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Predictors of Prostate Cancer Specific Mortality after Radical Prostatectomy: 10 year oncologic outcomes from the Victorian Radical Prostatectomy Registry

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Abstract

Purpose: To identify the ability of multiple variables to predict prostate cancer specific mortality (PCSM) in a whole of population series of all radical prostatectomies (RP) performed in Victoria, Australia.

Materials & Methods: A total of 2,154 open RPs were performed in Victoria between July 1995 and December 2000. Subjects without follow up data, Gleason grade, pathological stage were excluded as were those who had pT4 disease or received neoadjuvant treatment. 1,967 cases (91.3% of total) met the inclusion criteria for this study. Tumour characteristics were collated via a central registry. We used competing hazards regression models to investigate associations.

Results: At median follow up of 10.3 years pT stage of RP ($p<0.001$) and high Gleason score of the RP specimen ($p<0.001$ for ≥ 8 [Subhazard ratio (SHR) 11.19] and 4+3=7 [SHR 7.10]) compared with Gleason score 6 disease were strong predictors of progression to PCSM. Gleason score 3+4=7 was not at this time a significant predictor of PCSM ($p=0.08$, SHR 1.84). Predictors of PCSM, independent of stage and grade, included rural residency ($p=.003$), primary surgeon contributing less than 40 cases (low-volume) to the VRPR ($p=.025$) and the involvement of a trainee surgeon in the operation ($p=.031$).

Conclusion: The significant prediction of PCSM by pT cancer stage, Gleason score and primary Gleason pattern at RP in this whole of population study suggests a need to avoid understaging/grading in the process of cancer diagnosis and active surveillance protocols. Multi-modality therapy is likely to have a greater impact on PCSM in higher stage and Gleason grade disease. Identification of increased PCSM with rural residency and with involvement of a trainee

urologist, and reduction in PCSM with higher surgeon volume all suggest potential for improved PC outcomes to be achieved with changes to surgical training and service delivery.

Introduction

Since the introduction of prostate specific antigen (PSA) testing in the early 1990s, radical prostatectomy (RP) has been the dominant procedure in urologic practice for the management of organ confined prostate cancer (PC) for men under 70 years of age. Although the number of RP performed has reduced over the past 5 years subsequent to the introduction of active surveillance protocols, this form of intervention remains central to the management of prostate cancer [1].

With the more widespread introduction of RP to standard urologic practice in the early 1990's the Urological Committee of the Victorian Cooperative Oncology Group initiated the prospective collection of data on all RPs performed in Victoria in order to ascertain in a whole of population setting the outcomes from the use of RP. As a consequence, the Victorian Radical Prostatectomy Registry (RPR) was established within the Victorian Cancer Registry (VCR), to which there is mandatory notification from all hospitals and pathology laboratories by law of all human malignancies diagnosed in the state of Victoria, Australia. The VCR is managed by Cancer Council Victoria, and the establishment of the RPR was approved by The Cancer Council of Victoria's Human Research Ethics Committee.

The purpose of this study was to determine outcomes following treatment by RP in a whole of population cohort, and to identify factors that may contribute to reduced prostate cancer specific mortality for patients being treated by RP.

Methods

Patient Population:

All cases of prostate adenocarcinoma diagnosed in Victoria over the period 1995 – 2000 were identified via mandatory notification by hospitals and pathologists to the VCR. All RPs performed in the period from July 1995 to December 2000 were identified and followed up with the assistance of all urologists practising in the state of Victoria over that time. All patients were treated via an open retroperitoneal approach as laparoscopic and robotic technology for this procedure had not been introduced at that time. Patients who had undergone RP as part of a cystoprostatectomy for bladder cancer were excluded from the study.

Registry Data-Collection:

All notifications of prostate cancer by hospitals and pathologists were fast-tracked within the VCR to minimise the time lag between treatment and registration. Once the data were coded and registered on the cancer registry, if an RP had been performed a VRPR registration form was sent to the treating urologist for completion. For 5 successive years, on the anniversary of each registration, a follow-up form was sent to the treating urologist for completion. A health information manager was provided as required to visit the practices of participating urologists to assist with completing registration and follow-up forms, and to assist with data collection beyond 5 years of follow-up. If a patient ceased being followed post surgery by their primary treating urologist the doctor responsible for ongoing care was identified and requests for follow up information were made. Information on deaths was obtained from the VCR that receives notifications of all deaths in Victoria, and which is matched against the National Death Index on

regular basis to capture deaths that occur outside of the state. Prostate cancer specific mortality (PCSM) was recorded where prostate cancer was noted as the primary cause of death.

