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Risk Factors for Intraprostatic Incision into Malignant Glands at Radical Prostatectomy

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Abstract

Background—Histologically identified intraprostatic incision (IPI) into malignant glands is associated with an increase in biochemical recurrence following radical prostatectomy (RP). However, the predictor of IPI is poorly evaluated.

Objective—To evaluate the risk factors for IPI into cancer during RP for clinically localized prostate cancer (PCa).

Design, setting, and participants—Between January 1993 and July 2013, 19 986 men with clinically localized PCa underwent RP at our institution. This study includes 14 434 cases that had complete clinicopathologic data. IPI was defined as an iatrogenic incision into the prostate resulting in the presence of malignant glands at the inked surgical margin, regardless of accompanying pathologic features.

Intervention—Open, retropubic, robot-assisted laparoscopic and pure laparoscopic RP.

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Outcome measurements and statistical analysis—Univariate and multivariable logistic regression analyses were conducted for risk factors of IPI in RP specimens.

Results and limitations—The overall incidence of IPI into malignant tissue was noted in 410 (2.8%) cases. In multivariable analysis, obesity, lower prostate weight, surgeon experience, and pure laparoscopic RP were associated with a higher risk of IPI. The odds ratios (OR) for body mass index and prostate weight were 1.05 (95% confidence interval [CI], 1.03–1.08; $p < 0.001$) and 0.99 (95% CI, 0.98–0.99, $p < 0.001$), respectively. The ORs for surgeon experience (>250 cases) and pure laparoscopic RP compared to open RP were 0.71 (95% CI, 0.55–0.90, $p = 0.005$) and 2.05 (95% CI, 1.35–3.11; $p = 0.001$), respectively.

Conclusions—The risk of IPI during RP is higher in men with obesity and lower prostate weight. In addition, a pure laparoscopic RP and the early series of each surgeon were associated with a higher risk of IPI. However, tumor characteristics were not associated with the IPI occurrence.

Patient summary—Intraprostatic incision occurrence is associated with obesity, small prostate, and surgeon experience and laparoscopic technique but not Gleason score and tumor stage.

Keywords

Pathology; Prostate cancer; Prostatectomy

1. Introduction

Radical prostatectomy (RP) is a commonly performed procedure for treating clinically localized prostate cancer (PCa). Attempts have been made to evaluate the quality of RP through assessment of surgical margin status [1]. Positive surgical margin (PSM) is associated with decreased biochemical recurrence-free survival, as well as PCa specific survival [2]. However, PSM is significantly influenced by tumor characteristics such as Gleason score and pathologic stage. Therefore, it may not be the best quality tool for assessing the surgical technique.

PSM may occur as a consequence of intraprostatic incision (IPI), also known as capsular incision, when a surgeon inadvertently transects into an intraprostatic tumor [3–6]. Because histologic boundaries of the prostate are vague and benign prostate glands are seen admixed with skeletal muscle in the apex [5], a recent update recommended using IPI, not capsular incision, to describe this condition [4]. IPI has a significant negative impact on patient outcome following RP [6–9]. A high probability of IPI in obese patients could predict difficulty in achieving the optimal surgical approach and outcome, and it could also negatively impact disease-free survival of these men [10,11]. If the IPI rate is similar across the pathologic stage, IPI may be potentially used as a marker of violation of the surgical plane independent of tumor characteristics, and a tool to assess surgical quality. In addition, it is unclear what perioperative factors influence IPI.

In this study, we examined the prevalence of IPI according to pathologic stage using a large cohort of patients who underwent RP in a single center with standardized pathologic

examination of surgical specimens. Then we investigated the independent preoperative predictors of an IPI.

