

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Ranasinghe, W;Wang, LL;Persad, R;Bolton, D;Lawrentschuk, N;Sengupta, S

Title:

Survival outcomes in elderly men undergoing radical prostatectomy in Australia

Date:

2018-03-01

Citation:

Ranasinghe, W., Wang, L. L., Persad, R., Bolton, D., Lawrentschuk, N. & Sengupta, S. (2018). Survival outcomes in elderly men undergoing radical prostatectomy in Australia. [Abstract]. ANZ Journal of Surgery, 88 (3), pp.E189-E193. <https://doi.org/10.1111/ans.14166>.

Persistent Link:

<https://hdl.handle.net/11343/293468>

1. Title page

Title: Survival outcomes in elderly men undergoing radical prostatectomy in Australia

Running title: Prostatectomy outcomes in elderly

Weranja Ranasinghe¹ MBChB, Ph.D., Luke L. Wang² MBBS, BMedSci, Raj Persad³ MBBS, FRCS(Urology), Damien Bolton¹ MD, FRACS (Urology), Nathan Lawrentschuk¹ MBBS, FRACS (Urology), Shomik Sengupta¹ FRACS (Urology), MD

Affiliations:

¹ University of Melbourne, Department of Urology, Austin Health, Victoria, Australia

² Department of Urology, Eastern Health, Victoria, Australia

³ University Hospital, NHS Trust, UK

The corresponding author is not a recipient of a research scholarship

The paper is not based on any previous communication to a society or meeting

Figures: 2

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: [10.1111/ans.14166](https://doi.org/10.1111/ans.14166)

Tables: 2

Word count

Abstract: 244

Text: 1834

Corresponding author:

Name: Weranja Ranasinghe

Email: weranja@gmail.com

Postal address: 145 Studley Rd, Heidelberg, Victoria, Australia

Telephone: +61 (03)9496 5000

2. Abstract

Objective: To investigate the outcomes of patients older than 75 years of age in Victoria undergoing radical prostatectomy (RP) for prostate cancer (PC).

Materials and methods: Data on all men undergoing RP in Victoria between 1st January 2004 and 31st December 2014 were obtained from the Victorian Cancer Registry. Tumour characteristics including Gleason grade, stage of disease and cause of death were obtained. Statistical analysis was performed using Chi-squared test, Cox proportional hazards method and Kaplan-Meier analysis.

Results: 14686 men underwent RP during the defined period with a median follow up of 58 months. 332 of these were men over the age of 75. All parameters are comparisons between patients >75 years of age and men <75 years of age. Men >75 years had a higher proportion of Gleason grade ≥ 8 disease (16.6% vs 11.4%, $p < 0.001$) but had similar stage of disease. Men >75 had lower rates of 5- and 10- year overall survival (67.3% vs 96.3% and 27.7% vs 89.1%) and lower rates of 5- and 10- year PC specific survival (96.2% vs 99.3% and 94.3% vs 97.4%), respectively. Age was an independent risk factor for PC specific and overall mortality on multivariate analysis (HR 1.49, 95% CI 1.32 – 1.68; $p < 0.001$ and HR 4.26, 95% CI 2.15 – 8.42; $p < 0.001$), when adjusted for stage and grade.

Conclusion: Older men undergoing RRP in Victoria had higher-grade disease but similar stage. Age was an independent risk factor for worse prostate cancer specific and overall survival.

Keywords: cancer, elderly, prostatectomy, urology, surgery

3. Main text

Introduction

Australia historically has one of the highest rates of prostate cancer (PC) worldwide ^{1,2}. PSA screening resulting in high rates of detection of small volume cancer in younger men remains a significant issue. However, at the opposite spectrum an equally significant dilemma has arisen: the issue of clinically significant PC in older men. Guidelines advocating PSA screening to be done primarily in men with at least a ten-year life expectancy and that discourage the use of routine screening above the age of 75 are not always followed ³⁻⁸.

The incidence of screen detected PC is the highest among males aged 70–74 years ⁹. Studies have demonstrated that older men harbour more aggressive disease that could potentially be cured ⁹⁻¹¹. Thus the decision to screen for and surgically treat such cancers should ideally be based on health status rather than chronological age ¹². However, in practice this appears not to be the case, where older men may be preferentially offered non-surgical treatment modalities such as radiation therapy with androgen deprivation and in some cases not offered treatment at all ¹³. Recently there has been increased consideration of surgery in older men with high-risk disease with at least a ten-year life expectancy ^{10,11}. However, while radical

prostatectomy (RP) in this patient population may offer cure from PC it is not without potential for complications and even mortality.

