Variation in positive surgical margin status following radical prostatectomy for pT2 prostate cancer

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MicroAbstract (56/60 words)

Positive surgical margin (PSM) following prostatectomy for pT2 prostate cancer vary throughout the USA. We utilized the National Cancer Database and determined that patient, hospital and cancer-specific factors contributed 2.3%, 3.9% and 15.6% of PSM variation respectively. 84.8% of PSM variation are due to non-oncological factors which represent addressable factors in efforts to improve patient outcome.

Abstract (249/250 words)

Introduction

We evaluated patient, hospital, and cancer-specific factors associated with positive surgical margin (PSM) variability following radical prostatectomy in pT2 prostate cancer in the USA.

Material & Methods

A total of 45,426 men from 1,152 hospitals with pT2 prostate cancer and known margin status following radical prostatectomy were identified using the National Cancer Database (2010-2015). Patient, cancer, hospital factors and surgical approach were extracted. A mixed effects logistic regression model was computed to examine factors associated with PSM and partial-R^2 values to assess the relative contributions of patient, cancer and hospital variables to PSM status.

Results

Median PSM rate of 8.5% (IQR: 5.2-13.0%). Robotic (OR: 0.90, 95% CI: 0.83-0.99) and laparoscopic (OR: 0.74, 95% CI: 0.64-0.90) surgical approach, academic institution (OR: 0.87, 95% CI: 0.76-1.00) and high hospital surgical volume (>297 cases [OR: 0.83, 95% CI: 0.70-0.99) were independently associated with a lower PSM. Black men (OR: 1.13, 95% CI: 1.01-1.26) and adverse cancer specific features (PSA 10-20, PSA >20, cT3 stage, Gleason 7, 8, 9-10; all p>0.01) were independently associated with a higher PSM. Patient-specific, hospital-specific and cancer-specific factors had a contribution of 2.3%, 3.9% and 15.6% to the variation in PSM. Facility had a contribution of 23.7% to the variation in PSM.

Conclusion

Cancer-specific factors account for 15.2% of PSM variation with the remaining 84.8% of PSM variation due to patient, hospital and other factors not accounted within the model. Non-cancer-specific factors represent addressable factors which are important for policy makers in efforts to improve patient outcome.

Keywords: localized; prostate cancer; practice patterns; radical prostatectomy; surgical margin; variation

Introduction

Oncological principles of cancer surgery advocate complete excision of the cancer with negative surgical margins. In localised prostate cancer, the management of positive surgical margins (PSM) following radical prostatectomy remains controversial. PSM has been associated with a two-fold increased risk of biochemical recurrence although this has not been translated to cancer specific survival with long term follow-up.[1, 2]

PSM following radical prostatectomy for pT2 prostate cancer is considered a metric for surgical quality.[3] However, there is significant variation in PSM rates reported in the literature.[1, 4] Cancer specific risk factors for PSM following radical prostatectomy are well established. There is a clear stage correlation with risk of PSM where pT3 cancers report a PSM of as high as 29-50% compared to the 4-23% in pT2 cancers.[5] Inaccurate clinical staging based on pre-surgery magnetic resonance imaging (MRI) leading to the decision for nerve-sparing can be associated with a risk for PSM.[6] Surgical technique, surgeon's preference for a nerve-sparing approach and attempts to preserve maximal urethral length are factors affecting PSM rates.[7, 8] Anatomical location of cancer within the prostate can be a risk factor, where apical cancers in particular have a higher risk of PSM because the lack of a distinct capsule and high anatomical variability of the apex.[1]

What remains less clear is non-cancer specific risk factors. Reports have shown an association between higher surgeon operating volume and lower PSM rates.[7] However, PSM rates between open and robotic techniques are comparable.[9] Cancer specific factors and surgeon volume alone cannot account for the large variation in PSM. Significant variation in the management of prostate cancer has been widely reported. Variations in active surveillance and treatment outcomes for prostate cancer have been demonstrated.[10, 11] We hypothesised that other factors such as patient demographics, socioeconomic, geographic and surgical approach may have an association with PSM.

In this study, we sought to examine contemporary PSM rates in the United States using the National Cancer Data Base (NCDB) registry.[12] We used a multivariable mixed-effects model to estimate the association between PSM and patient demographics, socioeconomic, geographical, hospital, cancer-specific and surgical

approach factors. We then derived the corresponding contribution of each factor to variation in PSM.

