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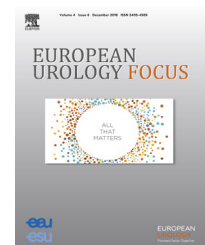
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Prostate Cancer

Survival Outcomes in Octogenarian and Nonagenarian Patients Treated with First-line Androgen Deprivation Therapy for Organ-confined Prostate Cancer

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Abstract

Background: The use of primary androgen deprivation therapy (PADT) is common in elderly men with early-stage prostate cancer (PCa), despite the absence of guideline recommendations.

Objective: To examine survival patterns of octo- and nonagenarian men with organ-confined PCa exposed to PADT, to assess whether their life expectancy warrants androgen deprivation therapy use.
Design, setting, and participants: In the Surveillance, Epidemiology, and End Results-Medicare-linked database, we identified 14 785 octo- and nonagenarian organ-confined PCa patients treated with PADT between 1991 and 2009.

Outcome measurements and statistical analysis: The smoothed cumulative incidence method was used to examine 10-yr overall mortality, cancer-specific mortality (CSM), and other-cause mortality (OCM) rates. Multivariable Cox regression analyses focused on the combined effect of age and Charlson comorbidity index (CCI) after adjusting for different confounders.

Results and limitations: Of all the deaths observed during the study period, 80% were due to non-cancer causes and 20% were due to PCa. The 10-yr overall survival (OS) rate in the overall population was 15.4%. The 10-yr OS rates ranged from 19.9% in patients aged 80–84 yr to 3.1% in those aged ≥90 yr. Similarly, the 10-yr OS rates ranged from 18.7% in patients with CCI = 0 to 11.5% in those with CCI ≥ 2. The 10-yr OCM rate in the overall population was 68.2%. The 10-yr OCM rates ranged from 64.6% in patients aged 80–84 yr to 77.2% in patients aged ≥90 yr. Similarly, the 10-yr OCM rates ranged from 62.1% in patients with CCI = 0 to 75.2% in those with CCI ≥ 2. The 10-yr CSM rate in the overall population was 16.4%. The 10-yr CSM rates ranged from 15.5% in patients aged 80–84 yr to 19.7% in those aged ≥90 yr, and from 19.2% in patients with CCI = 0 to 13.3% in those with CCI ≥ 2.

Conclusions: Of the elderly patients with organ-confined PCa exposed to PADT, only 15% survive at 10-yr follow-up. Mortality related to non-cancer causes is the leading cause of death in the same follow-up period. These figures question the rationale for PADT in elderly men with organ-confined PCa.

Patient summary: In this study, we looked at the survival patterns of octo- and nonagenarians treated with primary androgen deprivation therapy for organ-confined prostate cancer. We found that a small proportion of patients who received primary androgen deprivation therapy remain alive at 10-yr follow-up, and the leading cause of death was not attributable to prostate cancer.

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1. Introduction

Prostate cancer (PCa) represents the most common non-cutaneous malignancy in men [1]. Moreover, PCa has a predilection for older men [2,3]. The use of androgen deprivation therapy (ADT) is also common in elderly men with early-stage PCa [4–6], despite a lack of evidence for cancer control benefits [7–9] except in highly selected subgroups [9,10]. This study relied on a population-based cohort of octo- and nonagenarian men treated with primary ADT (PADT) for organ-confined PCa. Our intent was to evaluate 10-yr survival patterns, especially overall survival (OS), which represents the main drivers of life expectancy (LE). Moreover, we examined the likelihood of dying of noncancer causes after accounting for the risk of death of PCa. We postulated that poor OS may be recorded in this cohort and may indicate the absence of a rationale for PADT based on limited LE. To date, no such work has been completed. However, existing data have refuted the survival benefit of PADT in men with organ-confined PCa, irrespective of age [7–9].

2. Materials and methods

2.1. Data source

This study relied on the Surveillance, Epidemiology, and End Results (SEER)-Medicare insurance program-linked database. The SEER registries cover approximately 28% of all cancer cases in the USA. The Medicare-linked database is 98% complete for case ascertainment. It encompasses approximately 97% of Americans aged 65 yr or older in the USA. Linkage to the SEER database is complete for approximately 93% of the patients [11].