Given this background and the number of men being screened above aged 75 the detection of high risk PC in such men is likely to be more frequent. With a greater life expectancy in Australia, surgery could be considered in this cohort. Therefore we aimed to investigate the outcomes of men >75 years undergoing RP in Australia.

Materials and methods

Population and Demographics:

The Victorian Cancer Registry (VCR) is a well-established population-based cancer registry that receives mandatory cancer diagnosis notifications from 240 hospitals and pathology laboratories. The VCR has a comprehensive and longstanding database for PC identification including detailed histological diagnoses¹⁴. Victoria is the second largest state in Australia having a quarter of the nation's male at around 2,484,490 men¹⁵.

Data was obtained for all men diagnosed with PC who subsequently underwent radical prostatectomy from 2001-2014. Data on age, date of radical prostatectomy, final Gleason score on RP specimen, pathological T stage, mean PSA at diagnosis, date and cause of death were obtained.

Geographical location was classified to be either urban or rural as determined by Integrated Cancer Service network of Victoria. Patient locations were referred to as urban if they were within the catchment of the metropolitan cancer networks, with the remainder of the Victorian locations designated as being rural.

Statistical analyses

Student T tests and Chi squared tests were used to compare the patient characteristics. The overall survival rates for men undergoing RRP were compared using Kaplan Mier survival curves and Cox-proportional hazard methods using SPSS statistical software (version 17.0).

Results

14,686 men underwent RRP during the defined period with a median follow up of 58 months. 332 of these were men >75. All parameters are comparisons between patients >75 years of age and men <75 years of age. Men >75 years had a higher proportion of Gleason score e 8 disease (16.6% vs 11.4%, $p < 0.001$) but had similar stage of disease and N stage (Table 1). Men <75 had a higher mean PSA at the time of surgery.

From 2004 onwards the percentage of total radical prostatectomies performed on men >75 years increased from 1% to 5% in 2014 (Figure 1).

Outcomes post radical prostatectomy

Men <75 had higher rates of 5-year (96.3% vs 67.3%) and 10-year overall survival (89.1% vs 27.7%) compared to men >75 years, respectively (Figure 2A). Men <75 years also had higher rates of 5-year (99.3% vs. 96.2%) and 10-year PC specific survival (97.4% vs 94.3%) compared to men >75 years, respectively (Figure 2B). Men >75 years had higher rates of deaths from other causes (Figure 2C).

Age was an independent risk factor for PC specific and overall mortality on multivariate analysis (HR 1.49, 95% CI 1.32 – 1.68; $p < 0.001$ and HR 4.26, 95% CI 2.15 – 8.42; $p < 0.001$), when adjusted for stage, grade and PSA (Table 2).

On comparing outcomes of men >75 undergoing radical prostatectomy for PC between 2004-2008 with 2009 – 2014, there was no significant difference in PC specific mortality but there was a 52.9% reduction in overall deaths and a 51% reduction in deaths from other causes, when adjusted for stage, Gleason score and PSA.

Discussion

In our study we found that men over 75 years of age harboured more aggressive disease – postoperative tumour Gleason grade 8 or greater. This finding is supported by several studies¹⁶⁻¹⁸. Delongchamps et al¹⁷ studied autopsied prostate glands from 211 men who died of causes unrelated to PC, and found significantly larger and more clinically significant cancer in

men over 70. Similarly, Brassell et al¹⁶ examined 12,081 men and found pathological stage and grade to be significantly higher in men 70 years or older. The exact reason for this observation is unknown. It has been proposed that this could be due to the natural disease progression of undiagnosed prostate cancer. Another hypothesis suggested that this could be an adverse biological change secondary to hormonal dysregulation associated with aging¹⁶. Elderly patients with high-risk disease, in whom treatment toxicity may be less of a concern compared to younger cohort, may benefit from radical surgery to prevent potential rapid disease progression¹⁷.

