Transparency of Positive Surgical Margins after Radical Prostatectomy in the Benelux

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Abstract

Objective: The oncologic outcome after radical prostatectomy is negatively influenced by Positive Surgical Margins (PSM), as it increases the risk of disease recurrence. Analysis of the incidence of PSM could contribute in improving the surgical treatment of prostate cancer. To stimulate more transparency in this topic, we studied our own population.

Materials and Methods: 355 EERPE (Endoscopic Extraperitoneal Radical Prostatectomy) patients from a single-surgeon database were gathered in the period of 2006-2014 and analyzed retrospectively. Outcome was measured postoperatively in pathologically confirmed PSM. A chi-square test was performed to objectify the relation between PSM and tumor stage and nerve sparing procedures. A literature study was performed to evaluate numbers of other urologic departments in Belgium and the Netherlands.

Results: 36.6% of all EERPEs resulted in PSM, 23.3% of the pT2 tumors and 63.0% of the pT3 tumors. Advanced tumor stage was found to be a significant risk factor for PSM. Our results are consistent with the few results available in literature.

Conclusion: Our numbers prove the relation between PSM and tumor stage. At the moment, existing data in the Belgium and the Netherlands are insufficient for critical evaluation of the oncologic outcome of radical prostatectomy. In order to assess and improve the surgical treatment of prostate cancer, more transparency regarding PSM is necessary.

Keywords: Radical prostatectomy; Oncologic outcome; Positive surgical margin; Prostate cancer; Netherlands; Belgium

Radical Prostatectomy; rT: Radiological Tumor Stage; TNM: TNM Classification of Malignant Tumors; Metric units were used for the measurements of length, height, weight and volume.

Introduction

Positive Surgical Margins (PSM) in Radical Prostatectomy (RP) are considered an adverse pathologic feature [1-4]; however, their association with clinical progression and biochemical recurrence remains controversial [5,6]. Attention to surgical detail and precise preoperative tumor staging is essential to minimize the risk of PSM and thus minimize the potential risk of disease recurrence [6-8]. The likelihood of PSM is strongly influenced by the surgeon's experience irrespective of the surgical approach. Numbers of PSM range from 16-63% in the available literature in the Benelux, and PSM-rate is higher in men with a more advanced pathologic tumor stage. These numbers show that there is still room for improvement [9-15].

Beside numeric requirements (e.g. high volume surgeons), transparency of surgical margins can aid to interpret and improve the quality of care. Critical evaluation of the pathological outcome could provide new insights in the surgical treatment of prostate cancer and publication of the PSM-rate per surgeon and per center can be a first step. Permanent quality analysis, certainly during the learning curve, might help to improve surgical strategy and skills for each surgeon [16]. The aim of this study is to stimulate more transparency regarding this subject, starting with presenting our own series.

Patients and Methods

In the period from 2006 until 2014, 385 Endoscopic Extraperitoneal Radical Prostatectomy (EERPE) were performed in our department (2006-2008 in Bernhoven hospital and 2008-2014 in Máxima Medical Center). All patients, eligible for radical prostatectomy, were included and underwent an EERPE as described by Stolzenburg's [17], combined with lymph node dissection in all intermediate and high risk patients according to the d'Amico classification. Eligibility criteria were: male patients with life expectancy of at least 10 years, with local or locally advanced prostate cancer and eligible for curative treatment,

Abbreviations

cT: Clinical Tumor Stage; EERPE: Endoscopic Extraperitoneal Radical Prostatectomy; HiFu: High-Intensity Focused Ultrasound; IKNL: Integral Cancer Centre of the Netherlands; LPLND: Laparoscopic Pelvic Lymph Node Dissection; LRP: Laparoscopic Radical Prostatectomy; MMC: Máxima Medical Centre; MRI: Magnetic Resonance Imaging; NS: Nerve Sparing; NVU: Dutch Association of Urology; OR: Operating Room; PSA: Prostate Specific Antigen; PSM: Positive Surgical Margin; pT: Pathological Tumor Stage; RALP: Robot Assisted Laparoscopic Prostatectomy; RP: Radical Prostatectomy; RRP: Retropubic

Figure 1: Evolution of the surgical margins in EERPE in respect to the learning curve of a single surgeon (LF) over the period 2006-2014. % of the PSM rates over the time are illustrated in the columns

without contra-indication for surgery. In this period, eighteen EERPE procedures were performed by a second urologist. These patients were excluded from this study to avoid bias of intersurgical experience, creating a single surgeon database. For each patient, the pathological examination of the tumor was reviewed. Patients with a pathological T2 or T3 stage prostate adenocarcinoma were included in our series. All other pathological tumor stages were excluded ($n = 12$).

