

Prevalence and risk factors of contralateral extraprostatic extension in men undergoing radical prostatectomy for unilateral disease at biopsy: A global multi-institutional experience

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Abstract

Introduction: We assessed the incidence of contralateral prostate cancer (cPCa), contralateral EPE (cEPE) and contralateral positive surgical margins (cPSM) in patients diagnosed preoperatively with unilateral prostate cancer and evaluated risk factors predictive of contralateral disease extension.

Methods: The occurrence of cPCa, cEPE and cPSM and the side-specific nerve-sparing technique performed were collected postoperatively from 327 men diagnosed with unilateral prostate cancer at biopsy. Parameters, such as the localization, proportion, and percentage of cancer in positive cores, were prospectively collected.

Results: Overall, 50.5% of patients had bilateral disease, and were at higher risk when associated with a positive biopsy core at the apex ($p = 0.016$). The overall incidence of ipsilateral EPE and cEPE were 21.4% and 3.4%, respectively ($p < 0.001$). Compared to cPCa, ipsilateral disease was at an almost 4-fold higher risk of extending out of the prostate ($p < 0.001$). None of the criteria tested were identified as useful predictors for cEPE. The low incidence of cEPE in our cohort could limit our ability to detect significance. The overall incidence of ipsilateral PSM and cPSM were 15.3% and 5.8%, respectively ($p < 0.001$). More aggressive nerve-sparing was not associated with a higher incidence of PSM. Prostate sides selected for more aggressive nerve-sparing were associated with younger patients ($p < 0.001$), a smaller prostate ($p = 0.006$), and a lower percentage of cancer in biopsy material ($p = 0.008$).

Conclusion: Although the risk of cPCa is high in patients diagnosed with unilateral prostate cancer at biopsy, the risk of cEPE and cPSM is low, yet not insignificant. Contralateral aggressive nerve-sparing should be used with caution and should not compromise oncological outcome.

Introduction

Prostate cancer is the most prevalent cancer among men in North America.¹ The stage migration toward low-risk disease and in consequence prolonged survival of patients has shifted our attention towards the preservation of quality of life in men treated for prostate cancer. Current techniques used for radical prostatectomy (RP) cause urinary and erectile dysfunction in a significant proportion of patients, with 2% to 20% not recovering full continence² and about 50% not recovering sexual function within 1 year.³ Due to the proximity of the nerve bundles to the prostate gland, a technical and conceptual challenge resides in striking a balance between the preservation of the neurovascular bundle (i.e., nerve-sparing technique) and the risk of positive surgical margins (PSM). In a recent meta-analysis, the mean incidence of PSM was 15%.⁴ While the decision to perform nerve sparing is surgeon-dependent, several models have been developed to help identify good candidates for such procedures. As described by Ohori and colleagues, prostatic-specific antigen (PSA) levels, digital rectal exam findings, and biopsy Gleason score may predict the risk of side-specific extra-prostatic extension (EPE).^{5,6} Similarly, PSA, low prostate volume, a biopsy Gleason score of 7, and interfascial neurovascular bundle dissection were described as side-specific predictors of PSM by Secin and colleagues.⁷

There is little data on contralateral disease extension in unilateral prostate cancer diagnosed at biopsy. Few studies have focused on the reliability of unilaterally positive biopsies to adequately predict the presence of less invasive disease to the contralateral side.⁸⁻¹⁰ On the basis of these considerations, we assessed the incidence of bilateral disease, contralateral EPE (cEPE), and contralateral positive surgical

margins (cPSM) in patients diagnosed preoperatively with unilateral disease, and evaluated risk factors predictive of contralateral disease extension.

Methods

Cohort

Following institutional review board approval, we identified 327 patients who were diagnosed with unilateral prostate cancer at biopsy. All patients underwent robot-assisted radical prostatectomy (RARP) between 2010 and 2013 performed in 5 sites in Canada, the United States, and Turkey. Only patients who underwent the entire procedure in a standard fashion were included in the study. No men had prior pelvic radiation or neoadjuvant therapy. Patients underwent a 12-core biopsy scheme guided by bi-dimensional transrectal ultrasonography (TRUS). All centres perform at least 800 TRUS-guided biopsies yearly. Baseline parameters, localization of positive cores, proportion of positive cores, percentage of cancer in biopsy material, Gleason Score, and clinical tumour stage were recorded in a standardized data collection sheet.