Material and methods

Data source

We queried the NCDB, which represents a nationwide oncology database that contains details on cancer care and treatment outcomes across CoC hospital. Since 1989, all newly diagnosed cancers from 1,500 CoC-accredited programmes in the United States and Puerto Rico have been captured by the NCDB. This accounts for over 29 million cancer cases which represents over 50% of all newly diagnosed prostate cancer cases in the United States.[13]

Patient selection

All men diagnosed with prostate cancer between 2010-2015 treated with radical prostatectomy for adenocarcinoma of the prostate (code C61.9 from International Classification of Diseases for Oncology, 3rd edition)[14] according to National Comprehensive Cancer Network (NCCN) guidelines[15] were included for analysis. Patients with pT2N0M0 cancer were selected based on AJCC Cancer Staging Manual (7th edition).[16] Patients with unknown status of histological margin were excluded.

Variable of interest and covariates

PSM was defined as NCDB variable “RX_SUMM_SURGICAL_MARGINS”. Baseline patient specific variables include: patient age at diagnosis (categorised by quartiles: 40-57, 58-62, 63-67 or 68-75 years), prostate-specific antigen (PSA) at prostate cancer diagnosis (continuous), Gleason score (≤6, 7, 8, 9, 10), clinical T stage (cT1, cT2, cT3, cT4), race (Black, White, other), Charlson Comorbidity Index [CCI] (0, 1, ≥2) and year of diagnosis (2010, 2011, 2012, 2013, 2014, 2015). Socioeconomic variables include: insurance status (private, Medicaid, Medicare, other government [including TRICARE, Military, VA and Indian/ Public Health Service], uninsured), median household income within the ZIP code (≤$37,999, $38,000-$47,999, $48,000-$62,999, or ≥ $63,000) and median proportion of individuals within the ZIP code without a high school diploma (≤6.9%, 7%-12.9%, 13%-20.9%, or ≥ 21%).

Geographical and treating hospital variables include: urban/rural status (metropolitan, urban county, rural county), great circle distance(<6.3, 6.3-13.9, 14-35.6, >35.6 miles between a patient's residence based on the ZIP code centroid or city and the street address of the facility), census geographical region (New England, Middle Atlantic, South Atlantic, East North Central, East South Central, West North Central, West South Central, Mountain, or Pacific), type of treating hospital (community cancer program, comprehensive community cancer program, academic/ research programme, integrated network cancer programme) and hospital annual surgical volume according to quartiles (<89 cases, 89-164 cases, 164-296 cases, >297 cases). Surgical approach was defined as open, laparoscopic or robotic.

Statistical analysis

For descriptive statistics, frequency and proportions were used to report categorical variables and medians and interquartile ranges (IQR) were used to report continuous variables. Chi-square and Wilcoxon tests were used to analyse bivariate differences in categorical and continuous variables between patient groups respectively. To account for clustering within treating hospitals we used a random effect model and accounted for individual treating hospital.[17, 18]

A mixed effects logistic regression model was performed to predict the odds of a patient having a PSM following prostatectomy with treating hospital considered as a random effect. Fixed covariables included patient-specific factors (age, CCI, race, socioeconomic factors [education, income, insurance status], urban/ rural locality, great circle distance), cancer-specific factors (PSA at diagnosis, Gleason score, clinical T stage). Hospital-specific factors (surgical approach, treating hospital type, geographical area, hospital surgical volume). Hospital were ranked from least-likely to most-likely to have a patient with PSM following prostatectomy and plotted against the probability of a PSM.

Using a mixed effects logistic regression model, partial-R^2 values were derived for each variable to assess the contributions of patient, hospital and cancer-specific variables to variation in PSM as previously described.[11, 19] Partial R^2 represents the contribution of the variable to the variability in the probability of having a PSM and

was computed by subtracting the pseudo-R^2 value of the model without the variable of interest from the pseudo-R^2 of the complete model.

Data analyses were performed using Stata 15 (StataCorp, College Station, Texas). Statistical significance was defined as a 2-sided significance with $p < 0.05$. A waiver was obtained before commencement of the study by the Brigham and Women's Hospital Institutional review board in accordance with institutional regulation when using deidentified previously collected patient data.

Results

Baseline characteristics

A total of 45,426 men from 1,152 CoC accredited hospital met the inclusion criteria. The median age for the entire cohort was 61 years (IQR: 56-66 years). Table 1 reports the baseline patient demographics and comorbidities, cancer-specific, socioeconomic, geographical and hospital specific variables. Black patients (p=0.001), higher PSA (p<0.001), higher clinical T stage (p<0.001), higher Gleason score (p<0.001), more recent year of diagnosis (p=0.018), open surgical approach (p<0.001), lower income (p=0.006), higher education (p<0.001), nearer great circle distance (p<0.001), treatment at non-academic hospital (p<0.001) and lower hospital surgical volume (p<0.001) were associated with PSM on univariable analysis.