2. Patients and methods

Between January 1993 and July 2013, 19 986 men with clinically localized PCa underwent RP at our institution. This study included 14 434 men who had complete clinicopathologic data and those who received no neoadjuvant hormonal therapy. Cases with IPI into tumor were identified from RP final pathology reports. Our previous study on the impact of IPI on survival included only men with organ-confined disease, excluding those with extraprostatic extension (EPE), seminal vesicle invasion, and/or lymph node metastasis [8]. However, in this current study, all men were included regardless of accompanying pathologic features.

RP specimens were sectioned as previously described [5]. IPI was defined as an iatrogenic incision into the prostate resulting in the presence of malignant glands at the inked surgical margin. Cases with tumor extending to the inked margins in the same plane where benign prostatic glands also extended to those margins were considered to have a PSM due to IPI. At the apex, if the tumor was unassociated with benign prostatic glands at the inked edge, the tumor was classified as having a positive margin in an area where it was unclear if there was a PSM associated with EPE or IPI due to ambiguities of where the edge of the prostate was in this region; these cases were not considered in the current study as having IPI. Equivocal cases of whether or not IPI was present were reviewed and reclassified [5]. Prostate weight was determined by measuring gross RP specimen weight, including the seminal vesicles and vasal tips before October 2010, and excluding those after this date.

Differences in age, preoperative prostate-specific antigen (PSA), body mass index (BMI), prostate weight, surgery year, race, clinical stage, biopsy Gleason sum, operation type (open radical retropubic prostatectomy, pure laparoscopic RP, or robot-assisted laparoscopic RP [RARP]), and surgeon experience according to presence of IPI were compared using the student *t* test for continuous variables and the chi-square test for categorical variables. Age at RP, preoperative PSA level, BMI, prostate weight, and surgery year were examined as continuous variables. Race (Caucasian, African American, and others), clinical stage (T1, T2, and T3), biopsy Gleason sum (≤6, 7, ≥8), operation type, and surgeon experience were examined as categorical variables. To consider surgeon experience, an expert was defined as a surgeon who performed >250 cases in each operation type [12–14]. Univariate and multivariable logistic regression analyses were conducted to assess the prognostic significance of preoperative variables. All tests were two-sided, with $p < 0.05$ considered statistically significant. STATA 11.0 (Stata Corp., College Station, TX, USA) was used for the statistical analyses.

3. Results

Overall, IPI into malignant glands was diagnosed in 410 of the 14 434 RP specimens (2.8%). IPI was found in 289 (2.9%) for pT2, 97 (2.8%) for pT3a, 15 (3.0%) for pT3b, and 9 (3.1%) for pN+ ($p = 0.975$). Figure 1 shows that the probability of IPI was not associated with pathologic stages. However, the probability of PSM increased with advancing

pathologic stage ($p < 0.001$). The probabilities of PSM in pT2, pT3a, pT3b, and pN+ were 4.2%, 30.6%, 30.1%, and 36.9%, respectively. Unlike pathologic stages, surgeon experience was also associated with PSM and IPI.

In univariate analysis, men with IPI had a lower prostate weight ($p < 0.001$) and a higher BMI ($p < 0.001$) in more recent series (surgery year, $p = 0.036$). The incidence of IPI was higher in RARP and pure laparoscopic RP than open RP ($p < 0.001$). More IPIs were produced in each surgeon's earlier series (<250 cases; $p < 0.001$) (Table 1).

In multivariable analysis, obesity, lower prostate weight, pure laparoscopic RP, and surgeon experience were independently associated with a higher risk of IPI into tumor. The odds ratios (OR) of IPI for BMI and prostate weight was 1.05 (95% confidence interval [CI], 1.03–1.08; $p < 0.001$) and 0.99 (95% CI, 0.98–0.99; $p < 0.001$), respectively. The ORs of IPI for RARP and pure laparoscopic RP compared to open RP was 1.40 (95% CI, 1.00–1.97; $p = 0.052$) and 2.05 (95% CI, 1.35–3.11; $p = 0.001$), respectively. The risk of IPI for a surgeon with 250 prior cases decreased 29% (OR: 0.71; 95% CI, 0.55–0.90; $p = 0.005$) (Table 2).