For each registrant the data held by the VCR included demographic details as well as data on the individual cancer coded to ICDO-2. This included Gleason scores for both the biopsy and resection specimens, margin positivity status and TNM staging. The registration form captured additional information on mode of presentation, health system used for treatment (i.e. private or public), use of neo-adjuvant therapy; clinical stage; PSA test method and level at biopsy; biopsy method; operation type; surgeon ; laboratory that analysed the prostatectomy specimen and preoperative level of sexual function.

Patient Follow-up Data

The follow up form captured information relevant to the status of PC after initial surgery, including most recent PSA level and test method out to 13.5 years post surgery, adjuvant therapy, level of sexual function and continence post surgery and any further surgical intervention required (bladder neck incision, artificial sphincter, etc). Additional follow up included record linkage to Victorian pathology laboratories and radiotherapy facilities in order to collect full PSA testing histories (to identify time of any PSA failure) and salvage radiotherapy, respectively.

Exclusion criteria

Men without follow-up data were excluded. Subjects without a recorded pathological Gleason grade or T-stage were also excluded as were 50 men who received neoadjuvant therapy. Men

with pT4 disease (n=42, PCSM =4) were also excluded due to a lack of coherence in postoperative treatment (adjuvant ADT n=23, adjuvant EBRT n=4, adjuvant ADT and EBRT n= 6, no treatment n=3, unknown n=6). It was felt that the variability in management in this group was sufficiently different from the near uniform course of men with pT2-pT3 disease to preclude a reasonable comparison with this larger group.

Socio-economic and Geographic Data:

In order to classify individual subjects with respect to their socioeconomic status (SES), their usual residential address at time of surgery was coded to a geographic area indicator that was then used to assign the Index of Relative Disadvantage, a Socio-Economic Index For Area (SEIFA) – derived from five yearly national census data and published by the Australian Bureau of Statistics (ABS) [2].

Rural status was defined using the ABS remoteness structure, part of the 2001 Australian Standard Geographical Classification. This categorised census collection districts for Victoria into four classifications: Major cities, Inner regional, Outer Regional and Remote [3]. We defined rural as not residing in the "major cities" classification. The usual residential addresses of registrants were geocoded with latitude and longitude co-ordinates accurate to five decimal places which allowed categorisation into urban and rural residence.

The volume of RPs performed by individual surgeons was also evaluated as a predictive factor. In undertaking this analysis an arbitrary number of 40 cases (8 per year) contributed to the RPR

was chosen to distinguish higher from lower volume radical prostatectomy surgeons. This figure was chosen as on assessment of case number contributed to the registry it appeared to distinguish between surgeons who regularly undertook RP as a component of prostate cancer management throughout the study period, and those who were either very early I their learning curve or were only occasional users of this technique in the course of their clinical practice.

Statistical analysis

Univariable and multivariable competing risks regressions based on the Fine and Gray method were fitted to analyse PC specific mortality with other-cause-mortality as the competing hazard [4]. Formal statistical testing of the proportional hazards assumption by including interactions with a time variable found that it was not violated. Factors associated with mortality in univariate analyses were included simultaneously in multivariable regression models with stage and grade to identify independent predictor variables. Time from surgery was used as the time axis. All tests were two sided and significance level set at $p \leq 0.05$. Analyses were performed with Stata 12.1 SE (Statacorp, College Station, TX, USA).

Between 1st July1995 and 31st December 2000, 2154 eligible subjects were identified from pathology reports to the VCR as having had a RP, with 53 surgeons (excluding trainees) having been the primary surgeon for at least one operation. Demographic and baseline data together with detailed information on stage and grade of prostatectomy specimens for these subjects have been previously published, and provide insight into the clinical, biochemical and socio-economic features of men with PC treated by RP in this period [5].

Results

With on-going follow up of this patient group, information was available for 2,113 men (98.1%) with median time of follow up being 10.3 years (range 0.3 – 13.5 years). 1,967 (91.3%) men met the inclusion criteria for this study. At this duration of follow up there had been 75 deaths from PC (prostate cancer specific mortality, PCSM) in this cohort and 172 deaths from other causes. Table 1 shows the breakdown of this cohort according to the variables included in this study.