Multivariate logistic regression analysis

Independent factors associated with PSM were estimated using multivariable logistic regression as shown in Table 2. The only patient factor associated with a PSM was Black race (odds ratio [OR]: 1.13, 95% confidence interval [CI]: 1.01-1.26). Socioeconomic factors, rural/ urban county, great circle distance and comorbidity were not associated with PSM. Cancer-specific factors such as PSA of 10-20 ng/mL (OR: 1.18, 95% CI: 1.05-1.32), PSA of >20 ng/mL (OR: 1.36, 95% CI: 1.16-1.59), cT3-4 stage (OR: 1.25, 95% CI: 1.14-2.17), Gleason score 7 (OR: 1.61, 95% CI: 14.9-1.73), 8 (OR: 1.48, 95% CI: 1.28-1.69) and 9-10 (OR: 1.80, 95% CI: 1.46-2.23) were independently associated with a higher odds of PSM. Hospital-specific factors independently associated with lower odds of PSM were robotic (OR: 0.90, 95% CI: 0.83-0.99) and laparoscopic (OR: 0.74, 95% CI: 0.64-0.90) surgical approach, academic institution (OR: 0.87, 95% CI: 0.76-1.00), higher hospital surgical volume (>297 cases [OR: 0.83, 95% CI: 0.70-0.99) and East North Central USA (OR: 0.71, 95% CI: 0.52-0.96).

Variation in positive surgical margins

A total of 4,522 patients (11.1%) had a PSM. The rate of PSM for cases performed each year ranged from 9.1-11.0% between 2010- 2015. The median PSM rate was 8.5% (IQR: 5.2-13.0%) with a PSM range of 0-100%.

Figure 2 shows a caterpillar plot depicting the hospitals' adjusted risk of PSM ranked from lowest to highest adjusted for patient demographics, cancer-specific, socioeconomic, geographical and hospital specific variables. Partial-R^2- values computed from the mixed effects logistic regression model for the investigated variables are shown in Table 3. The overall model accounted for 24.9% of PSM variation. Patient-specific, hospital-specific and cancer-specific factors contributed 2.3%, 3.9% and 15.2% of the variation in PSM in pT2 patients, respectively, that was unexplained by all of the other predictors. The individual facility, regardless of any other characteristics, explained 23.7% of the variation in PSM unexplained by the other predictors.

Discussion

The key finding in this study is that there is significant variability in PSM rates following radical prostatectomy for pT2 prostate cancer. While cancer-specific variables such as Gleason score, clinical T stage and PSA at diagnosis are factors that influence the risk of PSM, non-cancer specific variables such as patient, hospital and surgical approach also account for variability in PSM even after adjustment in a multivariate model. In this study, we report that 2.3% and 3.9% of variation within the model are due to patient and hospital-specific factors while cancer-specific factors contributed 15.2% of PSM variation. Moreover, individual facility contributed 23.7% to the variability in the probability of having a PSM. While the sum of partial R^2 values can be above or below the total R^2, their relative magnitude can be compared to assess additional explanatory power. This population-based study also found that the median PSM rate for pT2 prostate cancer in the United States is 8.5%. This establishes a bench mark where poorer performing centres should strive to improve and highlights modifiable factors which can be addressed to improve patient outcome.

In an increasingly cost-conscious healthcare service, healthcare systems are shifting towards a pay-for-performance model. The traditional fee-for-service model reimburses healthcare providers based on quantity and complexity of services; in fact, subsequent procedures or complications are chargeable by the healthcare provider. Significant changes to bundled payments and pay-for-performance models promote high quality care as these improves efficiency within the service. However, often efforts to improve surgical outcome or medical service are multi-factorial and significant improvements represent the aggregation of marginal gains to achieve high quality outcome.

The median PSM rate in this study was 8.5% (IQR: 5.2-13.0%) which was lower compared to the 10.7-16.6% reported in a systematic review of cases published between 2002-2010.[4] The adoption of robotic prostatectomy may have indirectly led to the improvement in PSM rates by increased centralisation of care due to the high cost associated with the procurement of robotic technology. Indeed, between 2002 and 2010, the number of surgeons performing radical prostatectomy fell from 10,000 surgeons to 8,200 and the proportion of high volume surgeons (performing >24 prostatectomies annually) increased from 10% to 45%.[20] It is widely reported that

there is a strong correlation between surgical volume and risk of PSM.[7] We observed this only in the top quartile of hospital surgical volume which may be explained by increased centralisation of care. This in turn results in an overall increase in surgical case load of remaining centres which makes differences in surgical proficiency less apparent.