2.2. Study population

Between 1991 and 2009, data for 62 709 patients with histologically confirmed PCa (International Classification of Disease for Oncology site code 61.9, histologic code 8140), aged 80 yr or older who had both Medicare Part A and Part B claims available, and who were not enrolled in a health maintenance organization throughout the duration of the study were abstracted.

Patients were not included if PCa was diagnosed at autopsy or on the death certificate only ($n = 388$) or if PCa was not their first malignant disease ($n = 684$). Additional exclusions consisted of clinical stage T3 or T4 tumors ($n = 16\,423$), lymph node invasion ($n = 136$), and/or distant metastases ($n = 1020$).

We focused exclusively on patients treated with first-line ADT within the first 6 mo from diagnosis. Patients who received radical prostatectomy (RP), radiotherapy (RT), and brachytherapy (BT) as the first treatment or in combination within 6 mo from PCa diagnosis were excluded ($n = 28\,800$). ADT was defined as chemical castration (Gonadotropin-releasing hormone-GnRH agonist or antiandrogen or both) or surgical castration. Ascertainment of treatment selection was performed using Common Procedural Terminology (fourth edition), Healthcare Common Procedure Coding System, and International Classification of Disease-Ninth Revision (ICD-9) codes for ADT, RT, BT, and RP (Supplementary Table 1). Moreover, patients with an unknown Gleason grade ($n = 473$) were not considered. The final assessable population comprised 14 785 octo- and nonagenarian organ-confined PCa patients.

2.3. Variable definition

Demographic variables were age at diagnosis, year of diagnosis, race (white vs black vs other), marital status (single vs married vs separated/divorced vs widowed), US regions (Midwest vs Northeast vs South vs West—according to the US Census Bureau), and population density status (urban vs rural). Socioeconomic status was determined using three county-attribute variables provided by the SEER program: median family income, percentage of persons living below the poverty line, and percentage of persons without a high-school diploma. Subsequently, a composite score was created using the sum of the standardized scores from the three variables, as previously described [12,13]. Low and high socioeconomic statuses were established by dividing the population according to the median value of the composite score. The Charlson comorbidity index (CCI) was derived from the Medicare claims 1 yr before PCa diagnosis using a previously validated algorithm [14], and categorized as 0 versus 1 versus ≥ 2 . Tumor characteristics included clinical stage (T1 vs T2) and Gleason grade. Before 2003, Gleason grades of 2–4, 5–7, and 8–10 corresponded to well-differentiated, moderately differentiated, and poorly differentiated disease, respectively. Thereafter, Gleason grades of 2–4, 5–6, and 7–10 corresponded to well-differentiated, moderately differentiated, and poorly differentiated disease, respectively.

2.4. Outcomes

The cause of death was defined using the SEER cause of death code. Patients who died from PCa (ICD-9 185.9 or ICD-10 C619) were classified as expired due to cancer-specific mortality (CSM), while patients who died from other causes were classified as having succumbed to other-cause mortality (OCM) [15].

2.5. Statistical analyses

Frequencies and proportions were reported for categorical variables. Medians and interquartile ranges were reported for continuously coded variables. Our analyses consisted of four steps. First, estimates of 10-yr survival patterns in the overall population were plotted using the smoothed cumulative incidence method, as previously described [16]. Second, we repeated the same analyses after stratification according to age (80–84 vs 85–89 vs ≥ 90 yr) and CCI (0 vs 1 vs ≥ 2). Third, we repeated the same analyses in younger and healthier patients (age 80–84 yr + CCI = 0) versus older and sicker patients (age ≥ 85 yr + CCI ≥ 1). Finally, multivariable Cox regression analyses focused on the combined effect of age, CCI after adjusting for grade of disease, clinical stage, race, population density, socioeconomic status, marital status, US region, and year of diagnosis.