4. Discussion

IPI in the RP specimen is associated with an increased risk of progression following surgery [5–7,9]. Most studies that evaluated the prognostic significance of IPI reported the IPI rate in men with organ-confined (OC) disease only [6–9,15]. The current study was performed to evaluate the IPI rate across different pathologic stages and to identify predictors of IPI. Of 14 434 RP cases, 410 (2.8%) had an IPI. More importantly, the IPI rate across different pathologic stages was similar, suggesting that IPI may be a better indicator of surgical skills than PSM. The independent predictors of IPI included obesity, smaller prostate size, surgeon experience, and pure laparoscopic technique.

There is a significant variation in the reported IPI rate in men with OC disease. In the current study population of 10 105 men with OC disease, 289 (2.9%) were diagnosed with IPI. In our previous reports, isolated IPI rates in OC disease ranged from 1.8% to 2.3% [8,16]. However, others reported the IPI rates in OC disease as high as 20% [9,15]. This variation in IPI rate can be partly attributed to pathologic interpretation. For example, it is challenging to distinguish IPI from a PSM associated with EPE or equivocal PSM in an area where it is difficult to distinguish OC disease with tumor close to resection margins [5].

IPI occurs most commonly on the posterolateral section of the RP specimen [7–9]. One of the potential causes for IPI at this site may be the neurovascular bundle–sparing technique. There is also the potential risk of overcalling IPI if pathologists are less experienced in evaluating RPs. PCa extending out of the prostate may induce a desmoplastic reaction such that extraprostatic tumor is not seen in periprostatic adipose tissue. If pathologists do not recognize these foci as EPE, because they incorrectly require seeing tumor in adipose tissue to diagnose EPE, then a PSM associated with IPI will be diagnosed, as opposed to the correct diagnosis of a PSM with EPE (Fig. 2) [3,17,18]. Increased education of pathologists to recognize EPE in the absence of adipose tissue involvement may improve the accurate diagnosis of IPI.

There are few studies on the predictors of IPI in the RP specimen. In an open retropubic RP series, Freedland et al concluded that obesity is a risk factor for IPI [10]. They also showed that men with an IPI were younger, had lower Gleason sum, and a smaller prostate [10]. In the current study, we found obesity and smaller prostate weight were independent predictors of IPI in multivariable analysis. In addition, we found that laparoscopic technique was associated with an increased IPI rate. There is lack of tactile or visual feedback in pure laparoscopic surgery. RARP was also associated with a higher risk of IPI in earlier cases. In supplementary analysis, IPI rate of RARP has decreased to that of open RP. Five years of data show no significant differences of IPI rates between RARP and open RP (2.4% vs 1.7%, respectively; $p = 0.130$).

Surgeon experience is an important predictor of PSM in various types of surgery [12,14,19]. To define the acquisition of experience in each RP type, many studies tried to show cutoff numbers of surgery already performed. Vickers et al reported that the probability of PSM in open RP decreased to 25% for a surgeon with 250 prior cases [12]. Thompson et al showed that the risk of PSM for advanced stage in RARP gradually decreased, and reached a plateau at 200 to 300 cases [14]. In the current study, the probability of IPI (OR: 0.71; $p = 0.005$) decreased for experienced surgeons with 250 prior cases of each operation type.

Most studies on risk factors for PSM demonstrated that preoperative tumor characteristics, such as preoperative PSA level, biopsy Gleason score, clinical stage, and multiple positive biopsies, are strongly associated with the PSM [1,20,21]. Similar to the current study, obesity and smaller prostate weight were also associated with PSM [22–24]. Furthermore, surgery-related factors, such as operation type and surgeon experience, led to a change in PSM [25–29]. The risk factors for PSM are similar to those of IPI with the exception of tumor pathologic characteristics. Therefore, we suggest using IPI, rather than PSM, to assess the quality of surgery.

