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Positive surgical margins: Rate, contributing factors and impact on further treatment: Findings from the Prostate Cancer Registry

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Positive surgical margins: rate, contributing factors and impact on further treatment: findings from the Prostate Cancer Registry

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Abstract (466words)

Objectives

- To describe characteristics of patients with and without positive surgical margins (PSM) and describe the impact of PSM on secondary cancer treatment after radical prostatectomy (RP) with short-term follow-up.

Patients and Methods

- We analysed data from 2385 consecutive patients who were notified to the Prostate Cancer Registry by 37 Victorian hospitals between August 2008 and February 2012 and were treated by RP.
- Independent and multivariate models were constructed to predict the likelihood of PSM. Independent and multivariate predictors of secondary treatment following prostatectomy in the initial 12 months post diagnosis were also assessed.

Results

- Surgical margin status was collected for 2219/2385 (93%) cases. In total 592/2175 (27.2%) radical prostatectomies resulted in PSM; 102/534 (19.1%) cases in the low risk group, 317/1,218 (26.0%) cases in the intermediate risk group, 153/387 (39.5%) in the high risk group, and 9/11 (81.8%) in the very high risk disease group.
- PSM were significantly more likely for men having surgery in a hospital where less than ten RPs occur each year (Incidence rate radio[IRR] 1.44 confidence interval [CI] 1.07-1.93) and in the intermediate-, high-, or very-high-risk group, than those for those in the low risk group (Incidence rate radio (IRR) 1.34 [CI] 1.09-1.65, p= 0.007], 1.96 [CI: 1.57-2.45, p<0.001] 3.81 [CI: 2.60-5.60, p<0.001] and 2.50 [CI: 1.23-5.11, p=0.012] respectively). Patients with PSM were significantly less likely to have been treated at a private hospital than a public hospital (IRR=0.76, CI: 0.63-0.93, p=0.006)

or to have had robot-assisted surgery performed (IRR=0.69, CI: 0.55-0.87, p=0.002) than an open approach.

- Of the 2182 cases who underwent surgery in the initial 12 months post diagnosis, 1987 (91.1%) received no subsequent treatment, 123 (5.6%) received radiotherapy, 47 (2.1%) received androgen deprivation therapy (ADT) and 23 (1.1%) received a combination of radiotherapy and ADT. Two cases (0.1%) received chemotherapy combined with another treatment.
- At a multivariate level, predictors of additional treatment following surgery in the initial 12 months included having a PSM compared with clear margins (Odds ratio (OR)=5.61 CI: 3.82-8.22 p<0.001); pT3 compared with pT2 disease (OR 4.72, CI: 2.69-8.23, p<0.001); and having high or very-high risk disease compared with low risk disease (OR 4.36, CI: 2.24-8.50, p<0.001 and 4.50, CI: 1.34-15.17, p=0.015 respectively). Patient age, hospital location and hospital type were not associated with secondary treatment. Patients undergoing robotic-assisted surgery were significantly less likely to receive additional treatment compared with those receiving surgery using the open approach (OR 0.59, CI: 0.39-0.88, p=0.010).

Conclusions

- These data indicate an important association between hospital status and PSMs, with radical prostatectomy cases treated in private hospitals less likely than those in public hospitals to have PSM. Cases treated in lower volume hospitals were more likely to have PSM and less likely to receive additional treatment following surgery in the initial 12 months. Robot-assisted prostatectomy is associated with fewer positive surgical margins compared with the open approach in this non-randomised observational study. Surgical margin status and pathological T3 disease are both important and independent predictor of secondary cancer treatment for patients undergoing radical prostatectomy.

A robot-assisted radical prostatectomy approach appears to decrease the risk of men having subsequent treatment, when compared with the open approach.

Key words:

Prostatic neoplasm, Prostatectomy, Positive surgical margin, Hospitals, Private; Hospitals, Public

BACKGROUND

It is projected that in 2020 more than 25,000 new cases of prostate cancer will be diagnosed in Australia, more than any other cancer[1]. Prostate cancer is estimated to account for 15% of the cancer burden and 3% of the overall health burden in Australian men, second only to lung cancer[2]. Prostate cancer is principally a disease of older men, with the mean age of diagnosis being 68.4 years[2].

Over the past 15 years there has been a shift towards earlier diagnosis of prostate cancer and increasing use of surgery to treat the disease[3]. Radical prostatectomy (RP) provides 15-year prostate cancer-specific survival of up to 93% [4]. While there are a number of surgical approaches which can be used, including open, laparoscopic and robot-assisted techniques, all have the same goal: to resect the local tumour and cure the disease whilst minimising side effects to the patient.

One measure of the success of surgery is whether the cancer is contained within the resected prostate or has extended beyond the surgical margin. A review of the literature has identified the overall prevalence of positive surgical margins (PSM) to be 24% for open retropubic radical prostatectomy (ORP), 20% for laparoscopic radical prostatectomy (LRP) and 16% for robot-assisted laparoscopic radical prostatectomy (RALRP)[5]. The most well known risk factor associated with PSM is higher T category[6]. Other risk factors identified in the literature to varying extents include the skill of, and technique used by, the pathologist examining the specimen,[7, 8] pre-operative PSA level[6], surgical technique[9], surgical volume and surgeon experience[10]. PSM in organ-confined disease is widely regarded as a measure of surgical quality.