All statistical tests were performed using the RStudio graphical interface v.0.98 for R software environment v.3.0.2 (R Foundation, Vienna, Austria). All tests were two sided with a significance level set at $p < 0.05$.

3. Results

3.1. Baseline characteristics

Between 1991 and 2009, 14 785 men aged ≥ 80 yr exposed to PADT for organ-confined PCa were included (Table 1). Median age at diagnosis was 84 yr (interquartile range 81–86). Overall, 8730 (59%), 4803 (32.5%), and 1252 (8.5%) patients were aged between 80 and 84, 85 and 89, and ≥ 90 yr, respectively. Most patients were white (82.8%), married (52.8%), residing in the West of the USA (43.3%),

Table 1 – Descriptive characteristics of 14 785 octo- and nonagenarians treated with primary androgen deprivation therapy for organ-confined prostate cancer within the SEER-Medicare database between 1991 and 2009.

Variables	Overall
Age at diagnosis (yr)	
Median	84
IQR	81–86
Year of diagnosis	
Median	2003
IQR	2000–2005
Race, n (%)	
White	12 241 (82.8)
Black	1328 (9)
Other	1171 (7.9)
Unknown	45 (0.3)
Marital status, n (%)	
Single	865 (5.9)
Married	7800 (52.8)
Separated/divorced	302 (2)
Widowed	2409 (16.3)
Unknown	3409 (23.1)
US region ^a , n (%)	
Midwest	2660 (18)
Northeast	2887 (19.5)
South	2835 (19.2)
West	6403 (43.3)
Population density, n (%)	
Urban	12 002 (81.2)
Rural	2783 (18.8)
Socioeconomic status, n (%)	
Low	7210 (48.8)
High	7389 (50)
Unknown	186 (1.3)
CCI, n (%)	
0	6556 (44.3)
1	2789 (18.9)
≥2	5440 (36.8)
Grade, n (%)	
Well differentiated	435 (2.9)
Moderately differentiated	6287 (42.5)
Poorly differentiated	7975 (54.0)
Undifferentiated/anaplastic	88 (0.6)

CCI = Charlson comorbidity index; IQR = interquartile range; SEER = Surveillance Epidemiology and End Results.
^a Based on regions designated by the United States Census Bureau.

and living in urban areas (81.2%). Overall, 6556 (44.3%), 2789 (18.9%), and 5440 (36.8%) patients had a CCI of 0 versus 1 versus ≥2, respectively. The majority of patients (54.0%) had poorly differentiated disease.

3.2. Survival outcomes

The median follow-up in patients who survived was 50 mo. Of all the deaths observed during the study period, 1807 (20%) and 7135 (80%) were due to PCa and non-cancer causes, respectively.

The 10-yr OS rate in the overall population was 15.4% (Fig. 1). After stratification according to age, the 10-yr OS rate was 19.9% versus 10.0% versus 3.1%, respectively, in age categories 80–84 versus 85–89 versus ≥90 yr (Fig. 2A–C). After stratification according to CCI, the 10-yr OS rate was 18.7% versus 13.9% versus 11.5%, respectively, in CCI categories 0 versus 1 versus ≥2 (Fig. 3A–C). After combined stratification according to age and CCI, the 10-yr OS