Patient characteristics such as age, Gleason score, Prostate Specific Antigen (PSA), OR-time, tumor stage, risk classification, estimated blood loss, the surgical technique (nerve sparing or not), number treated per year, pathology reports, and peri- and postoperative data were gathered prospectively since 2006. The patients were analyzed retrospectively. Outcome was measured in the presence or absence of PSM, which was stated in the pathology report. For this study, patients were followed from the day of surgery to hospital discharge. No analyses regarding survival or prognostic value of PSM were included in this study.

We converted the patient data to an anonymous SPSS database for sufficient analysis. Descriptive statistics were used in order to interpret the patient characteristics pre-, peri and postoperatively in the total population, the patient group with PSM and the patient group without PSM. Differences between the PSM group and the non-PSM group were calculated using the Chi-square test for the categorical variables, the independent T test for continuous variables and the Mann-Whitney test was used to calculate differences in Gleason score. We calculated risk factors for PSM with an odds ratio using logistic regression.

To compare our results to other series in the Benelux, a PubMed and Cochrane search was performed using the items: radical prostatectomy, LRP (Laparoscopic RP), EERPE, RALP (Robot Assisted Laparoscopic Prostatectomy), oncologic outcome, positive surgical margin, PSM, urology, prostate cancer, the Netherlands, and Belgium.

Results

From 2006-2014, we totally included 355 patients which underwent an EERPE. Pre-, peri, and postoperative patient characteristics are illustrated in table 1. The median age of the

patients was 65 years at the time of operation. Pre-operative Gleason scores according to the TNM classification of 2002 ranged from 4-10 with a median of 6. The mean pre-operative PSA was 11.9 ug/ L and varied between 0.87 and 77 ug/ L with a median of 8.75. Patients with PSM had a significantly higher median PSA at baseline ($p = 0.012$). According to the d'Amico classification, 93 patients met the low risk criteria (26.2%), 113 patients had an intermediate risk (31.8%) and 149 patients were consistent with the high risk criteria (42.0%). The d'Amico risk was significantly different in patients with and without PSM ($p = 0.003$). Pre-operative clinical staging by urologist and radiologist resulted in 151 cT1c tumors (42.5%), 80 patients with a cT2a-2b tumor (22.5%) and 124 patients with a cT2c-3 tumor (34.9%). 12 patients were diagnosed with an rT3-stage tumor; in these patients the MRI showed extra capsular disease pre-operative (3.4%). Of these 12 patients, 58.3% were confirmed as a pathological T3 stadium ($n = 7$). In the other 5 patients, extra capsular extension was not pathologically confirmed.

Perioperative, 82 patients underwent bilateral nerve sparing NS technique and in 69 patients unilateral NS was performed. Laparoscopic Pelvic Lymph Node Dissection (LPLND) was performed in 226 patients (63.7%). The median estimated blood loss was 400cc and ranged from 10 –4000cc with an outlier of 6600cc. This patient encountered a rectal injury and severe bleeding perioperative. The OR took on average 210 minutes, ranging from 103 – 430 minutes with a median of 200 minutes, depending on performance of LPLND (median 160 min for EERPE only and 220 min for EERPE + LPLND). When performing lymph node dissection, the OR time was increased significantly ($p < 0.001$). After 4.6 days on average, with a median of 3 days, patients were fit to leave the hospital. Hospital stay ranged from 1-30 days with an outlier of 56 days. This patient suffered from severe comorbidities. His recovery was complicated by a postoperatively diagnosed rectal injury with sepsis, which was treated with relaparotomy twice and colostoma.

Pathology report showed 236 patients with a pT2-tumor and 119 patients with a pT3-tumor. The PSM-rate for the whole cohort was 36.6 %. Patients who underwent bilateral NS surgery had 34.6 % chance of PSM and those with unilateral NS surgery had 30.4 % of PSM. Patients with pT2-stage tumor had 23.3 % PSM and patients with pT3-stage tumor 63.0 % PSM. The results are displayed in table 2.