The European Association of Urology (EAU) guidelines for management of PC recommend that curative treatment to be offered to men with life expectancy greater than 10 years, taking into consideration the risk of dying from PC, potential adverse effects of treatment and patient preference¹⁹. However, due to limited evidence of specific treatment efficacy in men >75 years of age, combined with higher prevalence of co-morbidities, the decision to treat by RP is notoriously challenging in this population. This is further complicated by the fact that clinicians may do poorly at predicting life expectancy irrespective of level of training, and tend to underestimate how long patients have left to live²⁰. Additionally, studies have shown that history of stroke or cardiovascular disease increase risks of 30-day mortality; and that rates of postoperative complications and late urinary complications following RP were more influenced by comorbidity than age^{21,22}. To address these issues, the International Society of Geriatric Oncology (SIOG) working group updated the treatment guidelines for men with PC who are older than 70 years. The consensus was that older men with PC should be managed

according to their individual health status, not according to chronological age²³. Based on the G8 health status screening instrument, patients may be classed into three groups for treatment: fit patients who should be offered all available treatment options; vulnerable patients with reversible impairment who should receive standard treatment after medical optimisation; and frail patients with non-reversible impairment and poor prognosis who should receive adapted treatment²³. This tool, applied in pre-operative assessment settings, may assist physicians in more accurately determine the health state of elderly patients and offer curative treatment to the appropriate subgroup.

In our study we found that age was an independent risk factor for poorer cancer specific survival and overall survival in men > 75 post radical prostatectomy. Comparing survival outcomes of men over time there was over 50% reduction in both overall deaths and deaths from other causes. This likely reflects improved patient selection as well as overall health in the elderly population. Moreover, the case for offering curative treatment in this population is further supported by results of Alibhai et al²⁴ which showed increased life expectancy after curative therapy (RP or radiotherapy) compared with watchful waiting in patients with PC up to the age of 80 years. Similar results were demonstrated by Sun et al, who identified that in men with ≥ 10 years of life expectancy, RP was associated with an improved overall survival compared with observation. One potential downside is that postoperative complications as well as rates of biochemical recurrence post RP are higher in this population^{16,25,26}. We suspect the higher rate of aggressive disease in these patients is an important contributing factor. The Scandinavian Prostate Cancer Group 4 trial (SPCG-4)²⁷, however, found absolute

risk reduction is significantly reduced in patients over 70 years of age and that surgery was associated with lesser benefit in comparison to younger cohort. The results of SPCG-4 do not contradict the findings of our study. Unsurprisingly, men under 75 years of age in our cohort had better overall and prostate cancer specific survival. However, with improved contemporary treatment methods, together with better patient selection and improvement in overall health of the elderly population, results also demonstrated significant reduction in overall deaths and deaths from other causes in the latter time periods of 2009 – 2014 compared to 2004-2008 in the elderly cohort.

As robotic surgery has become one of the mainstay techniques for RP over the period of this study, this may provide a more attractive alternative for the elderly population with the potential for reduced complication rates and improved long-term functional outcomes²⁸. Currently there are no direct comparisons of outcomes between open and robotic techniques in this older cohort of patients. Trinh et al²⁶ reported retrospective data on 115,554 men aged ≥ 75 who underwent open RP, and found intra-operative and postoperative complications rates to be up to 2.9% and 22.2% respectively. As an indirect comparison, Babaian et al²⁹ analysed complications post robotic-assisted radical prostatectomy between men under 69 and over 70 in 868 men, and they found overall postoperative complication rate for over 70 at 15.4%. In addition, 12-month postoperative potency and continence rates have been reported to be 75% and 69 - 92%, respectively^{30,31}. Further studies of direct comparisons between these two techniques in this cohort would be advantageous, but current evidence is

encouraging for the robotic technique as a viable alternative in elderly men requiring curative surgery.

Limitations of our study relate to the nature of the data collection which is predominantly pathology based. Information regarding medical co-morbidities or frailty indices was not available, so the impact of such conditions on overall survival remains unknown. Importantly, data on post-operative morbidities and long-term quality of life were not available, which are often the reasons why older men are advised against radical surgery. This dataset is representative of only one Australian state, so the applicability of the results to the wider population including indigenous groups is uncertain but likely to be consistent given the nationalised health systems.

In conclusion, our study demonstrates older men (>75 years) undergoing RP in Victoria had higher-grade disease but similar stage to younger men. Age was an independent risk factor for worse PC specific and overall survival. However, age alone should not determine the need for surgery and careful selection of patients may improve outcomes in this cohort. Further data on quality of life and other clinical outcomes would be advantageous to assist in counselling such men and aiming to improve outcomes.