Surgical technique and specimen preparation

Surgeons had a minimum fellowship experience of 200 cases. RARP was performed in a standard fashion using the robotic da Vinci system (Intuitive Surgical Inc., CA).¹¹⁻¹³ Nerve preservation was performed according to the surgeon's preference and classified according to the extent of nerve sparing as interfascial (IF-NS), extrafascial/partial (EF-NS), and wide extrafascial resection (WEFR).

The surgical specimens were processed according to modified Stanford protocol¹⁴ and microscopically examined by an uro-pathologist.¹⁵ EPE was defined as cancerous tissue found on the outside of the limit of healthy prostatic tissue and associated with the stage pT3. PSM was defined as tumour cells present at the inked margin of the specimen.

The localization of the positive biopsy cores (available for 24% of patients), EPE (available for 57% of patients) and PSM (available for 37% of patients) were categorized as the apex, the mid region, and the base of the prostate. Data did not allow more precise substratification for the anterior/posterior regions of the apex and of the base, and for the anterior/anterolateral/posterolateral/posterior regions of the mid-gland.^{16,17}

Data analysis

Data were prospectively collected and retrospectively analyzed. All tests were two-sided and a *p* value of 0.05 was

deemed statistically significant. The IBM SPSS Statistics package (IBM Corporation, version 21, Armonk, NY) was used for analysis. Distribution was evaluated using the Shapiro-Wilk's test. Data were summarized using descriptive statistics, and central tendency was measured with the median followed by the first and third quartiles (25%–75%). Continuous variables were analyzed with the Mann Whitney U test. The chi-square test and the Fisher's exact test were used with categorical variables. Lastly, a univariate binomial logistic model was used to evaluate risk. Multivariate models encompassed all variables with a *p* < 0.3.

Results

Characteristics of the study population

Our cohort is composed of 327 men diagnosed with unilateral prostate cancer at biopsy. We tallied patient baseline characteristics (Table 1). On the ipsilateral side to the positive biopsy, 66.4% of patients underwent IF-NS, 27.5% EF-NS, and 6.1% did not undergo a nerve-sparing procedure. On the contralateral side, 81.5% of patients underwent IF-NS, 17.3% EF-NS, and 1.2% did not undergo nerve-sparing procedure. A significantly higher proportion of IF-NS was performed on the contralateral side of the prostate compared to the ipsilateral side (*p* < 0.001).

Table 1. Demographic and preoperative oncological parameters

Parameters	Cohort
Cohort size	327
Age, years	61.0 (55.0–65.0)
BMI, kg/cm ²	26.9 (25.0–29.4)
Race, %	Caucasian 92.1 (301)
	Black 2.1 (7)
	Other 5.8 (19)
Gleason score, %	≤ 6 41.0 (134)
	7 52.3 (171)
	≥ 8 6.7 (22)
TRUS prostate size, cc	38 (30–50)
Baseline PSA, ng/mL	5.3 (4.1–7.1)
Proportion of positive cores, %	20.0 (16.7–33.3)
Percentage of cancer in biopsy material, %	30.0 (15.0–64.0)
cStage (%)	cT1c 76.0 (240)
	cT2a 18.0 (56)
	cT2b 5.7 (18)
	cT3a 0.3 (1)
D'Amico risk categories	Low risk 47 (154)
	Intermediate risk 46 (151)
	High risk 7 (22)

Data presented as a median (Q1–Q3) or % (n). BMI: body mass index; TRUS: transrectal ultrasound; PSA: prostate-specific antigen; cStage: clinical stage.

Table 2. Anatomical localization of EPE and PSM in the prostate

Localization	Ipsilateral EPE	Contralateral EPE	Ipsilateral PSM	Contralateral PSM
Apex	14.6 (6/41)	0.0 (0/5)	43.5 (10/23)	60.0 (6/10)
Mid	58.5 (24/41)	40.0 (2/5)	39.1 (9/23)	30.0 (3/10)
Base	39.0 (16/41)	60.0 (3/5)	43.5 (10/23)	50.0 (5/10)

Data presented as a % (n). Missing data for iEPE n = 29, cEPE n = 6, iPSM n = 27, cPSM n = 9. EPE: extra-prostatic extension; PSM: positive surgical margins.