There is evidence that PSM post RP are independently associated with increased risk of biochemical progression, even after accounting for various pathological features, including

disease stage[6, 11]. The most striking effect is found for cases with intermediate and high risk disease[12]. There is less clear evidence of a link between PSM and metastases or death[6]. A Cochrane systematic review[13] and evidence-based guidelines from Canada[14], America[15], Europe[16], and Australia[17] suggest consideration of radiation treatment for men after RP, if found to have post-operative risk factors such as a PSM, pT3 disease, or a detectable PSA level. A secondary analysis of one of the three randomised comparative trials suggesting the benefit for postoperative treatment with radiation for men with high-risk disease noted the particular risk posed by a PSM[18]. A study of factors associated with the use of adjuvant therapies reported that patients with PSM were three times more likely than those without surgical margins to have additional treatment[19].

Little is known about PSM prevalence in Australia and whether PSM influence additional treatment. No multicentre studies have evaluated variation in PSM and its association with subsequent care. The purpose of this analysis was to describe characteristics of patients with and without PSM and describe the association of PSM with secondary cancer treatment post RP.

METHODS

Prostatectomy cases were obtained from the Prostate Cancer Registry, established in 2009 initially in four hospitals (accounting for 25% of all notifications to the Victorian Cancer Registry), to assess patterns of presentation, care and outcomes. An additional three hospitals joined the registry in late 2009, nine hospitals in 2010 and 22 hospitals in 2011 resulting in the registry accruing approximately 72% of Victorian prostate cancer incidence cases by February 2012. Registry recruitment is linked with mandatory notification of cancer status to the population-based Victorian Cancer Registry. Details of the recruitment strategy have been previously described[20].

Inclusion and exclusion criteria

Men from recruiting hospitals with a diagnosis of prostate cancer confirmed by histopathology report at time of biopsy or RP were eligible for inclusion in the study. Evidence from data collected by the Victorian Cancer Registry indicates that, in 1997, approximately 94% of prostate cancer diagnoses were histologically verified[21].http://onlinelibrary.wiley.com/doi/10.1111/j.1464-410X.2012.11530.x/full - b14 All RPs with unequivocal determination of surgical margin status performed to 29th February 2012 were included in analysis of risk factors for positive margins. Men who underwent RP and received additional immediate or delayed treatment in the initial 12 month period post diagnosis were included in analysis of factors associated with additional treatment. Men were ineligible if their diagnosing or treating doctor informed the registry that they were not capable of providing consent.

Case recruitment

Following approval from each hospital's human research ethics committee and the diagnosing or treating clinician (private patients) or Heads of Department (public patients), all cases diagnosed after authorisation date were progressively accrued. Hospitals provide details of each case to the registry to enable an explanatory statement to be sent approximately nine months after diagnosis, inviting participation and providing details of how men can opt off the registry if they choose not to participate. The statements are available in twelve common languages.

Data collection

Histopathological data are captured through hospital information systems and pathology reports. Histopathological data are collected at time of diagnosis and surgery, but not on biopsy specimens taken subsequent to diagnosis but prior to surgery (for active surveillance patients). Trained data collectors capture clinical information from medical records including treatment

and PSA level at diagnosis, prior to treatment and the level immediately preceding the 12-month follow-up date. In some instances a diagnosis was made in a notifying hospital and the patient subsequently underwent a RP at another hospital. In this situation the surgery data were requested by the notifying hospital. Cases are telephoned 12 months post diagnosis to confirm accuracy of treatment and most recent PSA level and collect quality of life information. Periodically, hospitals are asked to validate biopsies and RPs against International Classification of Disease (ICD-10) codes to confirm complete capture of cases.

Statistical analysis and Institutional Review Board approval

The NCCN risk criteria for disease progression was used to classify cases into low, intermediate and high risk disease (see Box 1) [15]. Where the clinical T category was not recorded, if the Gleason score was ≤ 6 and the PSA was <10ng/mL, the patient was deemed to be at low risk for disease progression. Frequencies were used to describe predictors of PSM with two-sided level of significance determined using Chi-squared test. PSM was assessed by patient age at surgery using the Kruskal-Wallis equality-of-populations rank test. Significant predictors of PSM at univariate level were investigated using unadjusted and adjusted Poisson regression, clustering by surgeon. The adjusted model was tested for significant interaction effects between model covariates.

Time from diagnosis to RP was compared according to hospital type (private/public) and location (metropolitan/regional hospitals) using Kruskal-Wallis equality-of-populations rank test. To determine predictors of further treatment, data was dichotomised into surgery only and surgery with additional treatment. Chi-squared test was used to determine significance at a univariate level and logistic regression with clustering by surgeon was used to determine significance at a multivariate level. Radiotherapy was deemed to be immediate if it commenced within six months following surgery and delayed if it was delivered more than 6

months post-surgery. Stata/IC 12.0 (StataCorp, TX, USA) was used for all analyses and a two-sided p-value <0.05 was considered to be statistically significant.