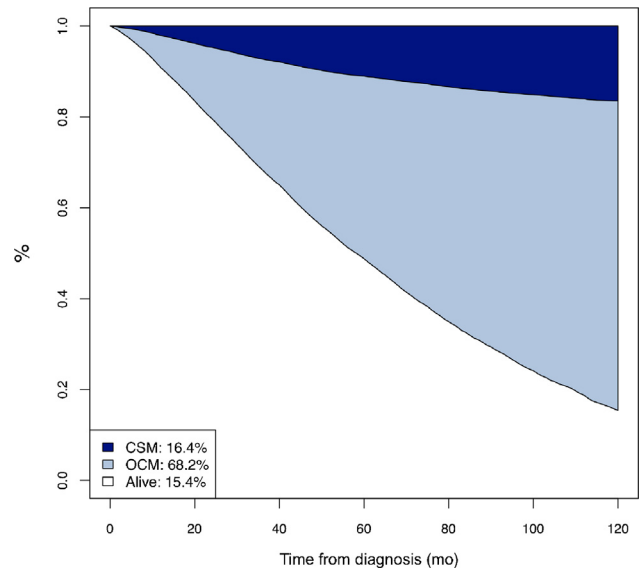


Fig. 1 – Cumulative incidence plot depicting cancer-specific mortality (CSM) and other-cause mortality (OCM) rates up to 10 years in 14 785 octo- and nonagenarian men with organ-confined prostate cancer exposed to primary androgen deprivation therapy. Legend. CSM = cancer-specific mortality; OCM = other cause mortality.

rate was 24.6% in younger and healthier patients (age 80–84 yr + CCI = 0) versus 7.1% in older and sicker patients (age ≥85 yr + CCI ≥ 1) (Fig. 4A and 4B). The 10-yr OCM and CSM rates in the overall population were 68.2% and 16.4%, respectively (Fig. 1). Stratification of OCM and CSM rates according to age categories, CCI, and combinations of age and CCI are shown in Figs. 1–4.

Table 2 shows the multivariable Cox regression model assessing survival in the overall population. Advanced age at diagnosis and a higher CCI score represented independent predictors of higher overall mortality (all $p < 0.001$).

4. Discussion

ADT is the cornerstone in the management of metastatic PCa [17], and it has shown survival benefits when used in

Table 2 – Multivariable analyses addressing overall mortality in 14 785 octo- and nonagenarian patients treated with primary androgen deprivation therapy for organ-confined prostate cancer ^a.

	Multivariable analyses	
	HR	p value
Age at diagnosis (yr)		
80–84	1.00 (Ref.)	–
85–89	1.45 (1.39–1.52)	<0.001
≥90	2.35 (2.19–2.52)	<0.001
CCI		
0	1.00 (Ref.)	–
1	1.22 (1.15–1.29)	<0.001
≥2	1.52 (1.45–1.59)	<0.001

HR = hazard ratio.
^a All variables were adjusted for clinical stage, grade, race, population density, socioeconomic status, marital status, US region, and year of diagnosis.

