT2b	11 (1.0%)	
· pT2c	264 (23.7%)	
· pT3a	421 (37.8%)	
· pT3b	348 (31.2%)	
· pT4	49 (4.4%)	
pN		
· pNx	92 (8.3%)	
· pN0	904 (81.1%)	
· pN1	115 (10.3%)	
· pN2	3 (0.3%)	
pGS		
· 10	14 (1.3%)	
· 9	199 (17.9%)	
· 8	214 (19.2%)	
· 7	504 (45.2%)	
· ≤ 6	183 (16.4%)	
Surgicalmargins		
· Positive	383 (34.4%)	
· Negative	731 (65.6%)	
Continence at last follow-up		
Continent patients	911 (81.8%)	
Incontinent patients	203 (18.2%)	
Follow-up		
Follow-up (mean ± SD)	74 ± 50 months	
Cancer related deaths	21 (1.9%)	
Other causes deaths	17 (1.5%)	
Alive with disease	339 (30.4%)	
Alivewithout disease	737 (66.2%)	
Grade	**Complications (treatment)**	**N° of patients**
I	Anastomotic dehiscence (prolonged catheterisation) Obturator nerve lesion (rehabilitation) Haemorrhage, haematoma (no transfusion)	14 (1.3%) 1 (0.1%) 8 (0.7%)

		Tot. = 23 (2.1%)
II	Urinary tract infections; septicemia (antibiotics) Haemorrhage (transfusions) Rectal lesion (medical therapy and NGT) Paralytic ileus (medical therapy and NGT) Ileallesion (medical therapy and NGT)	3 (0.3%) 132 (11.8%) 5 (0.4%) 4 (0.4%) 1 (0.1%) Tot. = 145 (13.0%)
III **IIIa** **IIIb**	 Lymphocele, lymphorrhea (percutaneous drainage) Rectal lesion (colostomy and recanalisation) Rectal-bladder/urethral fistula (surgery) Bladder-cutaneous fistula (surgery)	 11 (1.0%) 1 (0.1%) 3 (0.3%) 1 (0.1%) Tot. = 16 (1.4%)
IV **IVa** **IVb**	 Transient ischemic attack Iliac vein lesion	 1 (0.1%) 1 (0.1%) Tot. = 2 (0.2%)
V		0

Pathologic data for stPLND and ePLND

	ePLND	**stPLND**
N0	699 (89.5%)	217 (90%)
N1	80 (10.2%)	23 (9.5%)
N2	2 (0.3%)	1 (0.4%)
Tot.	781	241

Table 3: survival data

pT *	Relapse *	Adjuvant therapy*	Follow-up *
pT2 (296)			
	Relapse (126) (42.6%)	No adjuvant therapy (2) (1.6%)	Alive with disease (2) (100%)
		Adjuvant therapy (124) (98.4%)	Cancer deaths (2) (1.6%)
			Alive with disease (38) (30.7%)
			Alive without disease (84) (67.7%)
	No relapse **(170) (57.4%)	No adjuvant therapy (153) (90.0%)	Other causes deaths (3) (2.0%)
			Alive without disease (150) (98.0%)
		Adjuvant therapy (17) (10.0%)	Alive without disease (17) (100%)
pT3 (766)			
	Relapse (438) (57.2%)	No adjuvant therapy (53) (12.1%)	Cancer deaths (10) (18.9%)
			Other causes deaths (1) (1.9%)
			Alive with disease (32) (60.3%)
			Alive without disease (10) (18.9%)
		Adjuvant therapy (385) (87.9%)	Cancer deaths (4) (1.0%)
			Other causes deaths (3) (0.8%)
			Alive with disease (237) (61.6%)
			Alive without disease (141) (36.6%)
	No relapse ** (328) (42.8%)	No adjuvant therapy (274) (83.5%)	Cancer deaths (3) (1.1%)
			Other causes deaths (10) (3.6%)