Ethical approval was gained from participating hospitals, Monash University and the Cancer Council Victoria.

RESULTS

There were 6514 pathologically confirmed prostate cancer cases notified to the registry from recruiting hospitals between 1st August 2008 and 29 February 2012. Of the 6514 cases notified from recruiting hospitals, 1164 cases were ineligible: 619 (9.5%) were diagnosed prior to site commencing recruitment; 243 (3.7%) were both diagnosed and had treatment at a non-recruiting hospital; 136 (2.1%) were deceased; 110 (1.7%) were diagnosed before consent had been obtained from their diagnosing doctor; 31 (0.5%) were not recruited on their doctor's recommendation, 22 (0.3%) were too unwell or unable to consent due to cognitive deficit, and 3(0.05%) cases could not be contacted. A further 105 (1.6%) opted off because they were not interested in contributing to the registry. Of the 5,245cases or 80.5% of notified prostate cancer cases who were eligible and consented to contribute to the Prostate Cancer Registry, 2385 cases (45.5% of cases) underwent surgery and were the focus of this research. Treatment was confirmed by telephone interview with 2006/2385 (84.1%) cases. Reasons for loss to follow up are outlined in Figure 1.

RPs were performed at 23 Victorian hospitals. Pre-operative patient and tumour characteristics are described in Table 1. There were 113 cases classified as low risk disease on the basis of having a PSA <10 ng/mL and a Gleason score of ≤ 6 but without a clinical T stage recorded. Based on the NCCN risk stratification criteria 608/2385 (25.5%) were at low risk for disease recurrence, 1300/2385 (54.5%) of cases were intermediate risk, 423/2385 (17.7%) had high-risk disease and 32/2385 (1.4%) had locally advanced or metastatic disease and for 22 cases

(0.9%) a NCCN risk category could not be assigned. The median PSA level at diagnosis was 5.9ng/L (mean 8.3, SD=31.6 ng/L, range 1.2-1456 ng/L) and the median Gleason score was 7.

Surgical margins

Data collectors were instructed to record the margin finding as positive if it was explicitly stated on the pathologist report. Surgical margin status was reviewed in 2219/2385 (93.0%) cases. Margin status was unequivocal for 2175/2219 cases (98.0%) but for 44 cases (2.0%) a definitive status was unable to be made due to insufficient sample (n=7), unclear documentation (n=6) or margin status not stated on the pathology report (n=31). These cases were not included in further analyses.

PSM were identified for 592/2175 (27.2%) cases and were significantly less frequent for patients with pT2 disease compared with pT3 (16.1% vs 50.7%, p<0.001). Of the 542 prostatectomies performed at public hospitals, PSM status was known for 487 (90.0%) and of the 1817 prostatectomies performed at private hospitals, PSM was known for 1684 (92.7%). There were 27 cases where the surgical hospital was not recorded. The total number of PSMs reported from public hospitals was 170 (34.9%) of which 60 (35.3%) were for pT2 disease, 100 (58.8%) were for pT3 disease and 10 (5.9%) were not classified. The total number of PSMs reported from private hospitals was 421 (25.0%) of which 158 (37.5%) were for pT2 disease, 244 (58.0) were for pT3 disease and 19 (4.5%) were not classified. While there were significantly more PSMs for cases from public hospitals compared with private hospitals (34.9 vs 25.0%, p<0.001), there was no significant difference in pathological stage for cases where PSMs were present (p=0.692). Cases where margin status was unknown were more likely than those where status was known to have surgery at a regional hospital (21.0% vs 6.8%, p<0.001), be in the low (11.9%) or metastatic disease (19.1%) risk group compared with the intermediate (5.5%) and high (8.3%) risk group, have a low Gleason score on biopsy (11.3% missing if Gleason ≤6, 5.3% missing if Gleason sum=7 and 8.7% missing if Gleason sum 8-10), and be in

a higher PSA category at diagnosis (7.2% missing in <10ng/mL group, 9.0% in 10-20ng/mL and 16.3% in >20ng/mL group). No differences between known and unknown margin status were identified in relation to the patient's age, Gleason score at surgery, pathological T category or whether they had surgery at a private or public hospital.

Date of surgery was recorded for 2256/2385 (94.6%) cases. Where date of surgery was known, the vast majority of cases had their RP within 12 months of diagnosis (n=2182/2256 or 96.7%) and there was no difference in PSM according to whether or not surgery was performed within 12 months of diagnosis (PSM 27.1% vs 31.4%, p=0.423). Table 2 provides a summary of univariate factors associated with PSM. Table 3 provides results of the multivariate analysis. Patients with PSM were significantly more likely to be in the intermediate-, high- or very high-risk groups, or in the metastatic disease group, than in the low risk group (Incidence rate radio (IRR) 1.34 [CI] 1.09-1.65, p= 0.007], 1.96 [CI: 1.57-2.45, p<0.001] 3.81 [CI: 2.60-5.60, p<0.001] and 2.50 [CI: 1.23-5.11, p=0.012] respectively) PSMs were more prevalent in cases from hospitals performing less than ten RPs per year compared with those from hospitals with higher surgical volumes (IRR=0.76, CI: 0.63-0.93, p=0.006). Patients having their surgery at private hospitals were less likely to have PSM than those having surgery in public hospitals l (IRR=0.76, CI: 0.63-0.93, p=0.006). Using the robot-assisted approach was associated with a significantly lower likelihood of PSM compared with open approach (IRR=0.69, CI: 0.55-0.87, p=0.002) (Table 3).