4. Acknowledgement:

We would like to extend our gratitude to Vicky Thursfield, Cancer Control Information Manager Victorian Cancer Registry for data provision.

5. Disclosure statement.

Disclosure of sources of financial support: none.

Potential conflict of interest: none.

6. References

1. Ferlay J SH, Bray F, Forman D, Mathers C and Parkin DM. Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]. GLOBOCAN 2008: Lyon, France: International Agency for Research on Cancer 2010.
2. Ranasinghe WK, Kim SP, Lawrentschuk N, et al. Population-based analysis of prostate-specific antigen (PSA) screening in younger men (<55 years) in Australia. BJU international 2014;113:77-83.
3. Basch E, Oliver TK, Vickers A, et al. Screening for prostate cancer with prostate-specific antigen testing: American Society of Clinical Oncology Provisional Clinical Opinion. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2012;30:3020-5.
4. American Urological Association prostate- specific antigen best practice statement: 2009update. at <http://www.auanet.org/content/media/psa09.pdf>.)

5. Heidenreich A, Bastian PJ, Bellmunt J, et al. EAU guidelines on prostate cancer. part 1: screening, diagnosis, and local treatment with curative intent-update 2013. *European urology* 2014;65:124-37.
6. Kawachi MH, Bahnson RR, Barry M, et al. NCCN clinical practice guidelines in oncology: prostate cancer early detection. *J Natl Compr Canc Netw* 2010;8:240-62.
7. Litchfield MJ, Cumming RG, Smith DP, et al. Prostate-specific antigen levels in men aged 70 years and over: findings from the CHAMP study. *Med J Aust* 2012;196:395-8.
8. Wolf AM, Wender RC, Etzioni RB, et al. American Cancer Society guideline for the early detection of prostate cancer: update 2010. *CA Cancer J Clin* 2010;60:70-98.
9. AIHW. Prostate cancer in Australia. Cancer series 79 Cat no CAN 76 Canberra: AIHW 2013.
10. Paterson C, Alashkham A, Lang S, Nabi G. Early oncological and functional outcomes following radical treatment of high-risk prostate cancer in men older than 70 years: A prospective longitudinal study. *Urologic oncology* 2016.
11. Mandel P, Kriegmair MC, Kamphake JK, et al. Tumor Characteristics and Oncologic Outcome after Radical Prostatectomy in Men 75 Years Old or Older. *The Journal of urology* 2016.
12. Droz JP, Balducci L, Bolla M, et al. Management of prostate cancer in older men: recommendations of a working group of the International Society of Geriatric Oncology. *BJU international* 2010;106:462-9.
13. Bratt O, Folkvaljon Y, Hjalmar Eriksson M, et al. Undertreatment of Men in Their Seventies with High-risk Nonmetastatic Prostate Cancer. *European urology* 2015;68:53-8.
14. Victorian Cancer Registry. Victorian Cancer registry, 2012. (Accessed October 2012, at <http://www.cancervic.org.au/about-our-research/registry-statistics/vcr.>)

15. Australian Bureau of statistics website May 2011, at [http://www.abs.gov.au/ausstats/abs@.nsf/mf/4831.0.55.001/.](http://www.abs.gov.au/ausstats/abs@.nsf/mf/4831.0.55.001/))
16. Brassell SA, Rice KR, Parker PM, et al. Prostate cancer in men 70 years old or older, indolent or aggressive: clinicopathological analysis and outcomes. *The Journal of urology* 2011;185:132-7.
17. Delongchamps NB, Wang CY, Chandan V, et al. Pathological characteristics of prostate cancer in elderly men. *The Journal of urology* 2009;182:927-30.
18. Kunz I, Musch M, Roggenbuck U, Klevecka V, Kroepfl D. Tumour characteristics, oncological and functional outcomes in patients aged ≥ 70 years undergoing radical prostatectomy. *BJU international* 2013;111:E24-9.
19. Mottet N, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. *European urology* 2016.
20. Leung KM, Hopman WM, Kawakami J. Challenging the 10-year rule: The accuracy of patient life expectancy predictions by physicians in relation to prostate cancer management. *Canadian Urological Association journal = Journal de l'Association des urologues du Canada* 2012;6:367-73.
21. Alibhai SM, Leach M, Tomlinson G, et al. 30-day mortality and major complications after radical prostatectomy: influence of age and comorbidity. *J Natl Cancer Inst* 2005;97:1525-32.
22. Begg CB, Riedel ER, Bach PB, et al. Variations in morbidity after radical prostatectomy. *N Engl J Med* 2002;346:1138-44.
23. Droz JP, Aapro M, Balducci L, et al. Management of prostate cancer in older patients: updated recommendations of a working group of the International Society of Geriatric Oncology. *The Lancet Oncology* 2014;15:e404-14.