Table 2 gives insight into the PSM rates of the patients treated in the Bernhoven and MMC hospital from 2006 until 2014. The total PSM scores have been improving moderately over the years, which indicate a reasonable learning curve of the surgeon. However, comparing the PSM-rates of the two stages (pT2 and pT3) separately, an evident learning curve could be identified. The PSM rates in the pT2-tumors have improved from 33.3% in 2006 to 15.4% in 2014. Also the PSM-rates in the pT3-tumor have decreased from 71.4% in 2006 to 63.0% in 2014. Tumor stage is a proven risk factor for PSM and the ratio pT3:pT2 has increased over the years, which affects the total scores negatively. Therefore, the total scores only are not suitable to judge the presence of a learning curve in our series, which is clearly there.

Table 1: Patient Characteristics (pre-operative, perioperative, post-operative).

Patient Characteristics	Total (n = 355)	PSM+ (n = 130)	PSM- (n = 225)	p-value
Pre-operative	Median (range)	Median (range)	Median (range)	
Age (yrs)	65 (44-76)	66 (49-76)	64 (44-75)	0.063
Gleason score	6 (4-10)	6 (4-10)	6 (4-10)	0.363
PSA (ug/L)	8.75 (0.87-77)	9.5 (2-77)	8.3 (0.9-71)	0.012
d'Amico risk	N (%)	N (%)	N (%)	0.003
Low	93 (26.2)	26 (20)	67 (29.8)	
Intermediate	113 (31.8)	34 (26.2)	79 (35.1)	
High	149 (42.0)	70 (53.8)	79 (35.1)	
Perioperative	Median (range)	Median (range)	Median (range)	
Estimated blood loss (cc)	400 (10-6600)	400 (10-4000)	350 (20-6600)	0.586
Overall OR time (min)	200 (103-430)	212 (105-430)	197 (103-400)	0.279
OR time (min) No LPLND	160 (103-364)	164 (105-364)	159 (103-318)	
OR time (min) LPLND	220 (130-430)	220 (142-430)	220 (130-400)	
Nerve sparing procedure	N (%)	N (%)	N (%)	0.334
Unilateral	69 (19.4)	21 (16.2)	48 (21.3)	
Bilateral	82 (23.1)	28 (21.5)	54 (24.0)	
Total	151 (42.5)	49 (37.7)	102 (45.3)	
LPLND	226 (63.7)	88 (67.7)	138 (61.3)	0.231
Postoperative p-stage				< 0.0001
pT2	236 (66.5)	55 (42.3)	181 (80.4)	
pT3	119 (33.5)	75 (57.7)	44 (19.6)	
Total	355 (100)	130 (36.6)	225 (63.4)	

Table 2: Data of positive surgical margins (PSM) in EERPEs, performed by single surgeon (LF) over the period 2006 – 2014, MMC data.

Year	Total		NS unilateral		NS bilateral		pT2		pT3	
	N	PSM %	N	PSM %	N	PSM %	N	PSM %	N	PSM %
2006*	23	43.5	7	42.9	3	33.3	16	31.3	7	71.4
2007*	38	31.6	14	21.4	7	28.6	30	26.7	8	50.0
2008	41	41.5	8	62.5	8	37.5	26	26.9	15	66.7
2009	45	22.2	9	22.2	7	28.6	33	18.2	12	33.3
2010	40	37.5	9	22.2	9	22.2	26	19.2	14	71.4
2011	39	41.0	7	14.3	7	42.9	25	20.0	14	78.6
2012	33	39.4	1	100.0	6	50.0	18	22.2	15	60.0
2013	49	40.8	4	50.0	19	42.1	36	30.6	13	69.2
2014	47	36.2	10	20.0	16	25.0	26	15.4	21	61.9
Total	355	36.6	69	30.4	82	34.6	236	23.3	119	63.0

*Procedures performed in Bernhoven hospital by the same surgeon from 2006-2008

The results of the logistic regression analysis showed that the only significant variable related to a higher PSM rate was pT3 tumor stage (OR 5.35, 95% CI 3.18-8.98). Increasing PSA, a high risk according to d'Amico and nerve sparing procedures (both unilateral and bilateral) were not significantly related to postoperative PSM (table 3).

PSM Rates in Literature

We found eight publications from Belgian or Dutch centers on PSM after radical prostatectomy on PubMed. We compared the

type of surgery and the numbers performed. Data from all surgical techniques are available: open retropubic RP, laparoscopic RP, endoscopic extraperitoneal RP and robot assisted laparoscopic RP. Numbers treated by RP vary from 51-497 per center. The total PSM-rate is available for all studies and varies from 16-53.2 %. The study of Van Poppel, et al. [13] was excluded from this variation looking at the total PSM-rate because this study only included pT3-tumors. Data for the pT2-stage show a variation in PSM from 2.5-40.3 % and for the pT3-stage from 34.5-77.8 %. (Table 4).