There are several limitations to our study. In our study, significantly more open RPs were performed compared to minimally invasive surgery. The majority of these open RP cases were performed by more experienced surgeons, although this relative experience gap has decreased in recent years. We did not consider the number of positive cores and their location in our model because complete data on these variables were not available. Tumor volume might be correlated with IPI occurrence, although IPI was not associated with tumor grade and stage in the current study. In addition, the location and extent of IPI were not considered in this study. We also did not consider neurovascular-bundle preservation technique, although higher PSM rate was observed in cases with that technique [14,30]. Additional study including neurovascular-bundle preservation information may add more insight. Finally, to adjust for surgeon experience, we used a binary variable: whether or not a surgeon had already performed >250 cases in each surgery type. However, surgeons might need different numbers of surgery to overcome the learning curve in each surgery type.

5. Conclusions

The incidence of IPI is low (2.8%). Unlike PSMs, the rate of IPI into malignant glands is similar across different pathologic stages. Independent predictors of IPI in the RP specimen

were obesity, lower prostate weight, pure laparoscopic RP technique, and surgeon experience. We suggest using IPI, rather than PSM, to assess the quality of surgery.

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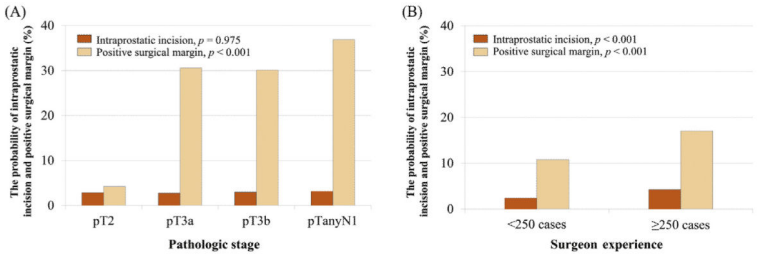

Fig. 1.

The probabilities of intraprostatic incision and positive surgical margin according to (A) pathologic stage and (B) surgeon experience. *P* values were calculated by chi-square test.

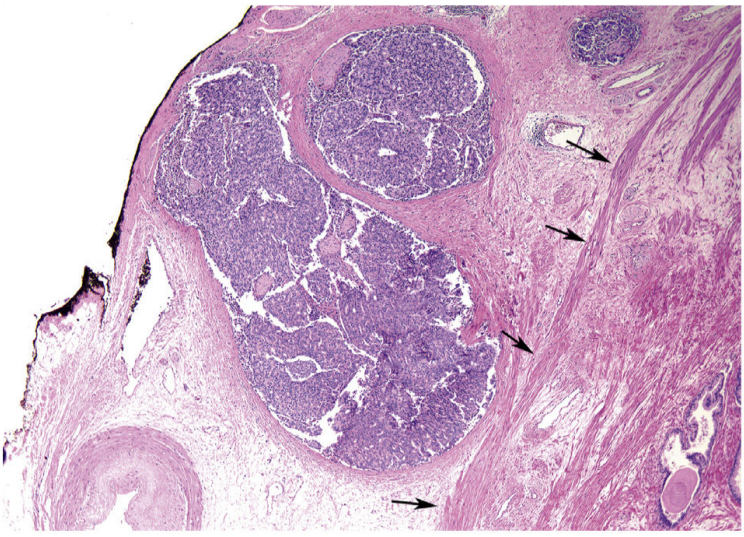

Fig. 2.

High-grade adenocarcinoma extending out of the prostate associated with a desmoplastic reaction, such that tumor is not seen with periprostatic adipose tissue (Hematoxylin & Eosin, reduced from X4). The edge of the prostate where the condensed smooth muscle of the prostate ends is noted by the arrows. If this tumor was at the margin, it would be extraprostatic extension with a positive surgical margin. If not recognized as extraprostatic extension because of the lack of fat invasion, it would incorrectly be designated as organ-confined disease with intraprostatic incision.