Predictors of further treatment

Patients treated at private hospitals were more likely than those treated at public hospitals to receive earlier surgery (median time from diagnosis to surgery=50 days (interquartile range (IQR)=35-77) vs 90 days (IQR= 64-133), p<0.001). Patients at metropolitan hospitals were more likely than those at regional hospitals to receive earlier surgery (median time from

diagnosis to surgery was 56 days (IQR= 39-91 days) vs 66 days (IQR= 45-103 days), p<0.001. There were 1987 (91.1%) cases that received surgery as a monotherapy in the initial 12 month period post diagnosis; 123 (5.6%) received surgery and radiotherapy; 47 (2.1%) had surgery and ADT; 23 (1.1%) had surgery, ADT and radiotherapy, one case (0.1%) had surgery, ADT and chemotherapy and one (0.1%) received surgery, radiotherapy, ADT and chemotherapy. Of the 147 cases who received radiotherapy with or without other treatment in the initial 12 months post-surgery, 32 (21.7%) received it within 6 months of surgery ("immediate"). The median PSA level taken preceding immediate radiotherapy was 0.23 ng/mL (n=23, IQR= 0.05-0.70), delayed radiotherapy was 0.14 (n=111, IQR= 0.09-0.3), ADT was 1.06 ng/mL (n=72, IQR= 0.17- 10.6) and chemotherapy was 11 (n=2, IQR= 8.3-13.7).

Independent factors associated with additional treatment post-surgery are outlined in Table 4. Table 5 outlines multivariate analysis of factors associated with additional treatment. Significant predictors include PSM compared to clear margins (Odds ratio OR=5.61 CI: 3.82-8.22 p<0.001), a pathological category of T3 compared with T2 (OR= 4.72, CI: 2.69-8.23, p<0.001) and high-risk or very high-risk disease compared with low risk disease (OR 4.36, CI: 2.24-8.50, p<0.001 and 4.50, CI: 1.34-15.17, p=0.015 respectively). Patients receiving robot-assisted surgery were significantly less likely to receive additional treatment in the initial 12 months post diagnosis compared with those receiving surgery using the open approach (OR= 0.59, CI: 0.39-0.88, p=0.010).

DISCUSSION

The purpose of this analysis was to describe the prevalence of PSM and the influence of PSM on subsequent additional treatment in the 12 month period post diagnosis, using data from a contemporary cohort of patients enrolled in a prostate cancer registry. We found that PSM were present in the resections from 27% of cases treated by radical prostatectomy and that cases treated at private hospitals, and with a robot-assisted technique were less likely to have

PSM compared with those treated at public hospitals using an open technique. There was a volume-quality relationship, with those hospitals performing less than 10 RPs per year having a higher rate of PSM compared with those performing more than 10 cases per year. The three most significant factors associated with cases receiving additional treatment in the initial 12 month period following diagnosis were pathological T category denoting invasion of seminal vesicle or beyond (nearly 5-fold increased risk), having high or very-high risk disease (4-fold increased risk) and having positive margins (a 5-fold increased risk).

Notwithstanding the observed association between post-operative risk factors and subsequent treatment, only a subset of men with adverse pathology after prostatectomy received additional treatment. This suggests that other factors besides pathology influence the use of additional treatments. North American population registry-based studies, in the period 2000-2007, also show small proportions of men (11.5%) with adverse pathology going on to postoperative radiation treatment [22].

PSM prevalence following prostatectomy in Victoria may have declined over recent years; in a review of all Victorian radical prostatectomies in the period 1995-2000, the overall PSM prevalence was 31%.[23] Our identified overall PSM prevalence of 27% is less than the 34% identified in a study of 1383 patients contributing to the CaPSURE database, yet is significantly higher for the subgroup of cases with a diagnosis PSA of 0-4 ng/mL (PSM =63/344 or 18.3% vs 34/450 or 7.6%, Fisher's Exact $p<0.001$)[24]. The PSM prevalence of 25% for laparoscopic and 20% for robot-assisted radical prostatectomy in our study is high compared with that from a single site study of 200 laparoscopic and 200 robot-assisted cases which reported prevalences of 12 and 13.5% respectively[25]. Our open radical prostatectomy PSM prevalence of 33% is marginally less than the 35% reported by Smith et al., yet the robot-assisted radical prostatectomy PSM prevalence of 15% reported by the same study is lower than ours (20%)[9].