Table 3: Logistic regression of PSM in the MMC series.

Risk factor	OR	95% CI	p-value
PSA	1.017	0.99-1.04	0.160
High risk d'Amico	1.652	0.91-3.02	0.102
Nerve sparing procedure	1.722	0.94-3.15	0.077
pT3 tumor stage	5.345	3.18-8.98	< 0.0001

Table 4: Summary of publications of PSM in radical prostatectomy in the Benelux.

References	Origin	Type	N	PSM rate %		
				Total	pT2	pT3
Mottrie, et al. [9]	Belgium	RALP	184	16	2.5	38
Klaver et al. [10]	Netherlands	RALP	400	19.2	13.4	34.5
Santeon 1. [11]	Netherlands	LRP	94	53.2	40.3	72.2
Santeon 2 [11]	Netherlands	RALP	497	40.6	30.3	57.8
Santeon 3 [11]	Netherlands	LRP	378	35.2	26.7	69.9
Roumeguere, et al. [12]	Belgium	RRP	77	40	7.3*	77.8
Roumeguere, et al. [12]	Belgium	LRP	230	26	7.8*	52.9
Joniau, Van Poppel, et al. [13]	Multi - Belgium	RRP	51	62.7	0	62.7
Wijerman, et al. [14]	Netherlands	LRP/EERPE	243	49.4	-	-
NVU* [15] *incomplete database with selection bias	Netherlands	LRP	629	40.2	27.3	61.3
		RRP	237	25.3	13.5	52.2
		RALP	3276	30.3	21.7	52.6
Fossion, et al. [22] *current series	Netherlands	EERPE	355	36.6	23.3	63.0

Data marked with '-' are unknown. RALP: Robot Assisted Laparoscopic Prostatectomy, RRP: Retropubic Radical Prostatectomy, LRP: Laparoscopic Radical Prostatectomy, EERPE: Endoscopic Extraperitoneal Radical Prostatectomy
* These numbers are including pT1 tumors.

We included data of the national database of the Dutch Association of Urology (NVU) [15] which have been published in 2014. These data show a large variation in PSM between the different surgical approaches. Total PSM-rate was 40.2 % for the laparoscopic approach, 30.3 % for the robot assisted approach and 25.3 % for open surgery. These data have been gathered since 2006, first on voluntary base and since 2013 the registration is obligatory. In 2014, 4142 RP procedures have been collected in total and were analyzed over a period of eight years.

Discussion

Our findings concerning the influence of higher tumor stage on the incidence of PSM are consistent with results in literature. The results show that outcome is surgeon specific and tumor stage is a proven risk factor for the incidence of PSM. This is not surprising due to the anatomic location of the prostate; it has expanded surrounding structures (rectum, bladder, sphincter, and symphysis) [2,4]. Radical removal of an invasive tumor in the bladder neck or surrounding muscles (pT3) is more complicated than a tumor which is restricted to the prostate only (pT2) [3]. Though nerve sparing procedures could hypothetically complicate malignancy free margins, we did not find any relation with increasing PSM in this group. Our PSM rates are comparable with other centers in literature and with other centers in the Benelux [9-15].

Publications on PSM

When analyzing the rates of other centers, we should remark that the PSM rate in Belgium is extremely low and comparable with the best centers in the world (Urology Department in Hamburg [18], Memorial Sloan-Kettering Cancer Center) [19]. Especially the PSM rate of pT3 tumors were very low looking at our own rate. It would be interesting to do more research on this remarkable difference between Belgium and the Netherlands and to find out what is the key to this success. Although, a limitation of two Belgian publications is the patient selection of PSM transparency for only pT2 or pT3 tumors, the inclusion of pT1 tumors and the relatively small study population. This makes these studies not ideal for comparison [12,13].

Secondly, we should realize several shortcomings from the Dutch national database [15]. First of all this database has been started in 2006, but is only mandatory from 2013 on. It is clear that several centers have omitted/forgotten to include their data in the database before 2013. We know that annually about 12.000 men are diagnosed with prostate cancer in the Netherlands. From the IKNL-data (Deelrapportage voor prostaatkanker- Januari 2014[®] IKNL [20]) we know that about 20% of these patients underwent a RP; this means annually about 2400 patients. In 2014, 4142 RP procedures have been collected and analyzed over

a period of eight years. This means that the data, published in 2014, do not represent the quality of RP in the Netherlands, but are only a reflection of the poor participation in quality analysis (4.142 out of +/- 19.200 RP performed over 8 years) when physicians are not obliged to participate in a national database.