We report that both robotic and laparoscopic prostatectomy had significantly lower PSM compared to open prostatectomy even after adjusting for cancer specific variables and hospital volume. However, there are variables that we could not account for. It is likely individual surgeons performing limited number of prostatectomies do not have access to the robotic platform and high-volume surgeons are more likely to perform radical prostatectomies robotically. Proponents for robotic prostatectomy might argue that a laparoscopic approach may allow better visualisation during apical dissection however, it is likely that PSM is influenced by individual surgical experience which we cannot account for in the NCDB.[8, 21]

It is widely accepted that Black patients have worse cancer outcomes following radical prostatectomy even after adjusting for Gleason score and disease stage.[22] However, the relationship between race and PSM is less certain. Previous retrospective studies have failed to find an association between race and PSM after controlling for cancer specific variables.[23, 24] More recently, Jalloh and colleagues studied 4,231 low risk prostate cancer patients treated with radical prostatectomy.[25] After adjusting for clinical variables, year of diagnosis and clinical site they report that Black men were at a higher risk of having a PSM. This study did not adjust for hospital surgical volume and had a relatively small cohort of Black men (n= 273) of which, 22 men had a robotic approach. Our findings concur with what has been reported and even after adjustment with a multivariable model, the association between Black men and higher PSM was still apparent.[25] Reasons for this remain unknown, although Black patients have an android shaped pelvis, which are taller and narrower possibly making apical dissection, a common site for PSM, more challenging. However, is also likely that Black patients have access to poorer quality care which may explain this disparity in surgical outcome.[10, 26]

Limitations in our study should be taken into account when interpreting the results. NCDB data collection is retrospective in nature. Data collected were from CoC

hospitals which are often larger tertiary hospitals and these findings may not be generalised to smaller group practices. Nevertheless, NCDB captures over 50% of patients diagnosed with prostate cancer providing good representation of the United States. We also do not have details on tumour anatomical location following radical prostatectomy to determine if the higher risk of PSM in Black men was due to higher proportion of apical cancers. Additionally, we do not have details about the preoperative decision to perform a nerve-spare approach which may increase the likelihood of a PSM. The use of intraoperative frozen section when performing nerve-sparing cannot be determine and this is an important consideration as this has been shown to reduce PSM.[27] There is also a lack of data on the length of PSM which has been shown to be an independent factor to biochemical recurrence.[28] Finally, while hospital case volume is reported, we cannot determine individual surgeon case volume.

Conclusion

There is significant variation in PSM following radical prostatectomy for pT2 disease. Patient-specific, hospital-specific and cancer-specific factors contributed 2.3%, 3.9% and 15.2% to the variation in PSM in pT2 patients respectively. A total of 84.8% of PSM variation due to patient, hospital and other factors not accounted for in the model. Non cancer-specific factors represent potentially addressable factors which are important for policy makers in their efforts to improve patient outcomes.

Clinical Practice Points (179/250 words):

- Positive surgical margin (PSM) following radical prostatectomy for pT2 prostate cancer is considered a metric for surgical quality. However, there is significant variation in PSM rates.
- In this study, we examined contemporary PSM rates in the United States using the National Cancer Data Base (NCDB) registry and used a multivariable mixed-effects model to estimate the association between PSM and patient demographics, socioeconomic, geographical, hospital, cancer-specific and surgical approach factors.
- We report that robotic and laparoscopic surgical approach, academic institution and high hospital surgical volume were independently associated with a lower PSM. Black men and adverse cancer specific features (PSA 10-20, PSA >20, cT3 stage, Gleason 7, 8, 9-10; all p>0.01) were independently associated with a higher PSM.
- The overall mixed effects logistic regression model accounted for 24.9% of PSM variation. Patient-specific, hospital-specific and cancer-specific factors had a contribution of 2.3%, 3.9% and 15.6% to the variation in PSM. Facility had a contribution of 23.7% to the variation in PSM.
- Non cancer-specific factors represent potentially addressable factors which are important for policy makers in their efforts to improve patient outcome.

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Tables:

Table 1: Baseline patient demographics, socioeconomic, geographical, hospital and cancer-specific factors stratified according to positive surgical margin (PSM) status.

Table 2: Multilevel Hierarchical Mixed Effects Logistic Regression Model to determine variables independently associated with a PSM in pT2 prostate cancer patients treated with radical prostatectomy.

Table 3: Multilevel hierarchical logistic regression model to determine pseudo-R2-values and significance of patient, hospital and cancer-specific variables.

Figures:

Figure 1: Inclusion and exclusion criteria used to determine study cohort.

Figure 2: Variation in PSM frequency adjusted for patient demographics, comorbidity, socioeconomic, geographical, hospital and cancer-specific factors.

482 Table 1: Baseline patient demographics, socioeconomic, geographical, hospital and
483 cancer-specific variables stratified according to positive surgical margin (PSM)
484 status.