24. Alibhai SM, Naglie G, Nam R, Trachtenberg J, Krahn MD. Do older men benefit from curative therapy of localized prostate cancer? *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2003;21:3318-27.
25. Ko J, Falzarano SM, Walker E, et al. Prostate cancer patients older than 70 years treated by radical prostatectomy have higher biochemical recurrence rate than their matched younger counterpart. *The Prostate* 2013;73:897-903.
26. Trinh QD, Schmitges J, Sun M, et al. Open radical prostatectomy in the elderly: a case for concern? *BJU international* 2012;109:1335-40.
27. Vickers A, Bennette C, Steineck G, et al. Individualized estimation of the benefit of radical prostatectomy from the Scandinavian Prostate Cancer Group randomized trial. *European urology* 2012;62:204-9.
28. Yaxley JW, Coughlin GD, Chambers SK, et al. Robot-assisted laparoscopic prostatectomy versus open radical retropubic prostatectomy: early outcomes from a randomised controlled phase 3 study. *Lancet* 2016;388:1057-66.
29. Babaian KN, Skarecky D, Liss MA, Osann K, Lusch A, Ahlering TE. A comparative analysis of complications after robot-assisted radical prostatectomy for men aged ≤ 69 and ≥ 70 years. *Journal of endourology / Endourological Society* 2014;28:1435-8.
30. Basto MY, Vidyasagar C, te Marvelde L, et al. Early urinary continence recovery after robot-assisted radical prostatectomy in older Australian men. *BJU international* 2014;114 Suppl 1:29-33.
31. Greco KA, Meeks JJ, Wu S, Nadler RB. Robot-assisted radical prostatectomy in men aged > 70 years. *BJU international* 2009;104:1492-5.

7. Figure legends

Figure 1 Changes in rates of radical prostatectomy for men ≤ 75 over time

Figure 2 A) Kaplan Meier curve of overall survival of men <75 years vs >75 years; **B)**

Kaplan Meier curve of PC-Specific survival of men <75 years vs >75 years; **C)** Kaplan Meier curve of death from other causes comparing men <75 years vs >75 years.