Disease extension

Overall 50.5% (165/327) of patients had bilateral disease according to the postoperative pathological report. On the ipsilateral side to the positive biopsy, 21.4% (70/327) had EPE. On the contralateral side, the overall proportion of cEPE was significantly lower than on the ipsilateral side with an incidence of 3.4% (11/327) ($p < 0.001$). In fact, using a binomial logistic regression model, our results show that the risk of ipsilateral disease extending out of the prostate is almost 4 times higher than the risk of contralateral disease extending out of the prostate (odds ratio [OR] 3.813, 95% confidence interval [CI] 1.958–7.425, $p < 0.001$). The localization of ipsilateral EPE (iEPE) and cEPE is reported in Table 2.

In a univariate model, preoperative predictive parameters of increased risk for contralateral prostate cancer (cPCa) and cEPE were also evaluated (Table 3). For predictors of cPCa, the subsequent multivariate analysis showed that a positive biopsy at the apex was associated with a 4-fold higher risk of cPCa in patients diagnosed with unilateral prostate cancer at biopsy (OR 4.565, 95% CI 1.333–15.630, $p = 0.016$).

None of all parameters tested to evaluate the risk of cEPE were significant (Table 3).

Positive surgical margins

Overall, the incidence of ipsilateral PSM (iPSM) in our cohort was of 15.3% (50/327). The side of the prostate with iEPE was associated with a significant 4-fold higher risk of being associated with iPSM compared to those without iEPE (OR 4.356, 95% CI 2.290–8.287, $p < 0.001$). On the contralateral side of the positive biopsy, the cohort's overall incidence of cPSM was 5.8% (19/327) and was significantly lower than the incidence of iPSM ($p < 0.001$). cEPE was associated with an almost 7-fold higher risk of cPSM compared to prostate sides without cEPE (OR 6.844, 95% CI 1.656–28.289, $p = 0.008$) (Fig. 1). The localization of PSM is presented in Table 2.

Lastly, less aggressive nerve sparing (WEFR or EF-NS) was not associated with significantly different rates of PSM on the ipsilateral and contralateral sides, with rates of 17.3% (14/81) and 27.6% (8/29), respectively ($p = 0.234$). With the IF-NS technique, the rates of iPSM tended to be higher

Table 3. Univariate analysis of potential predicting factors of cPCa and cEPE

Univariate analysis	Unilateral PCa	Bilateral PCa	OR (95% CI)	p value	No cEPE	cEPE	OR (95%CI)	p value
Age, years	61.0 (56.0–65.0)	60.0 (54.0–65.0)	0.969 (0.943–0.996)	0.025	61.0 (55.0–65.0)	59.0 (52.0–64.0)	0.992 (0.927–1.060)	0.806
BMI, kg/cm ²	26.6 (25.0–29.5)	27.2 (24.9–29.3)	1.021 (0.966–1.079)	0.456	26.9 (25.1–29.5)	27.1 (23.6–28.5)	0.931 (0.814–1.065)	0.294
Baseline PSA, ng/mL	5.3 (4.17–7.01)	5.3 (4.08–7.34)	1.013 (0.957–1.072)	0.653	5.3 (4.1–7.1)	6.7 (4.3–8.1)	1.019 (0.882–1.178)	0.794
Proportion of positive cores, %	20.0 (16.7–33.3)	16.7 (8.3–33.3)	1.000 (0.984–1.016)	0.986	20.0 (16.7–33.3)	33.3 (16.7–43.7)	1.029 (0.989–1.072)	0.161
Percentage of cancer in biopsy material, %	30 (18–61)	25 (10–70)	0.999 (0.992–1.006)	0.795	30 (15–60)	65 (20–80)	1.014 (0.994–1.034)	0.166
Biopsy Gleason score ≥ 8 , %	6.2 (10/162)	7.3 (12/165)	1.192 (0.500–2.842)	0.692	7.0 (22/316)	0.0 (0/11)	–	0.998
TRUS prostate size, cc	40 (30–51)	60 (54–65)	0.992 (0.978–1.005)	0.227	38 (30–50)	38 (28–47.5)	0.995 (0.961–1.031)	0.778
Biopsy localization, %	Apex (11/33)	62.2 (28/45)	3.294 (1.284–8.448)	0.013	47.1 (33/70)	75.0 (6/8)	3.364 (0.635–17.827)	0.154
	Mid (26/33)	73.3 (33/45)	0.740 (0.255–2.147)	0.580	75.7 (53/70)	75.0 (6/8)	0.962 (0.177–5.220)	0.964
	Base (18/33)	62.2 (28/45)	1.373 (0.551–3.418)	0.496	60.0 (42/70)	50.0 (4/8)	0.667 (0.154–2.888)	0.588