Of interest was the finding that robot-assisted surgery was associated with a 30% decreased risk of PSM compared with an open approach, even after taking into account factors such as the stage of disease at diagnosis (including in the model PSA level, clinical T stage and Gleason score). There have been contradictory results produced from comparisons of open and robot-assisted techniques [9, 26]. Smith et al examined PSM using a single institution study of 200 robotic assisted operations with 200 open radical retropubic operations between 2002 and 2006 and reported that the robot-assisted approach was associated with fewer PSMs (9.4% vs 24.1% for pT2, $p<0.001$ and 50% vs 60% for pT3 disease)[9]. This finding was contrary to that of another single institution study conducted between 2003 and 2008 which demonstrated that when propensity matching of cases based on age, race, preoperative PSA level, biopsy Gleason score and clinical stage was used, both open and laparoscopic approaches yielded a lower PSM prevalence compared with the robot-assisted technique[26]. This difference may be due to the fact that the study by Smith et al reviewed cases of only four surgeons who were proficient at robot-assisted surgery while the study by Magheli et al included only surgeons who had completed their urological training, but the majority had performed less than 150 robot-assisted RPs in total. Magheli et al stated that the open technique provided tactile information which assisted the surgeon in reducing PSMs. It may be that our study found a lower PSM prevalence for cases treated by the robot assisted technique because of a learning curve phenomenon. Urologists performing robotic assisted surgery were experienced in the technique. In contrast, many open prostatectomies at public hospitals are performed by training surgeons. Had the registry commenced data collection at a time when the urologists were learning the robotic technique, then the PSM prevalence may have been higher.

Similarly, we found that cases managed at private hospitals were less likely to have PSM compared with those treated at public hospitals. Reasons for this are unknown. It may reflect surgeon experience, as operations performed at private hospitals are usually performed by a

consultant surgeon while many undertaken at public hospitals are performed by trainees under supervision. Surgeon experience has been shown to affect PSM when laparoscopic[27], open[28], and robot-assisted [29] approaches are used. It may also indicate a difference in patient profile and specimen review processes across public and private hospitals. Of interest was our finding that there was no association between PSM prevalence and whether patients were treated in regional or metropolitan hospitals.

Our finding that patients having surgery performed at a low surgical volume hospital (defined as less than 10 cases/year) were more likely to have PSM compared with those treated at higher volume hospitals , even after taking into account surgical approach and disease stage, is at odds with Lawrentschuk et al's study, which was confined to cases with pathological stage T2 disease.[30] Chun et al similarly found that PSM was not affected by surgical volume for men with low and intermediate risk disease, but that surgeons who operated on higher volumes of high risk men could expect to have a significantly lower PSM prevalence compared with that of surgeons who operated on lower volume [31]. A limitation of both our study and Lawrenschuk's is that neither could analyse PSMs based on surgical volume, without knowledge of individual surgeon case-load outside the reporting hospitals. Sammon et al did not examine PSM prevalence but found that high surgical volume centres showed more favourable outcomes for both ORP and RARP in regard to most intraoperative and post-operative complications compared with low surgical volume hospitals.[32]

Given that PSM are a known independent predictor of biochemical recurrence and cancer-specific mortality, a common goal of surgeons should be to avoid PSM where possible. In this paper we provide some indication of factors associated with high PSM in an Australian prostatectomy sample. However, there are a number of limitations to this study which may limit its interpretation. Importantly, we did not determine how specimens were sectioned, nor did we assess the experience of the pathologist undertaking the review, both of which have

been associated with PSM status[7, 33]. A study by van der Kwast found that review of specimens by an expert urologic pathologist after an initial review by a general pathologist resulted in only 69.4% agreement (kappa=0. 45) in regard to PSM status[33]. Ekici et al found that partial sectioning of specimens resulted in good agreement between pathologists regardless of their level of experience, but when an expert pathologist employed complete sectioning technique there was a significant difference in PSM status[7]. Evans et al found that when 12 expert urologic pathologists compared their results, there was good sensitivity and specificity in determining PSM status (83.3% and 97.5% respectively)[8]. These studies suggest that both the technique and the experience of pathologist will affect interpretation of PSM status. Having a centralised pathology review system would provide greater understanding of whether the PSM differences identified in this study are the result of variation in the quality of the surgery or pathology review across sites. _ENREF_8

The Prostate Cancer Registry does not collect the site and number of positive margins so we were unable to report on location of the PSM. There is evidence that the prostate apex is the most common site of PSM and that postolateral margins place the patient most at risk for disease recurrence.[34] However, Grossfeld et al found that the number of positive margins and location of PSM had no significant impact on PSA recurrence nor on non-adjuvant secondary treatment[24]. Stephenson et al found that neither the number of PSMs or the location demonstrated enhanced capacity to predict biochemical recurrence over a simple model containing only whether the patient had positive or negative margins[35]. In addition, the PCR does not collect details of the patient's body mass index, which has also been shown to be associated with PSM[34]._ENREF_15 As discussed earlier, another known limitation of our study is that, while the registry collects details of surgeon volume in contributing sites, it does not assess surgeon volume at non-participating sites, so the impact of individual surgeon volume-quality relationship on PSM and subsequent treatment could not be assessed. Finally,

as this was an observational study and not a randomised controlled clinical trial, we cannot rule out other patient factors which were not collected but might account for differences in PSM prevalence and subsequent treatments.