	All patients (n=45,426)	Positive surgical margin (p=4,522)	No positive surgical margin (n=40,904)	P value
Age at diagnosis, n (%)				
32-56 yr	12,167 (26.8)	1,223 (27.1)	10,994 (26.7)	0.325
57-61 yr	10,662 (23.4)	1,021 (22.6)	9,641 (23.6)	
62-66 yr	11,537 (25.4)	1,188 (26.3)	10,349 (25.3)	
67-90 yr	11,060 (24.4)	1,090 (24.1)	9,970 (24.4)	
Race, n (%)				0.001
White	38,729 (85.3)	3,800 (84.0)	34,929 (85.4)	
Black	4,699 (10.3)	543 (12.0)	4,156 (10.2)	
Other	1,392 (3.1)	119 (2.6)	1,273 (3.1)	
Unknown	606 (1.3)	60 (1.4)	546 (1.3)	
Charlson Comorbidity Index, n (%)				0.195
0	37,738 (83.1)	3,718 (82.2)	34,020 (83.2)	
1	6,643 (14.6)	702 (15.5)	5,941 (14.5)	
>1	1,045 (2.3)	102 (2.3)	943 (2.3)	
Prostate specific antigen at diagnosis ng/ mL, n (%)				<0.001
<10	33,009 (72.7)	3,309 (73.2)	29,700 (72.6)	
10-20	3,436 (7.6)	415 (9.2)	3,021 (7.39)	
>20	1,582 (3.5)	212 (4.7)	1,370 (3.4)	
Unknown	7,399 (16.3)	586 (13.0)	6,813 (16.6)	
Clinical T stage, n (%)				<0.001
cT1	1,120 (2.5)	88 (2.0)	1,032 (2.5)	
cT2	39,773 (87.6)	4,020 (88.9)	35,753 (87.4)	
cT3-4	668 (1.5)	91 (2.0)	577 (1.4)	
Unknown	3,865 (8.5)	323 (7.1)	3,542 (8.7)	
Gleason score, n (%)				<0.001
≤6	19,408 (43.7)	1,577 (34.9)	17,831 (43.6)	
7	15,675 (34.5)	1,913 (42.3)	13,762 (33.6)	
8	2,537 (5.6)	296 (6.6)	2,241 (5.5)	
9-10	851 (1.9)	118 (2.6)	733 (1.8)	
Unknown	6,995 (15.3)	618 (13.6)	6,337 (15.5)	
Year of diagnosis, n (%)				0.018
2010	9,844 (21.7)	981 (21.7)	8,863 (21.7)	
2011	9,675 (21.3)	958 (21.2)	8,717 (21.3)	
2012	7,312 (16.1)	711 (15.7)	6,601 (16.1)	
2013	6,837 (15.0)	621 (13.7)	6,216 (15.2)	
2014	5,966 (13.1)	617 (13.7)	5,349 (13.1)	
2015	5,792 (12.8)	634 (14.0)	5,158 (12.6)	
Surgical approach, n (%)				<0.001
Open	8,890 (19.6)	945 (20.9)	7,945 (19.4)	
Laparoscopic	1,882 (4.1)	159 (3.5)	1,723 (4.2)	
Robotic	33,347 (73.4)	3,240 (71.7)	30,107 (73.6)	
Unknown	1,307 (2.9)	178 (3.94)	1,129 (2.8)	
Insurance status, n (%)				0.199
Private	28,557 (62.9)	2,810 (62.1)	25,747 (62.9)	
Medicaid	827 (1.8)	91 (2.0)	736 (1.8)	
Medicare	14,088 (31.0)	1,407 (31.1)	12,681 (31.0)	
Other government	714 (1.6)	75 (1.7)	639 (1.6)	
Uninsured	582 (1.3)	75 (1.7)	507 (1.2)	
Unknown	658 (1.5)	64 (1.4)	594 (1.5)	
Median income quartiles within ZIP code, n (%)				0.006
≥$63,000	17,849 (39.3)	1,691 (37.4)	16,158 (39.5)	
$48,000-$62,999	12,434 (27.4)	1,251 (27.7)	11,183 (27.3)	
$38,000-$47,999	9,305 (20.5)	956 (21.1)	8,349 (20.4)	
≤$37,999	5,727 (12.6)	605 (13.4)	5,122 (12.5)	
Unknown	111 (0.2)	19 (0.4)	92 (0.2)	