Pathologic T stage was a strong predictor of prostate cancer specific mortality for patients undergoing RP (figure 1). Subhazard ratios of 13.8 and 3.5 in univariable analysis were observed for T3b and T3a disease respectively ($p<0.001$) compared with patients with T2 (organ confined) disease.

Similar risks were associated with the Gleason score of the primary tumour (figure 2). Subhazard ratios of 11.2 and 7.10 ($p<0.001$) in univariable analysis were noted for Gleason score ≥ 8 and 4+3=7 compared with Gleason score 6 disease at total prostatectomy. A trend toward increased PCSM was noted, but statistical significance was not achieved, for patients with Gleason score 3+4=7 disease at this time (SHR 1.84, P=0.08), suggesting that primary Gleason pattern at RP is a key factor in determining patient outcomes after radical prostatectomy. The significant risks maintained statistical significance ($p<0.005$) when both stage and grade were entered simultaneously in a multivariable model.

Other factors also appear to influence progression to PCSM after RP. After adjustment for stage and grade, rural residence was a strong independent predictor of PCSM (p=0.003), as was involvement of a trainee surgeon in the operation (p=0.031). This latter feature also may have been reflected in a non-significant trend for progression to PCSM after RP for patients treated in public compared with private hospitals (p=0.084).

The volume of RPs performed by individual surgeons was also evaluated as a predictive factor. (an arbitrary number of 40 cases (8 per year) contributed to the RPR being chosen to distinguish higher from lower volume radical prostatectomy surgeons). Using this cut off, a lower risk (p=0.025) of PCSM was observed for surgeons handling a higher volume of RPs.

Other factors were evaluated for possible associations with risk of PCSM independent of stage and grade. No significant associations were identified with socio-economic status of patients undergoing RP (p=0.21) and number of radical prostatectomy specimens evaluated by the reporting pathology laboratory (<100 specimens vs >100 specimens p=0.26). Age at surgery greater than 65 years was also found to be a non-significant predictor of PCSM (p=0.95). Using univariate analysis, PSA level at diagnosis and margin positivity status were strong predictors of PCSM but these factors were strongly correlated with stage and grade. Margin status is correlated on univariate analysis with stage and grade to a level of p<0.0001for both variables, but was not associated with pcsm independent of these variables (p=0.901). The practical reason for this finding may be that margin status may matter at the individual surgeon level, but at the population level where this analysis is primarily directed the individual surgeon contribution to

quality of surgery is averaged out. Consequently the main driver of margin status in this study is the tumours themselves rather than an effect by any outlying surgeon.

Discussion

Few whole of population datasets have been published in reference to RP. Although the significance of data from multi-centre or centre of excellence series is unquestioned, whole of population series provide a real-life evaluation of treatment, including that delivered by surgeons in regional and remote locations and by those with all levels of post-certification training and experience, with reduced potential for results to be confounded by institutional referral, treatment or selection biases. This study reports PCSM outcomes on all patients treated by RP in Victoria over a 10 year time frame.

The purpose of the VRPR when it was established was to provide a detailed description of the whole of population patient casemix, and to identify correlations between baseline characteristics and outcomes from RP, and to assist in providing future direction as to the most appropriate strategies of PC detection and treatment in order to optimise outcomes. The availability at this time of 10 year median follow up data permits us the opportunity to make valid observations in regard to these aims based on PCSM rather than upon PSA detected biochemical recurrence. Although biochemical recurrence may necessitate treatment using salvage radiation or androgen deprivation therapy with consequent side effects, cost and impact upon quality of life, PCSM remains the ultimate measure of the impact of prostate cancer. Measures ideally should be taken to treat otherwise healthy patients before they reach high risk groups for PCSM, or to initiate personalised treatment plans including the option for multi-modality therapy in this setting.

Despite extensive work on PC biometrics, PCSM data post RP based on 10 year median follow up have not previously been available for a whole of population series.

The strong correlation observed in this study between PCSM and advanced pT stage of cancer at RP may be seen as a justification for PSA based detection of early stage PC. In a situation where PC has been diagnosed it also suggests potential value for detailed evaluation using radiologic or template biopsy techniques in order to avoid clinically understaging or undergrading PC, especially where consideration is being given to management in an active surveillance protocol. It is logical to assume that improvements in PCSM could be made by treating at an earlier stage those patients who subsequently were noted to have pT3 disease at RP.