Conclusions

Radical prostatectomy cases with PSM are significantly more likely to receive additional treatment compared with those having clear surgical margins. Being treated at a private hospital using a robot-assisted technique appears to be associated with a lower risk of PSM even after taking into account the patient's age and disease stage. This needs further investigation as it may simply reflect surgeon experience and case selection. Any effort to reduce the frequency of PSM will undoubtedly also result in better outcomes, both in terms of patient psychological wellbeing and financial burden to the health system.

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Box 1: National Comprehensive Cancer Network (NCCN) risk categories

Category	Definition
Clinically localised disease: very low risk for disease progression	T1a AND Gleason ≤ 6 AND PSA <10 ng/mL AND Fewer than 3 biopsy positive cores, ≤ 50% cancer in each core AND PSA density < 0.15 ng/mL/g
Clinically localised disease: low risk for disease progression	cT1-cT2a AND Gleason score 2-6 ng/mL AND PSA < 10ng/mL
Clinically localised disease: intermediate risk for disease progression	cT2b-T2c OR Gleason score 7 OR PSA 10-20ng/mL
Clinically localised disease: high risk for disease progression	cT3a OR Gleason score 8-10 OR PSA>20 ng/mL
Locally advanced disease: very high risk for disease progression	cT3b-T4; N0, M0
Locally advanced disease: metastatic disease	any cT, N1, M1

Figure 1: Recruitment frame

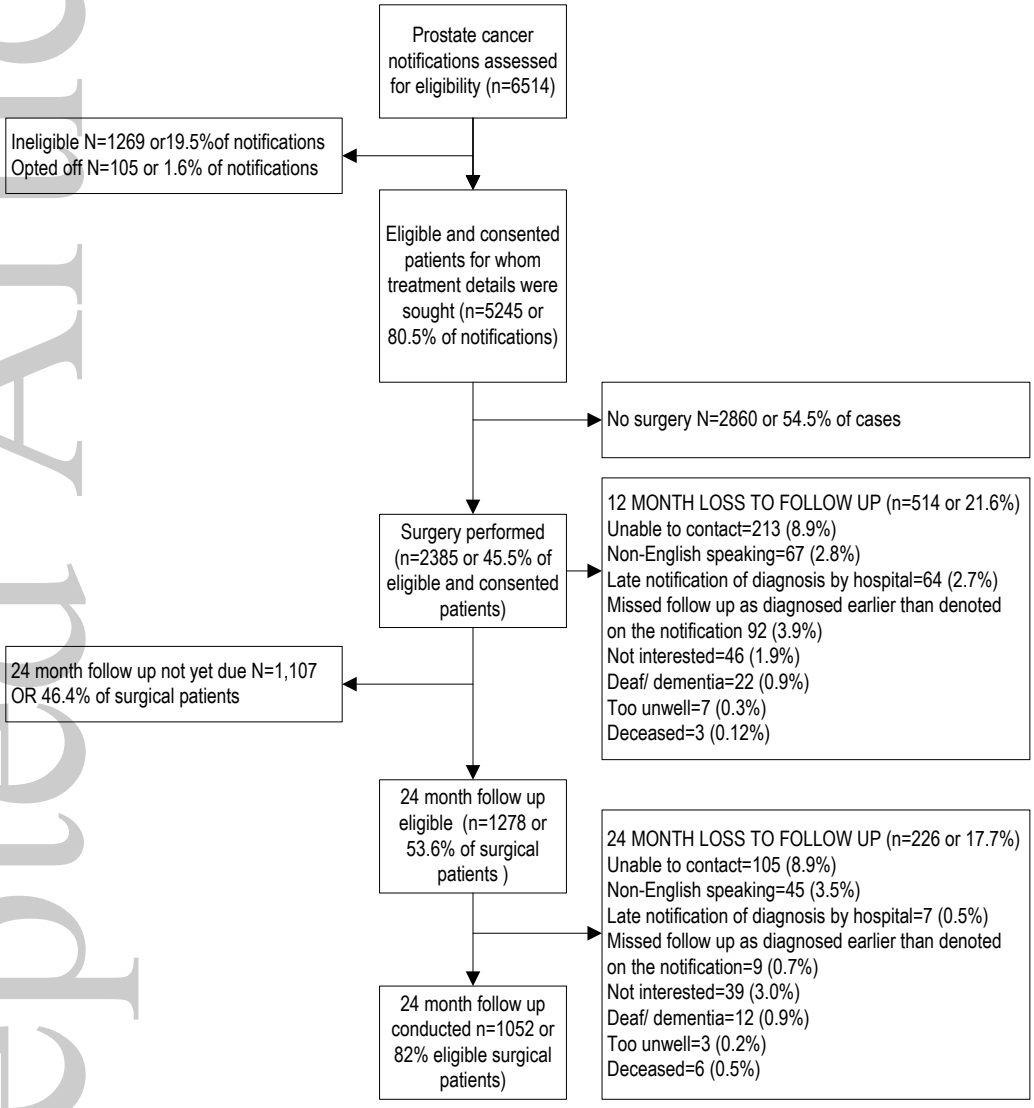

Table 1 Hospital and patient characteristics of all recruited prostatectomy cases notified to the registry between Aug 2008 and February 2012