Percentages of no high school degree, n (%)				0.001
≥21%	5,628 (12.4)	603 (13.2)	5,025 (12.3)	
13-20.9%	10,219 (22.5)	1,003 (22.2)	9,216 (22.5)	
7-12.9%	15,084 (33.2)	1,553 (34.3)	13,531 (33.1)	
≤6.9%	14,398 (31.7)	1,345 (29.7)	13,053 (31.9)	
Unknown	97 (0.2)	18 (0.4)	79 (0.2)	
Urban/ rural status of county, n (%)				0.593
Metropolitan	37,148 (81.8)	3,664 (81.0)	33,484 (81.9)	
Urban	6,267 (13.8)	649 (14.4)	5,618 (13.7)	
Rural	885 (2.0)	92 (2.0)	793 (1.9)	
Unknown	1,126 (2.5)	117 (2.6)	1,009 (2.5)	
Great circle distance, n (%)				<0.001
<6.3 miles	11,197 (24.7)	1,215 (27.0)	9,982 (24.5)	
6.3-13.9 miles	11,388 (25.1)	1,156 (25.7)	10,232 (25.1)	
14-35.6 miles	11,399 (25.2)	1,144 (25.4)	10,255 (25.1)	
>35.6 miles	11,338 (25.0)	986 (21.9)	10,352 (25.4)	
Treating hospital, n (%)				<0.001
Comprehensive community cancer programme	18,705 (41.2)	2,001 (44.3)	16,704 (40.9)	
Community cancer programme	2,474 (5.5)	307 (6.8)	2,167 (5.3)	
Integrated Network Cancer Programme	5,034 (11.1)	613 (13.6)	4,421 (10.8)	
Academic	19,148 (42.2)	1,594 (35.3)	17,554 (43.0)	
Hospital surgical volume, n (%)				<0.001
<89 cases	10,098 (22.2)	1,158 (25.6)	8,940 (21.9)	
89-163 cases	11,380 (25.1)	1,245 (27.5)	10,135 (24.8)	
164-296 cases	11,554 (25.4)	1,181 (26.1)	10,373 (25.4)	
>297 cases	12,394 (27.3)	938 (20.7)	11,456 (28.01)	
Census division of treatment facility, n (%)				<0.001
New England	2,058 (4.5)	202 (4.5)	1,856 (4.5)	
Middle Atlantic	7,226 (15.9)	697 (15.4)	6,529 (16.0)	
South Atlantic	9,282 (20.5)	917 (20.3)	8,365 (20.5)	
East North Central	7,865 (17.3)	769 (17.1)	7,096 (17.4)	
East South Central	3,895 (8.6)	305 (6.8)	3,590 (8.8)	
West North Central	4,530 (10.0)	462 (10.2)	4,068 (10.0)	
West South Central	3,434 (7.6)	358 (7.9)	3,076 (7.5)	
Mountain	2,060 (4.5)	272 (6.0)	1,788 (4.3)	
Pacific	5,011 (11.1)	533 (11.8)	4,478 (11.0)	

499 Table 2: Multilevel Hierarchical Mixed Effects Logistic Regression Model to
500 determine variables independently associated with a positive surgical margin in pT2
501 prostate cancer patients treated with radical prostatectomy.

Variables	Odds ratio	95% CI	P value
Patient-specific			
Age at diagnosis			
32-56 yr			
57-61 yr	0.91	0.83-0.99	0.031
62-66 yr	0.96	0.88-1.05	0.389
67-90 yr	0.92	0.82-1.03	0.146
Year of diagnosis			
2010			
2011	0.98	0.89-1.08	0.620
2012	0.93	0.84-1.04	0.209
2013	0.84	0.75-0.94	0.003
2014	0.95	0.85-1.07	0.416
2015	0.98	0.87-1.09	0.685
Race			
White			
Black	1.13	1.01-1.26	0.024
Other	0.86	0.70-1.05	0.132
Unknown	0.96	0.72-1.28	0.787
Charlson Comorbidity Index			
0			
1	1.06	0.97-1.15	0.238
>1	0.95	0.77-1.18	0.672
Insurance status			
Private			
Medicaid	1.02	0.80-1.29	0.892
Medicare	0.98	0.89-1.08	0.716
Other government	0.97	0.75-1.24	0.800
Uninsured	1.24	0.95-1.63	0.109
Unknown	1.00	0.75-1.34	1.000
Median income quartiles within ZIP code			
≥$63,000			
$48,000-$62,999	1.03	0.94-1.13	0.555
$38,000-$47,999	1.06	0.94-1.19	0.349
≤$37,999	1.11	0.95-1.29	0.187
Unknown	0.72	0.09-5.82	0.756
Percentage of no high school degree			
≥21%			
13-20.9%	0.94	0.84-1.06	0.336
7-12.9%	1.02	0.89-1.16	0.802
≤6.9%	0.93	0.80-1.08	0.348
Unknown	1.09	0.08-14.29	0.948
Urban/ rural status of county			
Metropolitan			
Urban	1.03	0.92-1.16	0.577
Rural	1.01	0.79-1.29	0.931
Unknown	1.03	0.82-1.27	0.816
Great circle distance			
<6.3 miles			
6.3-13.9 miles	1.00	0.92-1.10	0.970
14-35.6 miles	1.01	0.93-1.12	0.740
>35.6 miles	0.98	0.88-1.10	0.781
Cancer specific			
Prostate specific antigen			
<10			
10-20	1.18	1.05-1.32	0.004
>20	1.36	1.16-1.59	<0.001
Unknown	0.80	0.72-0.89	<0.001
Clinical T stage			
cT1			
cT2	1.25	0.99-1.57	0.060