Similar observations may be made about Gleason score at RP. In this study the primary Gleason pattern appears to have major significance in predicting for PCSM. This is of relevance contemporaneously as some active surveillance protocols have suggested the potential for inclusion of Gleason score 3+4=7 disease for such management [6]. While this may be appropriate for some instances of small volume disease it would seem imperative that defintive intervention be considered before disease progression to 4+3=7 cancer, which is clearly associated with increased PCSM after RP at 10 year follow up in this series.

Rural residence of patients which also was identified as a strong predictor of PCSM in this study is a multifactorial issue. Although living in smaller rural communities most of these patients were treated surgically at larger regional and urban centres. More detailed assessment of this

association will be the subject of further analysis, but it is reasonable to observe that patients living in rural areas may often have further to travel for post operative review and may live in areas with reduced access to ancillary services and salvage therapy even after having had an RP at the same institution as a patient who lives in an urban area. Progress towards availability of telemedicine and regional facilities for salvage therapy such as external beam radiation/ IMRT therefore may assist in optimizing disease control in this setting.

The impact upon PCSM noted for patients who had their RP performed by lower vs higher volume surgeons also is noteworthy. While several publications have reported an association between surgeon volume and margin status, this study demonstrates this to extend to an independent influence upon PCSM [7-9]. Such a finding may be of further significance contemporaneously given that the number of RP procedures undertaken has reduced since its peak, that there has been an increase in the number of urologists trained to perform this procedure, and that there has been progression towards RP being undertaken by robot assisted methods which have themselves been associated with a long learning curve and an increased risk of positive surgical margin for cases early in an individual surgeon's experience. Consideration may need to be given in time to consolidating performance of RP to those surgeons who fall into a higher volume group in order to limit the potential for avoidable PCSM [10].

A similar issue is the increased PCSM associated with involvement of a trainee surgeon at RP ($p=0.031$). This finding is independent of cancer stage, margin status and Gleason score, and suggests a requirement to modify teaching strategies. No trainee urologist can be an assistant forever, but clearly this issue must be addressed to limit unnecessary PCSM. Given that surgeon

volume was also identified as a risk factor for PCSM it may be that measures such as earlier streaming of trainees into uro-oncologic vs other subspecialties where RP is not undertaken may be warranted, as may be introduction of modulated teaching programs which require competence in one area of RP to be demonstrated before more complex components of RP are undertaken. It may be of significance that when the RP in this series were undertaken this procedure was being widely popularized, and most urologists including those later characterised as high volume were at a comparatively early point in their learning curve.

Although the results reported by this study reflect outcomes post RP rather than Robot Assisted Radical Prostatectomy (RARP) the development of dual console systems for this procedure may be seen as progress in this regard that is worthy of evaluation with respect to PCSM. It may well be that with increased experience in directly supervised RARP in training, as opposed to assisting at RP, that the difference in PCSM seen for higher volume vs lower volume surgeons in this study reduces or only becomes apparent at a greater case load. Other aspects of prostate cancer management also have evolved over this period of extended follow-up, including greater usage of active surveillance protocols, MRI and multidisciplinary panel assessment in patient selection for RP [11-14]. Despite these adjustments impacting the type of patient who proceeds to surgery, especially by reducing the number of Gleason score 6 patients, these factors would not be expected to have influenced stage and Gleason score specific PCSM. Similarly the results of this study would be expected to be independent of the variability in methods of contemporaneously assessing prostate tumour volume [15].

PCSM was noted in this study where it was listed as the primary cause of death. Instances where longer term consequences of treatment of prostate cancer may have contributed to a reduction in life-expectancy were not recorded as PCSM. Such instances may include where a patient dies from cardiovascular disease after some years of treatment with anti-androgen therapy. Accordingly the impact of PC on patient mortality may be greater than that identified in this series. The low PCSM for Gleason score 6 disease treated by RP would appear to justify the more conservative approach to management of this form of PC that has been advocated since the commencement of this study [16].

Many RP databases have been established worldwide to evaluate this technique as treatment for PC. In order to provide a broad based assessment these are often based upon multiple hospitals from different areas or major centres serving a wide referral base [17-19]. Much of the established data underpinning our assumptions on RP at different cancer stage and Gleason score is drawn from such patient databases. The hospitals coordinating these series are often centers of excellence, and referral patterns and case selection for RP may differ from smaller urban centres or hospitals in rural/regional areas. The availability of a whole of population series such as the VRPR invites comparison with alternative approaches to this question.