Age at radical prostatectomy (RP)	N=2385 (100%)
Mean age in years (± SD)	62.2 (6.7) years
Median are in years (range)	62.9 (45.8, 83.9)
First diagnosing hospital	N=2257
Metropolitan	1847 (81.8%)
Regional	374 (16.6%)
Interstate/overseas	36 (1.6%)
Notifying hospital	N=2385
Metropolitan	2163 (90.7)
Regional	222 (9.3)
Time from diagnosis to RP	N=2256
Mean days from diagnosis to RP (± SD)	86 (100) days
Median days from diagnosis to RP (interquartile range)	57 (39, 92) days
Range	1-1088 days
Surgical hospital location	N=2357
Metropolitan	2162 (91.7%)
Regional	195 (8.2%)
Surgical hospital type	N=2359
Public	542 (23.0%)
Private	1817 (77.0%)
Hospital surgical volume	N=2272
Less than or equal to 10 cases/year	61 (2.7%)
More than 10 cases per year	2211 (97.3%)
Clinical T category at diagnosis	N=1961
≤T1c	1052 (53.6%)
T2a	458 (23.4%)
T2b	211 (10.8%)
T2c	123 (6.3%)
T3a	78 (4.0 %)

T3b-T4	12 (0.6%)
N1, M1	21(1.1%)
Not assessed	6 (0.3)
Gleason score at biopsy	N=2355
4	3 (0.1%)
5	7 (0.3%)
6	734 (31.2%)
7	1268 (53.8%)
8	212 (9.0%)
9	124 (5.3%)
10	7 (0.3%)
PSA level at diagnosis	N=2345
0-10 ng/mL	1987 (84.7%)
10.01-20 ng/mL	266 (11.3)
>20.0 ng/mL	92 (3.90%)
NCCN risk of disease progression at diagnosis	N=2363
Low risk	608 (25.7%)
Intermediate risk	1300 (55.0%)
High risk	423 (17.9%)
Locally advanced disease: very high risk	11 (0.5%)
Locally advanced: metastatic disease	21 (0.9%)
Surgical (prostatectomy) pathological T category	N=2083
pT2 disease	1384 (66.4%)
pT3 disease	699 (33.6%)

Table 2: Univariate analysis of predictors of PSMs

Variable	Surgical margin status			P value
	Positive margin 592 (27.2%)	Negative margin 1583 (72.8%)	Total no. 2175 (100)	
Age at surgery	586	1568	2154	0.368[KW]
Mean age (± SD)	62.5 (6.8)	62.1 (6.7)		
Median age in years	63.4	62.6		
Range	45.8-77.9	45.6-81.4		
Surgical hospital location	591	1580	2168	0.862
Metropolitan	550 (27.3)	1467 (72.7)	2017	
Regional	41 (26.6)	113 (73.4)	154	
Hospital type	591	1580	2171	<0.001
Public	170 (34.9)	317 (65.1)	487	
Private	421 (25.0)	1263 (75.0)	1684	
Hospital surgical volume*				
≤10 cases/year	19 (47.5)	21 (52.5)	40	
>10 cases/year	555 (26.4)	1544 (73.6)	2099	0.003
Surgical approach	591	1582	2173	<0.001
Open RP**	376 (32.6)	776 (67.4)	1152	
Robot-assisted RP*	172 (20.4)	672 (79.6)	844	
Laparoscopic RP*	43 (24.7)	131 (75.3)	174	
Other†	0	3 (100)	3	
Clinical T category	455	1311	1757	<0.001
≤T1c	190 (20.2)	749 (79.8)	939	
T2a	123 (28.7))	306 (71.3)	429	
T2b	60 (30.0)	140 (70.0)	200	
T2c	39 (33.6)	77 (66.4)	116	
T3a	34 (48.6)	36 (51.4)	70	
T3b	9 (75.0)	3 (25.0)	12	
PSA at diagnosis	585	1565	2150	<0.001
0-10.0	453(24.7)	1378 (75.3)	1831	
10.1-20.0	89 (26.8)	153(63.2)	242	
Greater than 20	43 (55.8)	34 (44.2)	77	
Biopsy Gleason score	590	1578	2155	<0.001
≤6	131 (19.8)	530 (80.2)	661	
7	342 (28.6)	852 (71.4)	1194	
8-10	117 (37.4)	196 (62.6)	313	
NCCN risk rating	590	1577	2168	<0.001
Low	102 (19.1)	432 (80.9)	534	
Intermediate	317 (26.0)	901 (74.0)	1218	
High	153 (39.5)	234 (60.5)	387	
Locally advanced-very high risk	9 (81.8)	2 (18.2)	11	
Metastatic disease	9 (52.9)	8 (47.1)	17	

KW= Kruskal-Wallis equality-of-populations rank test

* cases were removed where diagnosis was made in a recruiting hospital but prostatectomy was undertaken in a non-recruiting hospital as volume could not be distinguished..