8. Tables:

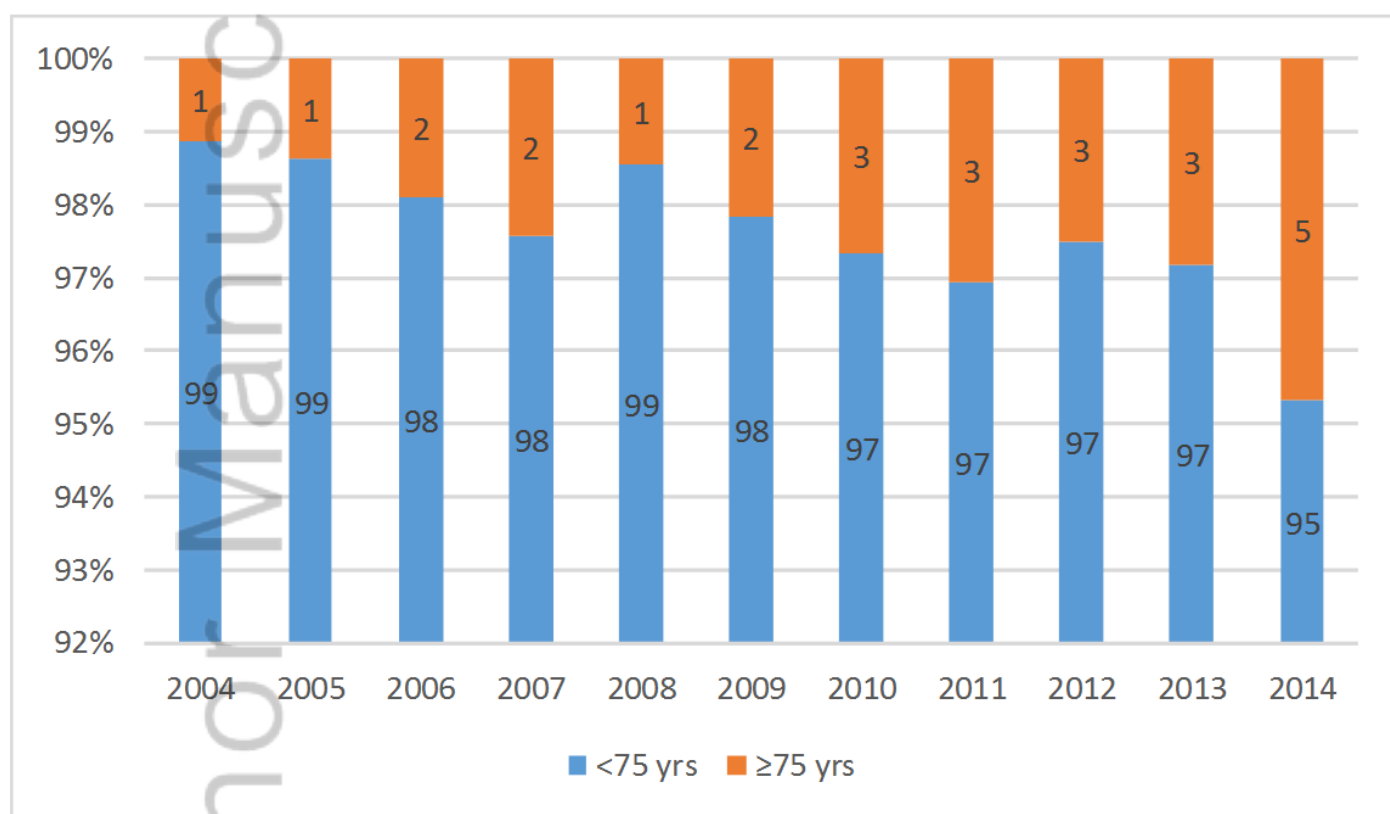
Table 1 Patient characteristics

	<75 years (%)	≥75 years (%)	P value
Number	14324	332	
Gleason score			
≤6	3646 (25.5)	105 (29)	<0.01
7	7730 (54)	172 (47.5)	0.66
≥8	1630 (11.4)	25 (16.6)	0.04
Unknown	1318 (9.2)	25 (6.9)	0.38
T stage			
T1/2	9599 (67)	232 (66.9)	0.15
T3/4	4577 (32)	116 (32)	0.20
Unknown	148 (1)	14 (3.9)	<0.01
N stage			
N0	5296 (37)	246 (74.1)	<0.01
N1	143 (1)	11 (3)	<0.01
Mean PSA	8.2	7.3	0.03