cT3-4	1.57	1.14-2.17	0.006
Unknown	1.11	0.86-1.42	0.438
Gleason score			
≤6			
7	1.61	1.49-1.73	<0.001
8	1.48	1.28-1.69	<0.001
9-10	1.80	1.46-2.23	<0.001
Unknown	1.19	1.06-1.35	0.003
Hospital level variables			
Surgical approach			
Open			
Robotic	0.90	0.83-0.99	0.029
Laparoscopic	0.74	0.62-0.90	0.002
Unknown	1.25	1.04-1.51	0.018
Treating hospital			
Comprehensive community cancer programme			
Community cancer programme	1.17	0.98-1.40	0.079
Integrated Network Cancer Programme	1.08	0.91-1.28	0.378
Academic	0.87	0.76-1.00	0.044
Hospital surgical volume			
<89 cases			
89-163 cases	1.01	0.90-1.13	0.897
164-296 cases	0.92	0.81-1.05	0.240
>297 cases	0.83	0.70-0.99	0.038
Census division of treatment facility			
New England			
Middle Atlantic	1.05	0.81-1.36	0.729
South Atlantic	0.93	0.72-1.20	0.576
East North Central	1.02	0.79-1.31	0.867
East South Central	0.71	0.52-0.96	0.025
West North Central	1.03	0.78-1.37	0.833
West South Central	1.04	0.78-1.39	0.789
Mountain	1.36	1.00-1.85	0.053
Pacific	1.10	0.85-1.44	0.463

Table 3: Multilevel hierarchical logistic regression model to determine pseudo-R2- values and significance of patient, hospital and cancer-specific variables.

Variables	**Partial R^2**
Overall model (including random effect)[a]	0.24852
Single facility	0.23698
Patient-specific variables[a]	0.02270
Age (quartiles)	0.00257
Race (White, Black, other, unknown)	0.00402
CCI (0, 1, >1)	0.00079
Insurance status (private, Medicaid, Medicare, other government, uninsured, unknown)	0.00144
Median income quartiles within ZIP code (quartiles)	0.00094
Quartiles of no high school degree (quartiles)	0.00246
Urban/ rural status of county (metropolitan, urban, rural, unknown)	0.00019
Great circle distance (quartiles)	0.00000
Year of diagnosis (2010, 2011, 2012, 2013, 2014, 2015)	0.00519
Hospital-specific variables[a]	0.03875
Surgical approach (open, laparoscopic, robotic, unknown)	0.01146
Treating hospital (Academic, CCP, CCCP, INCP, unknown)	0.00507
Hospital surgical volume (quartiles)	0.00333
Census division of treatment facility	0.01173
Cancer-specific variables [a]	0.15181
PSA at diagnosis (quartiles)	0.02102
Clinical T stage (cT1, cT2, cT3, cT4)	0.00452
Gleason score (≤6, 7, 8, 9, 10, unknown)	0.09474

[a]Random effect model

Figure 1: Inclusion and exclusion criteria used to determine study cohort.