*RP= Radical prostatectomy †Other= radical perineal prostatectomy or cystoprostatectomy

Table 3: Multivariate analysis of predictors of PSMs

Variable	IRR*	95% confidence interval	P value
Hospital type			
Public (reference)	1.00	-	-
Private	0.76	0.63 – 0.93	0.006
Hospital surgical volume			
>10 cases/year	1.00		
≤ 10 cases/year	1.44	1.07-1.93	0.017
Surgical approach			
Open RP (reference)	1.00		
Robot-assisted RP	0.69	0.55-0.87	0.002
Laparoscopic RP	0.73	0.53-1.01	0.055
NCCN risk of disease progression			
Low risk	1.00		
Intermediate risk	1.34	1.09-1.65	0.007
High risk	1.96	1.57-2.45	<0.001
Very high risk	3.81	2.60-5.60	<0.001
Metastatic disease	2.50	1.23- 5.11	0.012

***Incidence rate ratio**

Table 4: Univariate analysis of predictors of receiving secondary cancer treatment following prostatectomy in the 12 month period post diagnosis

Variable	Surgery status			P value
	Surgery only	Surgery + other treatment	Total no.	
	1987 (91.1%)	195 (8.9%)	2182 (100%)	
Age at surgery	1973	195	2168	0.532[KW]
Mean age years (± SD)	62.1 (6.7)	62.5 (6.5)		
Median age in years (IQR)	62.8 (57.8, 67.1)	63.2 (57.5, 67.6)		
Range	45.5-83.9	46.7-76.6		
Less than 65 years	1260 (91.2)	121 (8.8)	1381	0.616
65 years and older	713 (90.6)	74 (9.4)	787	
Surgical hospital location	1982	195	2177	0.769
Metropolitan	1 831 (91.1)	179 (8.9)	2010	
Regional	151 (90.4)	16 (9.6)	167	
Hospital type	1982	195	2177	<0.001
Public	425 (86.7)	65 (13.3)	490	
Private	1 557 (92.3)	130 (7.7)	1687	
Hospital surgical volume	1948	187	2177	0.587
≤10 cases/year	43 (93.5)	3 (6.5)	46	
>10 cases /year	1905 (91.2)	186 (8.8)	2089	
Surgical approach	1980	195	2175	<0.001
Open radical prostatectomy	1026 (88.5)	134 (11.5)	1160	
Robot-assisted radical prostatectomy	783 (94.1)	49 (5.9)	832	
Laparoscopic radical prostatectomy	167 (93.8)	11 (6.2)	178	
Other	4 (80.0)	1 (20.0)	5	
Clinical T category	1606	151	1757	<0.001
≤T1c	884 (95.4)	43 (4.6)	927	
T2a	396 (91.0)	39 (9.0)	435	
T2b	176 (86.7)	27 (13.3)	203	
T2c	102 (86.4)	16 (13.6)	118	
T3a	51 (69.9)	22 (30.1)	73	
T3b	6 (54.5)	5 (45.5)	11	
PSA at diagnosis	1964	194	2158	<0.001
0-10.0	1705 (92.8)	133 (7.2)	1838	
10.1-20.0	209 (86.4)	33 (13.6)	242	
Greater than 20	50 (64.1)	28 (35.9)	78	
RP Gleason score	1961	194	2155	<0.001
≤6	304 (97.4)	8 (2.6)	312	
7	1512 (93.0)	114 (7.0)	1626	
8-10	145 (66.8)	72 (33.2)	217	
NCCN risk rating	1977	195	2172	<0.001

Low	500 (97.1)	15 (2.9)	515	
Intermediate	1160 (94.1)	73 (5.9)	1233	
High	299 (75.3)	98 (24.7)	397	
Very high	5 (50.0)	5 (50.0)	10	
Metastatic disease	13 (76.5)	4 (23.5)	17	
Pathological T category	1826	183	2009	<0.001
pT2 disease	1298 (97.4)	35 (2.6)	1333	
pT3 disease	528 (78.1)	148 (21.9)	676	
Positive surgical margins (PSM)	1916	184	2100	<0.001
No PSM	1484 (96.9)	47 (3.1)	1531	
PSM	432 (75.9)	137 (24.1)	569	

KW= Kruskal-Wallis equality-of-populations rank test

Table 5: Multivariate analysis of predictors of receiving secondary cancer treatment following prostatectomy

Variable	Odds ratio	95% confidence interval	P value
Hospital type			
Public (reference)	1.00	-	-
Private	0.76	0.47-1.22	0.254
Surgical approach			
Open (reference)	1.00		
Robot-assisted RP	0.59	0.39- 0.88	0.010
Laparoscopic RP	0.59	0.29-1.19	0.144
Margin status			
Negative (reference)	1.00	-	-
Positive	5.61	3.82 – 8.22	<0.001
NCCN risk category			
Low risk	1.00		
Intermediate risk	1.15	0.686-2.02	0.620
High risk	4.36	2.24-8.50	<0.001
Very high risk	4.50	1.34-15.17	0.015
Metastatic disease	1.56	0.29-8.31	0.601
Pathological category			
pT2 disease	1.00	-	-
PT3 disease	4.72	2.69-8.23	<0.001

Conflicts of Interest:

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