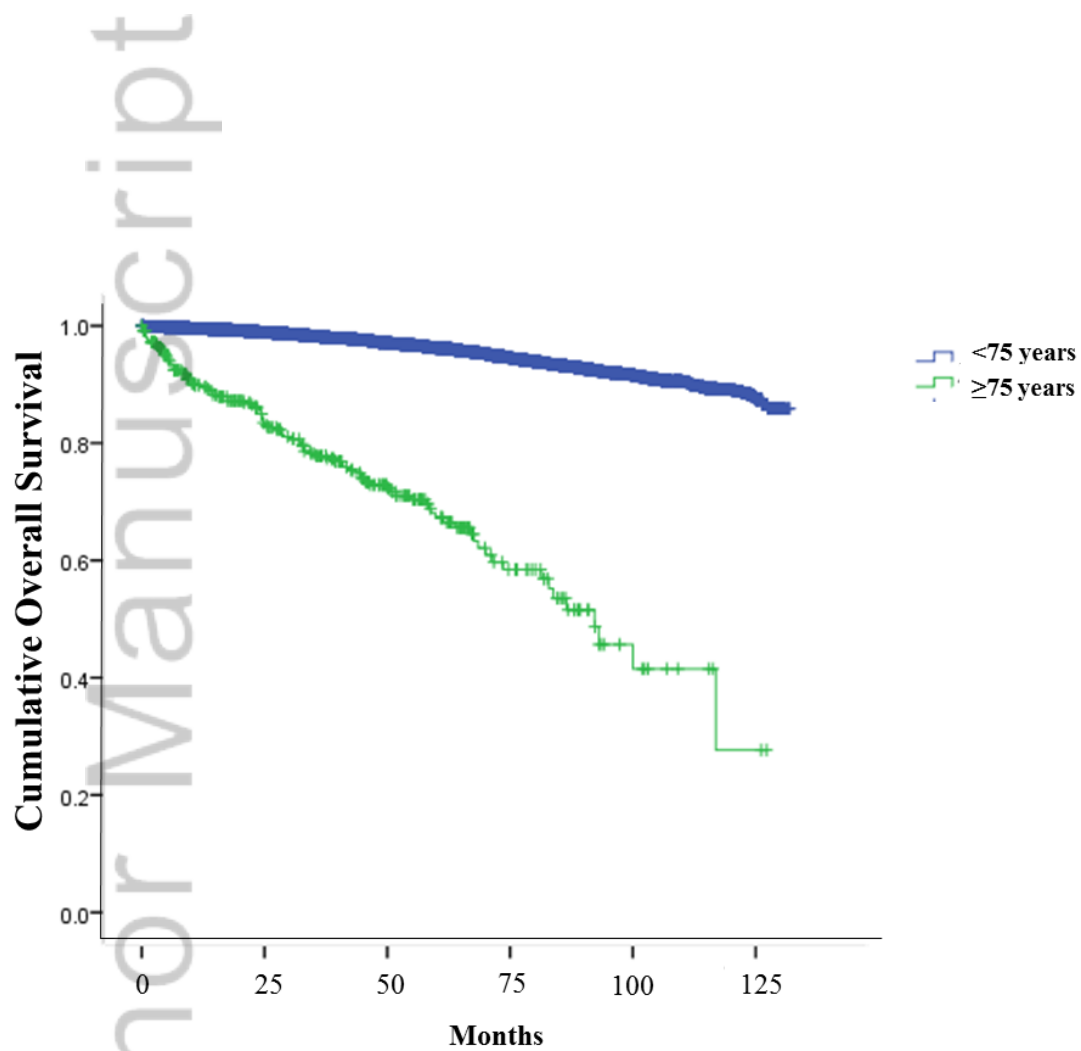
Table 2 Univariate and multivariate analyses of age (adjusted for Gleason score, stage and PSA) on prostate cancer outcomes

	Univariate	P value	Multivariate	P value
Overall Death	10.72 (8.67- 13.3)	<0.01	11.08 (7.82 – 15.71)	<0.01
Ca specific death	4.99 (2.54 – 9.84)	<0.01	3.46 (1.06 – 11.27)	0.04
Death from Other cause	13.02 (9.89- 17.14)	<0.01	14.95 (9.60- 23.29)	<0.01