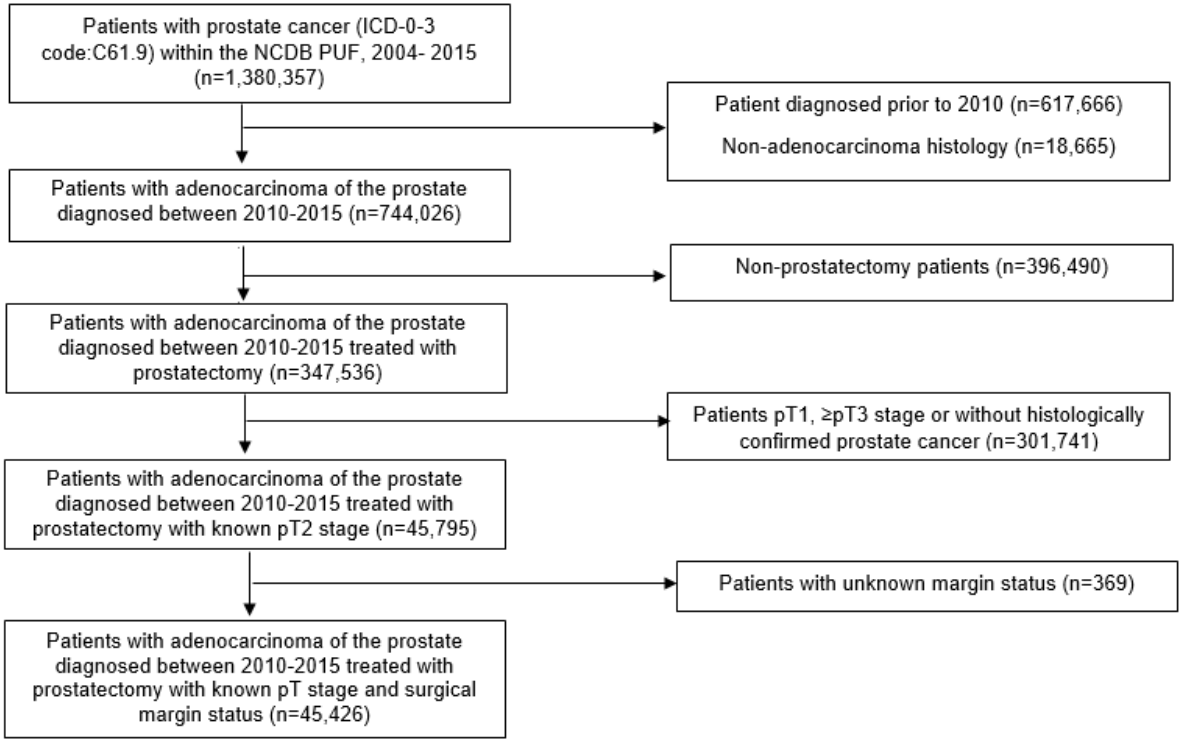
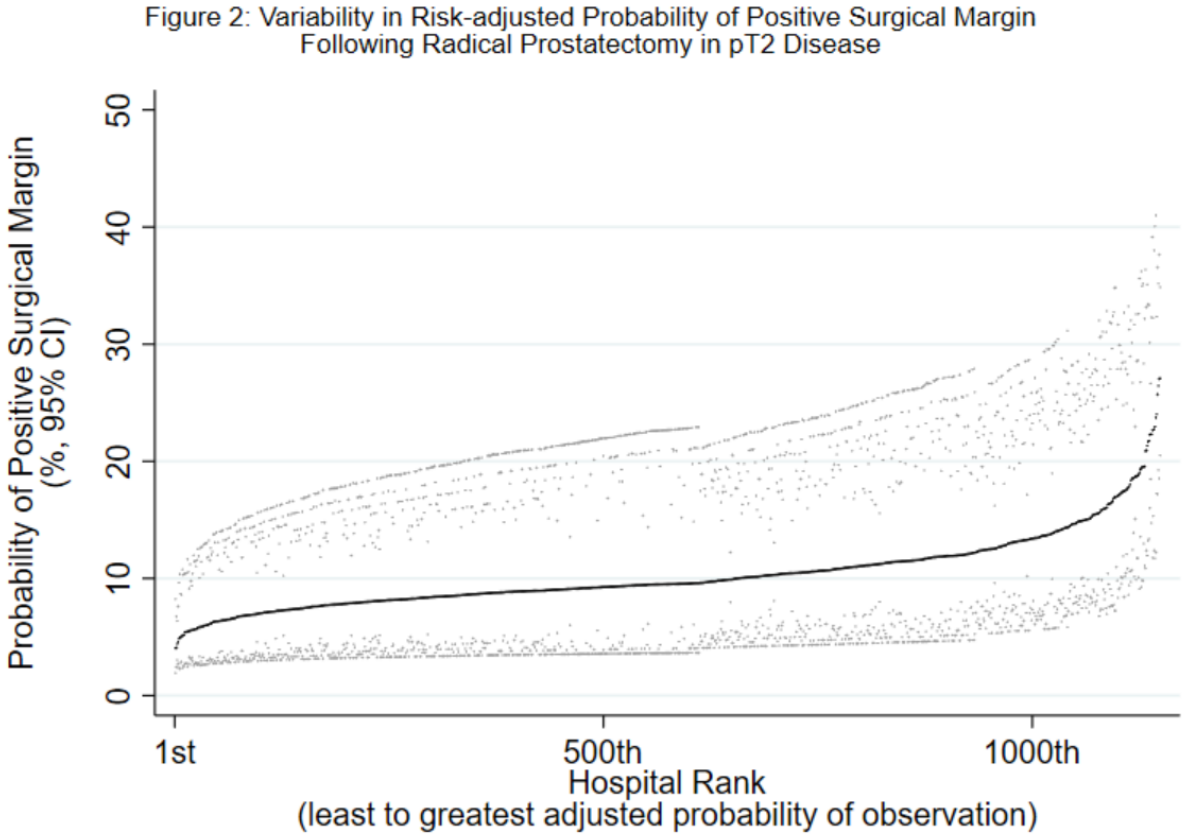


Figure 2: Variation in positive surgical margins frequency adjusted for patient demographics, comorbidity, socioeconomic, geographical, hospital and cancer-specific factors.



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