One of the limitations of a whole of population study is that end points for outcome measures are necessarily defined to reduce subjectivity, in order to provide for accuracy across multiple locations of treatment. Hence in this study secondary effects of PC treatment may be reflected in patient deaths from other causes but not PCSM. Similarly quality of life outcomes would have required use of validated instruments administered in a standardised fashion, and this was felt to

be beyond the funding and administrative capacity of this project at inception. Consequently we have examined only those objective measures with potential to have impacted upon PCSM.

Although multiple variables assessed in this study appear to have an association with PCSM independent of stage and grade, in this whole of population study the nature of the primary tumour at the time of treatment by RP appears to have the greatest correlation with PCSM. This analysis should assist patients and clinicians in making decisions about staging, surveillance, and timing of surgical intervention in PC treatment.

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Ethical Consideration:

As detailed in the manuscript this project was approved by the ethics committee of Cancer Council Victoria in accordance with the standards prescribed and reported annually to the Australian National Health and Medical Research Committee.

Conflict of Interest Statement:

No author of this manuscript has any financial, regulatory or governance conflict of interest pertaining to the publication of this article.

Author Contribution Statement:

All coauthors of this publication have contributed to its construction by means of one or more of project development and oversight, data collection and analysis, and manuscript production and review, and all authors offer their consent for its publication

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Table 1: Pathologic and Demographic distribution of patients included in this study

	Total patients n=1967 (% of total)	Other cause mortality n=172 (% of category)	PCSM n=75 (% of category)
Gleason grade			
6	1147 (50.3)	94 (8.2)	19 (1.7)
7 (3+4)	500 (25.4)	43 (8.6)	14 (2.8)
7 (4+3)	186 (9.5)	17 (9.1)	20 (10.8)
8-10	134 (6.8)	18 (13.4)	22 (16.4)
pT-stage			
T2	1499 (76.2)	127 (8.5)	25 (1.7)
T3a	305 (15.5)	26 (8.5)	17 (5.6)
T3b	163 (8.3)	19 (11.7)	33 (20.2)
Residence			
Urban	1532 (77.9)	135 (8.8)	47 (3.9)
Rural	435 (22.1)	37 (8.5)	28 (6.4)
Surgeon			
Consultant only	1583 (82.5)	146 (9.2)	57 (3.6)
plus Trainee	335 (17.5)	22 (6.6)	16 (4.8)
Surgeon volume			
≥ 40 cases	1572 (79.9)	135 (8.6)	54 (3.4)
< 40 cases	395 (20.1)	37 (9.4)	21 (5.3)
Hospital system			
Private	1531 (77.8)	139 (9.1)	54 (3.5)
Public	436 (22.2)	33 (7.6)	21 (4.8)
Laboratory			
≥ 100 cases	1496 (76.1)	137 (9.2)	55 (3.7)
< 100 cases	471 (23.9)	35 (7.4)	20 (4.2)
SES quintile (17 missing)			
Q5 (most advantaged)	682 (34.7)	59 (8.7)	22 (3.2)
Q4	394 (20.0)	34 (8.6)	8 (2.0)
Q3	292 (14.8)	23 (7.9)	8 (2.7)
Q2	307 (15.6)	31 (10.1)	22 (7.2)
Q1 (least advantaged	275 (14.0)	23 (8.4)	14 (5.1)
Age at surgery			
≥ 65	597 (30.4)	91 (15.2)	28 (4.7)
< 65	1370 (69.6)	81 (5.9)	47 (3.4)

Table 2: Patient and demographic factors' association with PCSM where grade and stage are entered as covariates in a multivariable model. Each of these factors is entered in separate models.

Factor	SHR	95% CI	p-value
Margin (4 missing)			
Negative	1.0		
Positive	0.97	0.57 – 1.64	0.901
Residence			
Urban	1.0		
Rural	2.08	1.28 – 3.37	0.003
Surgeon			
Consultant only	1.0		
plus Trainee	1.90	1.06 – 3.40	0.031
Surgeon volume			
≥ 40 cases	1.0		
< 40 cases	1.80	1.08 – 3.01	0.025
Hospital system			
Private	1.0		
Public	1.61	0.94 – 2.76	0.084
Laboratory			
≥ 100 cases	1.0		
< 100 cases	1.38	0.79 – 2.39	0.258
SES			
Per 100 unit decrease	1.21	0.90 – 1.63	0.205
Age at surgery			
≥ 65	1.0		
< 65	1.01	0.63 – 1.63	0.951

SHR = subhazard ratio ; CI = confidence interval

Figure 1.