Another remarkable finding is the proportion of RALP-data. These are overwhelming in comparison to the other surgical techniques (open RP and EERPE). However, from literature we understand that PSM outcome is similar, regardless the approach which was used [21]. One should admit that at least the robotic surgeons are more willing to show their data than others [9-11,15].

And a last important remark regarding the interpretation of these data concerns the lack of information on the inclusion criteria for the different techniques. One can imagine the influence of an investment in e.g. a robotic system on the choice for operative approach in comparison to other treatment options as active surveillance, HiFU, brachytherapy and external radiotherapy with curative intention. This phenomenon has two consequences: one is the accelerating effect on the learning curve and thus the surgeon's experience and the other is the positive effect of the lower PSM-rate in small lower stage tumors on the number of PSM.

Interpretation of urologic data

Data analysis helps to understand and compare outcome with other surgeons and centers. Since 2013 data on RP are gathered by the national urology associations in both the Netherlands and Belgium. Still those data are not available for both patients and insurance companies. One can understand that the latter groups need adequate help for careful and correct interpretation of these data. This can become the task for the experts of the national urology association itself. An annual quality report on RP, together with an explanation for those data (inclusion criteria and effect of these criteria on the PSM rate), which are hard to interpret for laymen, would help to improve patients quality of care. In the meanwhile, insurance companies have already accessed these data, judging medical centers and surgeons on their performance. These companies decide whether these urology departments are competent enough to perform RP surgery, although they interpret these numbers without any medical background and without the knowledge of the inclusion criteria. One can conclude that the content of national databases and their publications on outcome is very fragile information.

Still there is one major bias in gathering these data: it is the person or organization which collects the data. And this is also the shortcoming of our study. Impartiality and capability should always be insured, and this is nowadays not the case. One should realize that all reports (e.g. pathology, operation, complications...) should be standardized and according the same grading systems (e.g. ASA-classification, TNM-classification, Clavien - Dindo classification...) to make a comparison fair and possible. A crucial role can be played by the national cancer registry (IKNL in the Netherlands and National Kanker Register in Belgium) to collect these data in a uniform template and insure impartiality.

A single surgeon study is a good way to analyze a learning curve and individual progression. It shows that achieving radical prostatectomy with no PSM, is an accomplishment that can be taught. However, the limitation of this study design is that it contains results of one urologist only and is therefore less applicable to others. We tried to compensate for this fact by including other publications on PSM of other urologists or centers. Another possible limitation is confounding, because we only analyzed urologic variables (such as d'Amico risk and pathological tumor stage) regarding PSM, and did not take ASA-score or perioperative complications into account. These factors might have influenced the ability of extensive procedure and therefore PSM.

Several patient characteristics can influence peri- and postoperative outcome, both for oncologic and functional results [16,22]. Transparency of these data is essential for correct interpretation of the outcome data. Still a standardized format is not available. Research need to be done to quantify and assign those parameters which do influence patient outcome after surgery. The criteria have evolved from the trifecta, to the pentafecta and now octofecta to demonstrate quality of care in RP. Besides, not in all patients with a PSM disease recurrence automatically occurs. According to a study conducted by van Oort, et al. [23] and Pettenati, et al. [5], the five-year risk of developing biochemical recurrence was approximately one-third in the PSM patients. Note that biochemical recurrence is not the same as disease recurrence and hence could still not be of any clinical relevance to the patient. When disease recurrence does occur, treatment options are still available, like salvage radiotherapy. This multimodality therapy has proved to offer still a good chance of complete remission during the EORTC trial [24] and the SWOG 8794 study [25].

Conclusion

Our data confirm the relation between the tumor stage and the incidence of positive surgical margins after radical prostatectomy in our department. It was also proved that a learning curve contributes to lower PSM rates.

Comparison with other centers is difficult because of the limited existing publications on this subject in the Benelux. Uniform, mandatory registration in a national database of all performed radical prostatectomy's can be the key for annual reporting on quality of surgical care, thus improving transparency towards patients. The national urology association should help both patients and insurance companies in the interpretation of the published report.

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Declarations

The authors certify that there is no conflict of interest with

any financial, research, and academic organization, with regards to the research work discussed in the manuscript.

Since this work contains data gathered retrospectively using an anonymous database, no effort regarding ethical approval was conducted.

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