Table 1

Preoperative clinical and pathologic characteristics (N = 14 434)

	Intraprostatic incision		*p* value
	No	Yes	
Patients, no. (%)	14 024 (97.2)	410 (2.8)	
Age, yr, median (IQR)	58 (53–63)	58 (53–62)	0.133
Race, no. (%)			0.713
Caucasian	12 239 (87.3)	360 (87.8)	
African American	1192 (8.5)	36 (8.8)	
Others	593 (4.2)	14 (3.4)	
PSA level, ng/ml, median (IQR)	5.5 (4.1–7.7)	5.5 (4.4–7.9)	0.647
Clinical stage, no. (%)			0.618
T1	10 081 (71.9)	303 (73.9)	
T2	3888 (27.7)	105 (25.6)	
T3	55 (0.4)	2 (0.5)	
Biopsy Gleason sum, no. (%)			0.608
4–6	10 084 (71.9)	301 (73.4)	
7	3368 (24.0)	96 (23.4)	
8–10	572 (4.1)	13 (3.2)	
BMI, kg/m^2, median (IQR)	26.6 (24.8–29.0)	27.3 (25.1–30.1)	<0.001
Prostate weight, g, median (IQR)	50 (41–62)	47 (39–56)	<0.001
Surgery year, median (IQR)	2002 (1999–2008)	2003 (2000–2007)	0.036
Cases by experts, no. (%)	10 799 (77.0)	266 (64.9)	<0.001
Operation type, no. (%)			<0.001
Open	11 910 (84.9)	303 (73.9)	
Robot-assisted laparoscopic	1628 (11.6)	75 (18.3)	
Laparoscopic	486 (3.5)	32 (7.8)	

BMI = body mass index; IQR = interquartile range; PSA = prostate-specific antigen.

Table 2

Univariate and multivariable analyses for risk of intraprostatic incision according to preoperative variables in men undergoing radical prostatectomy between 1993 and 2013 (*N* = 14 434)

	Univariate			Multivariable		
	OR	**(95% CI)**	***p* value**	**OR**	**(95% CI)**	***p* value**
Race (Caucasian)	1.00					
African American	1.03	(0.73–1.45)	0.882	–	–	–
Others	0.80	(0.47–1.38)	0.425	–	–	–
Age, yr/10	0.89	(0.77–1.05)	0.133	–	–	–
PSA level, ng/ml	1.01	(0.99–1.02)	0.647	–	–	–
BMI, kg/m^2	1.05	(1.03–1.08)	<0.001	1.05	(1.03–1.08)	<0.001
Prostate weight, g/10	0.87	(0.81–0.92)	<0.001	0.88	(0.82–0.93)	<0.001
Surgery year	1.02	(1.00–1.04)	0.036	0.99	(0.97–1.02)	0.575
Clinical stage (T1)	1.00					
T2	0.90	(0.72–1.13)	0.351	–	–	–
T3	1.21	(0.29–4.98)	0.792	–	–	–
Biopsy Gleason sum (≤6)	1.00					
7	0.96	(0.76–1.21)	0.698	–	–	–
8–10	0.76	(0.43–1.34)	0.341	–	–	–
Experts (No: cases ≤250, no.)	1.00			1.00		
(Yes: Cases >250, no.)	0.55	(0.45–0.68)	<0.001	0.71	(0.55–0.90)	0.005
Operation type (Open)	1.00			1.00		
Robot-assisted laparoscopic	1.81	(1.40–2.34)	<0.001	1.40	(1.00–1.97)	0.052
Laparoscopic	2.59	(1.78–3.77)	<0.001	2.05	(1.35–3.11)	0.001

BMI = body mass index; CI = confidence interval; OR = odds ratio; PSA = prostate-specific antigen.