Data presented as a median (Q1–Q3) or % (n). BMI: body mass index; PSA: prostate-specific antigen; TRUS: transrectal ultrasound; PCa: prostate cancer; OR: odds ratio; CI: confidence interval; cEPE: contralateral extra-prostatic extension.

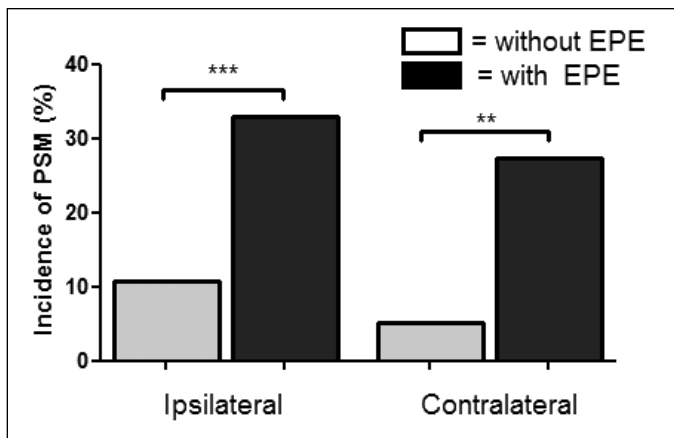


Fig. 1. Rates of positive surgical margins (PSM) without extra-prostatic extension (EPE) (white) and with EPE (black) on the ipsilateral and contralateral side of the positive biopsies. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

at 17.0% (27/159) compared to rates of cPSM with 9.3% (9/97) ($p = 0.085$). Interestingly, rates associated with IF-NS were similar to those associated with WEFR/EF-NS on the ipsilateral side (17.0% vs. 17.4%, $p = 0.953$) and were significantly lower when associated with IF-NS on the contralateral side (27.6% vs. 9.3%, $p = 0.011$). To understand why more aggressive nerve sparing did not result in more PSM, a multivariate analysis was performed and showed that prostate sides dissected with IF-NS were associated with younger patients ($p < 0.001$), a smaller prostate size ($p = 0.006$), and a lower percentage of cancer in biopsy material ($p = 0.008$).

Discussion

In unilaterally positive biopsies of the prostate, a more aggressive contralateral nerve-sparing approach is attractive. In fact, unilateral nerve sparing may help preserve the neurovascular bundle on a side less likely to be affected by prostate cancer.¹⁸ However, few studies have investigated the incidence and extent of contralateral disease extension in such cases. In regards to disease extension within the contralateral lobe, a laparoscopic series by Frota and colleagues showed that unilaterally positive biopsies correlated weakly with both prostate cancer and PSM localization.¹⁹ They reported that 79% and 82% of prostates in which biopsies were only positive on the right and left lobe had bilateral disease, respectively. Similarly, a study by Gallina and colleagues of 321 consecutive low-risk patients with unilateral disease at biopsy showed that 60.7% had bilateral disease following RP.²⁰ In our cohort, the incidence of bilateral disease at resection was lower (50.5%). The Gleason score, clinical stage, PSA, and number of biopsy cores were not markedly different compared to the studies from Frota and colleagues¹⁹ and Gallina and colleagues.²⁰ This difference could be explained by our multi-institutional cohort.