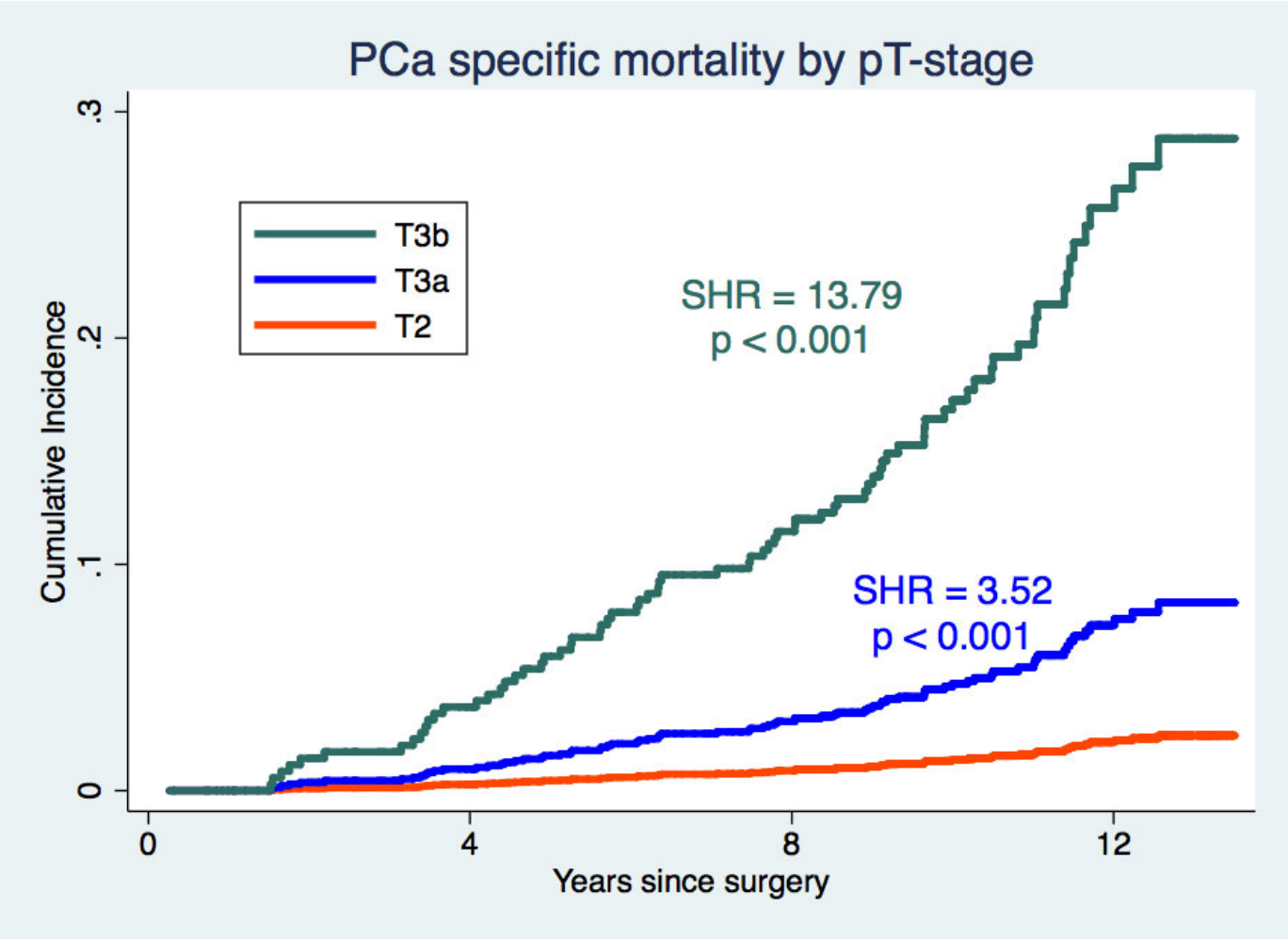

Figure 2