			Alive without disease (261) (95.3%)
		Adjuvant therapy (54) (16.5%)	Alive with disease (1) (1.9%)
			Alive without disease (53) (98.1%)
pT4 (49)			
	Relapse (27) (55.1%)	No adjuvant therapy (0)	
		Adjuvant therapy (27) (100%)	Alive with disease (22) (81.5%)
			Alive without disease (5) (18.5%)
	No relapse ** (22) (44.9%)	No adjuvant therapy (18) (81.8%)	Cancer deaths (1) (5.6%)
			Alive without disease (17) (94.4%)
		Adjuvant therapy (4) (18.2%)	Alive without disease (4) (100%)

* (n° pz)

** Patients with biochemical recurrence and patients with persistent d[i][e]sease after surgery

Table 4: predictors for BR

Univariate analysis			Multivariate analysis		
Age at prostatectomy	HR (CI 95%) 0.98 (0.97 – 0.99)	< .0001	**Age at Prostatectomy**	HR (CI 95%) 0.98 (0.97 – 0.99)	0.0005
pT	HR (CI 95%)	< .0001	**pT**	HR (CI 95%)	< .0001
T2*	1		T2*	1	
T3	1.8 (1.5 – 2.3)		T3	1.7 (1.4 – 2.1)	
T4	2.4 (1.6 – 3.4)		T4	2.2 (1.5 – 3.2)	
pN	HR (CI 95%)	< .0001	**pN**	HR (CI 95%)	0.0011
N0*	1		N0*	1	
N1 + N2	1.7 (1.4 – 2.2)		N1 + N2	1.6 (1.2 – 2.0)	
Nx	1.2 (0.9 – 1.5)		Nx	1.2 (0.9 – 1.5)	
Surgical margins	HR (CI 95%)	< .0001	**Surgical margins**	HR (CI 95%)	0.0083
Negative*	1		Negative*	1	
Positive	1.4 (1.2 – 1.6)		Positive	1.2 (1.1 – 1.5)	
pGS	HR (CI 95%)	0.0465			
7*	1				
≤ 6	1.2 (1.0 – 1.5)				
8	1.3 (1.1 – 1.6)				
9	1.3 (1.0 – 1.6)				
10	1.1 (0.5 – 2.1)				
Lymphadenectomy	HR (CI 95%) 0.9 (0.7 – 1.2)	0.4061			
PSA pre	HR (CI 95%) 1.004 (1.000 – 1.007)	0.0230			

*Reference category

Table 5: predictors for OS and CSS

Univariate analysis		
pT	HR (CI 95%)	0.4836
T2*	1	
T3	2.5 (0.7 – 15.7)	
T4	2.4 (0.3 – 20.6)	
pN	HR (CI 95%)	0.0025
N0*	1	
N1 + N2	5.6 (1.9 – 14.5)	
Nx	1.2 (0.3 – 3.9)	
§pGS	HR (CI 95%)	0.0003
≤ 6*	1	
7	2.0 (0.3 – 40.8)	
8	9.0 (1.4 – 172.9)	
9	22.5 (4.3 – 411.4)	
10	26.3 (1.0 – 668.4)	
Surgical margins	HR (CI 95%)	0.7715
Negative*	1	
Positive	0.9 (0.4 – 2.1)	
PSA pre	HR (CI 95%)	0.3764
	0.99 (0.95 – 1.01)	

*Reference category

§pGS was the only variable that maintained statistical significance at multivariate analysis.

Table 6: conrespondance between clinical and pathological stage

Clinical stage	Pathological stage
cT1 (237)	pT2 (64); pT3 (173)
· cT1b (2)	· pT3a (1); pT3b (1)
· cT1c (235)	· pT2a (10); pT2b (5); pT2c (49); pT3a (97); pT3b (74)
cT2 (334)	pT2 (227); pT3 (107)
· cT2a (101)	· pT2a (9); pT2b (1); pT2c (20); pT3a (38); pT3b (33)
· cT2b (15)	· pT2b (4); pT2c (2); pT3a (3); pT3b (6)
· cT2c (218)	· pT2a (1); pT2b (1); pT2c (189); pT3a (14); pT3b (13)
cT3 (490)	pT2 (5); pT3 (484); pT4 (1)
· cT3a (294)	· pT2a (1); pT2c (4); pT3a (263); pT3b (25); pT4 (1)
· cT3b (196)	· pT3a (1); pT3b (195)
cT4 (48)	pT4 (48)