A series by Sfoungaristos and colleagues identified PSA density and percentage of cancer in biopsy material as independent predicting factors of bilateral disease.¹⁰ In our report, a positive biopsy at the apex was a predictor of contralateral disease. In fact, the apex represents a much smaller proportion of the gland than the mid and base regions. The disease will likely spread to the contralateral side. While this hypothesis warrants further investigation, this could be used as a red flag to exert additional care during the dissection of the apex. In fact, the highest rate of PSM was found at the apex both on the ipsilateral (43.5%) and contralateral (60.0%) sides. A study from Smith and colleagues reported similar results with the most common localization for PSM after RARP at the apex (52%).²¹ The high incidence of PSM at the apex may be due to the technical difficulty associated with its dissection. As described by Tewari and colleagues the prostatic apex is the “Achilles heel” of prostate cancer surgery. This may be explained by the challenge of differentiating the prostate from the dorsal venous complex and the sphincter of the urethra.²²

The overall incidence of cPSM was low (6%). PSM may occur following a surgical incision through the prostate or through preexisting EPE. Prostates with cEPE were associated with a high incidence of cPSM (27.3%) and a near 7-fold higher risk of PSM compared to those without EPE. In fact, when comparing rates of PSM in lobes with no EPE, we found similar rates of capsular incisions with 10.7% on the ipsilateral side and in patients with contralateral disease, and 10.9% on the contralateral side. These results compare favourably with rates obtained by Kwak and colleagues.²³ In their cohort, they reported 15.6% of PSM for organ-confined disease. Although contralateral disease was common, it was associated with a low risk of extension beyond the contralateral capsule. Specifically, the overall incidence of cEPE was low (3.4%). The localization of EPE was mainly in the mid region or the base of the gland both on the ipsilateral and the contralateral sides. We did not find predictors of cEPE. This may be due to the low incidence of cEPE in our cohort. While some studies have investigated predicting factors of PSM⁷ and EPE,^{5,6} few have specifically reported predictors of cEPE in unilateral prostate cancer. Such findings could help anticipate contralateral extension and help identify patients suitable for more aggressive contralateral nerve sparing.

Lastly, our results show that the nerve-sparing methods yielded similar rates of PSM when associated with ipsilateral and contralateral prostate cancer. We did not find a significant increase in PSM with more aggressive nerve-sparing techniques. Surprisingly, IF-NS resulted in less PSM than the less aggressive methods on the contralateral side. In our cohort, a lower percentage of cancer in biopsy material, a younger age, and a smaller prostate are independent predictors of IF-NS. Conversely, some studies show that age >60 and a prostate size >60 g protect against PSM.^{7,24} Therefore, a lower percentage of cancer in biopsy material seems to be the only

independent factor to explain favourably our results. Patient criteria used to perform aggressive nerve sparing were surgeon-dependent and may consequently not be identified by the multivariate model. Another explanation for our results is the fact the biggest proportion of PSM is localized at the apex, where little maneuver variation is possible²⁵ and the use of nerve sparing is limited. This may contribute to why more aggressive nerve sparing did not result in more PSM.

Our study was not devoid of limitations. The low incidence of cEPE and cPSM may have limited the statistical ability to detect significant differences. Additionally, as multiple surgeons from multiple institutions participated in this study, the lack of central pathology may induce an inter-observer bias in reporting EPE and PSM. Nonetheless, it did allow for a larger and more diverse cohort, which we feel makes the study more generalizable.

Conclusion

Aggressive contralateral nerve sparing on patients with unilateral disease on preoperative biopsy is attractive, but the risk of contralateral disease is high. However, cPCa is at a lower risk of EPE than disease on the ipsilateral side and, although not insignificant, the overall incidence of cEPE and cPSM is low. We found that a positive biopsy at the apex predicts cPCa and a higher proportion of PSM. This could be used as a red-flag to exert additional care during the dissection of the apex. This study suggests that aggressive contralateral nerve sparing does not increase the risk of PSM if performed with caution based on preoperative risk factors and intra-operative surgical judgement.

Competing interests: Dr. Bienz, Dr. Hueber, Dr. Trudeau, Dr. Alenizi, Dr. Valdivieso, Dr. Alom, Dr. Balbay, Dr. Canda, Dr. Mouraviev, Dr. Albala, Dr. El-Hakim, and Dr. Trinh and Dr. Latour declare no competing financial or personal interests. Dr. Saad is a member of the advisory boards for Amgen, Astellas, Janssen, Abbott, Sanofi and Bayer. He has also received research grants and honoraria from Amgen, Astellas, Janssen, Abbott, Sanofi and Bayer. He has participated in clinical trials in the past 2 years for Amgen, Astellas, Janssen, Sanofi, and Bayer. Dr. Zorn is an advisor, speaker, and proctor for Greenlight laser surgery from AMS. Dr. Trinh received honorarium from Intuitive Surgical in the past.

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