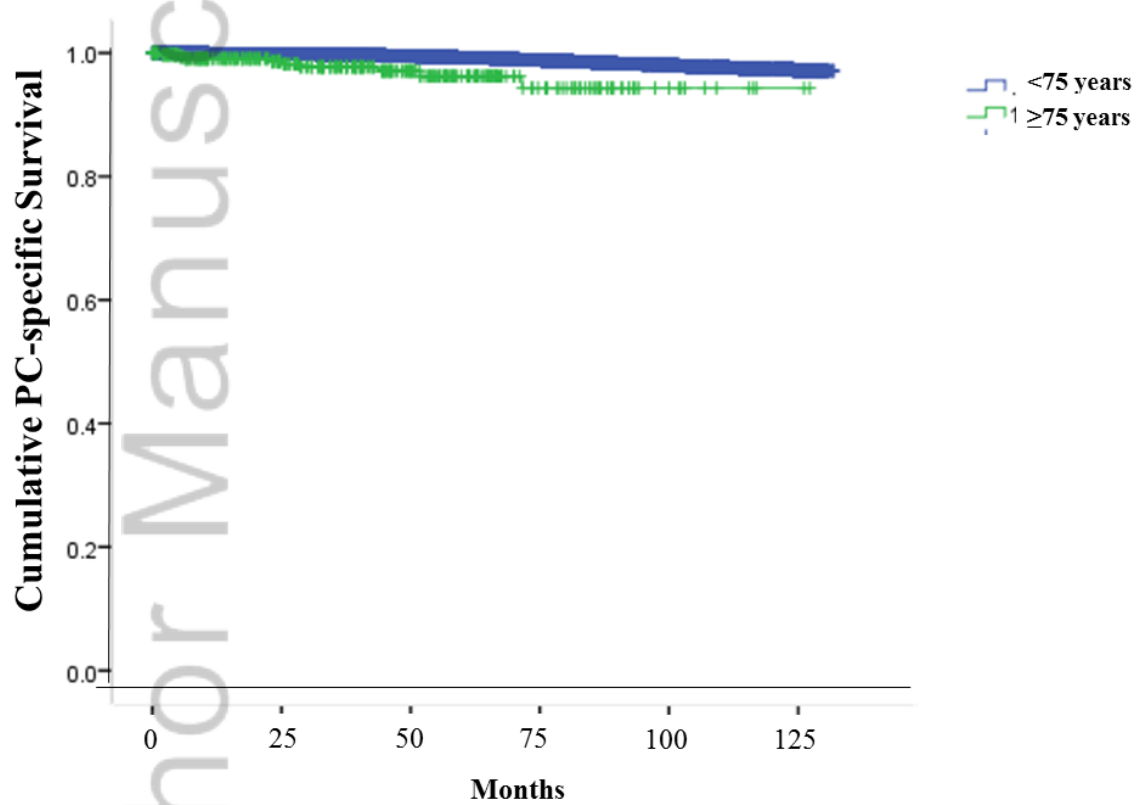
Author Manuscript



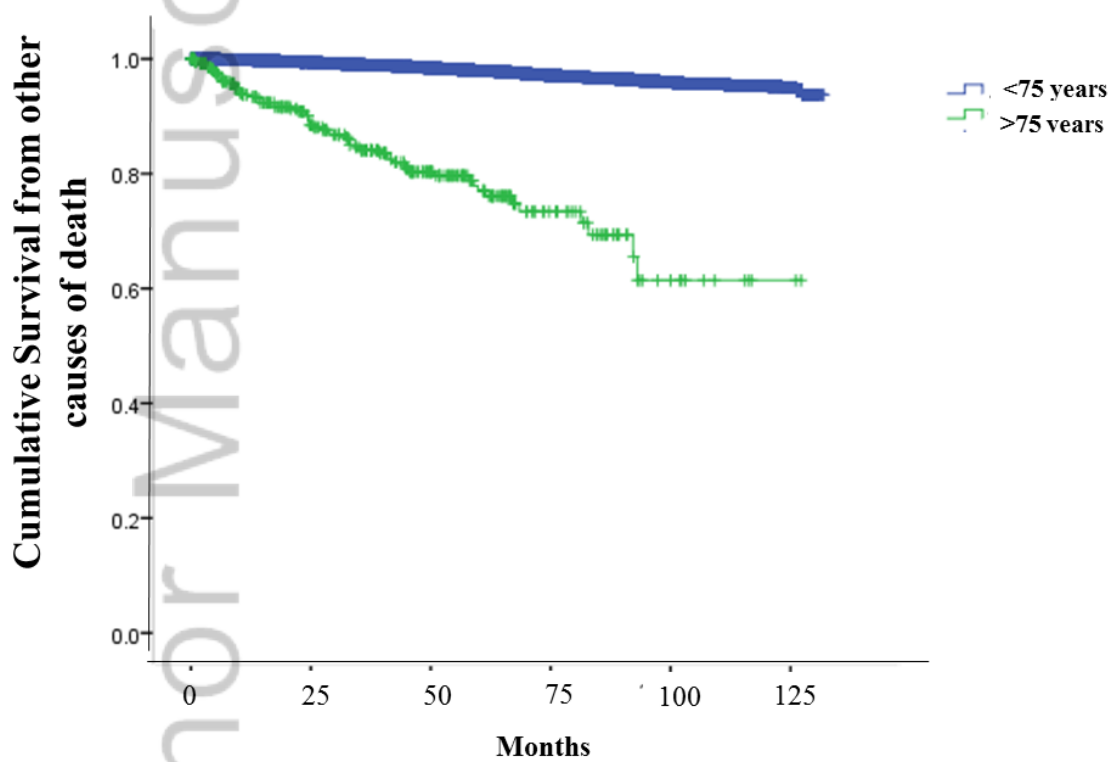
Slide1.TIF



Slide2.TIF



Slide3.TIF



Slide4.TIF