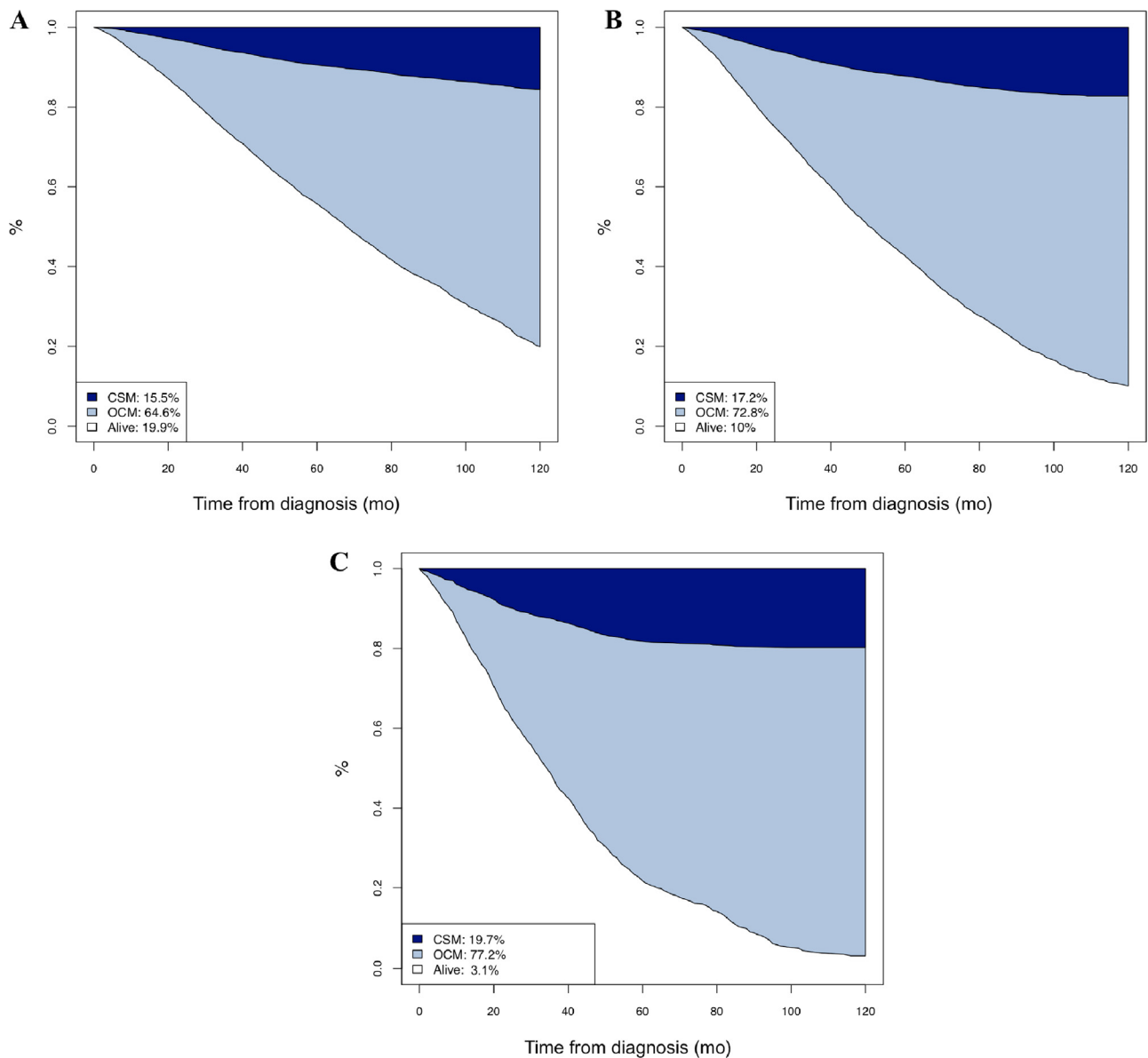


Fig. 2 – Cumulative incidence plots depicting cancer-specific mortality (CSM) and other-cause mortality (OCM) rates up to 10 years in patients aged 80–84 (A), 85–89 (B) and 90 or more (C), exposed to primary androgen deprivation therapy for organ-confined prostate cancer. legend. CSM = cancer-specific mortality; OCM = other cause mortality.

combination with RT for intermediate- or high-risk PCa [18–20], and in combination with RP and pelvic lymphadenectomy in patients with lymph node metastasis [21,22]. To date, no survival benefit was shown for PADT in the setting of early-stage PCa [7–9], except for in men who harbor aggressive disease [9,10]. Despite this lack of evidence-based recommendations for the use of PADT for organ-confined PCa, a growing number of elderly patients with organ-confined disease are treated with PADT as an alternative to RP, RT, or conservative management [4–6]. We hypothesized that the use of PADT in elderly patients may not be warranted based on poor OS and limited LE. To test our hypothesis, we examined 10-yr survival patterns in elderly patients with organ-confined PCa exposed to PADT.

Our results demonstrated that in elderly patients exposed to PADT for organ-confined PCa, OS is indeed poor.

Specifically, only 15% of such individuals were alive at 10-yr follow-up. Moreover, even in the youngest of elderly patients (patients aged 80–84 yr), the 10-yr OS rate was only 20%. Similarly, in the healthiest of elderly patients (CCI = 0), the 10-yr OS rate was only 19%. Finally, after restricting our analyses to younger and healthier patients (age 80–84 yr and CCI = 0), a 10-yr OS rate of only 25% was recorded. Taken together, our data highly conclusively showed that, of individuals with organ-confined PCa who are exposed to PADT, at best 25% remained alive at 10-yr follow-up. Such findings question the rationale for ADT as a primary treatment modality in these individuals. Unfortunately, our findings cannot be directly compared with other cohorts, since to the best of our knowledge, similar population-based analyses focusing on older individuals were not reported. Consequently, our data represent the first

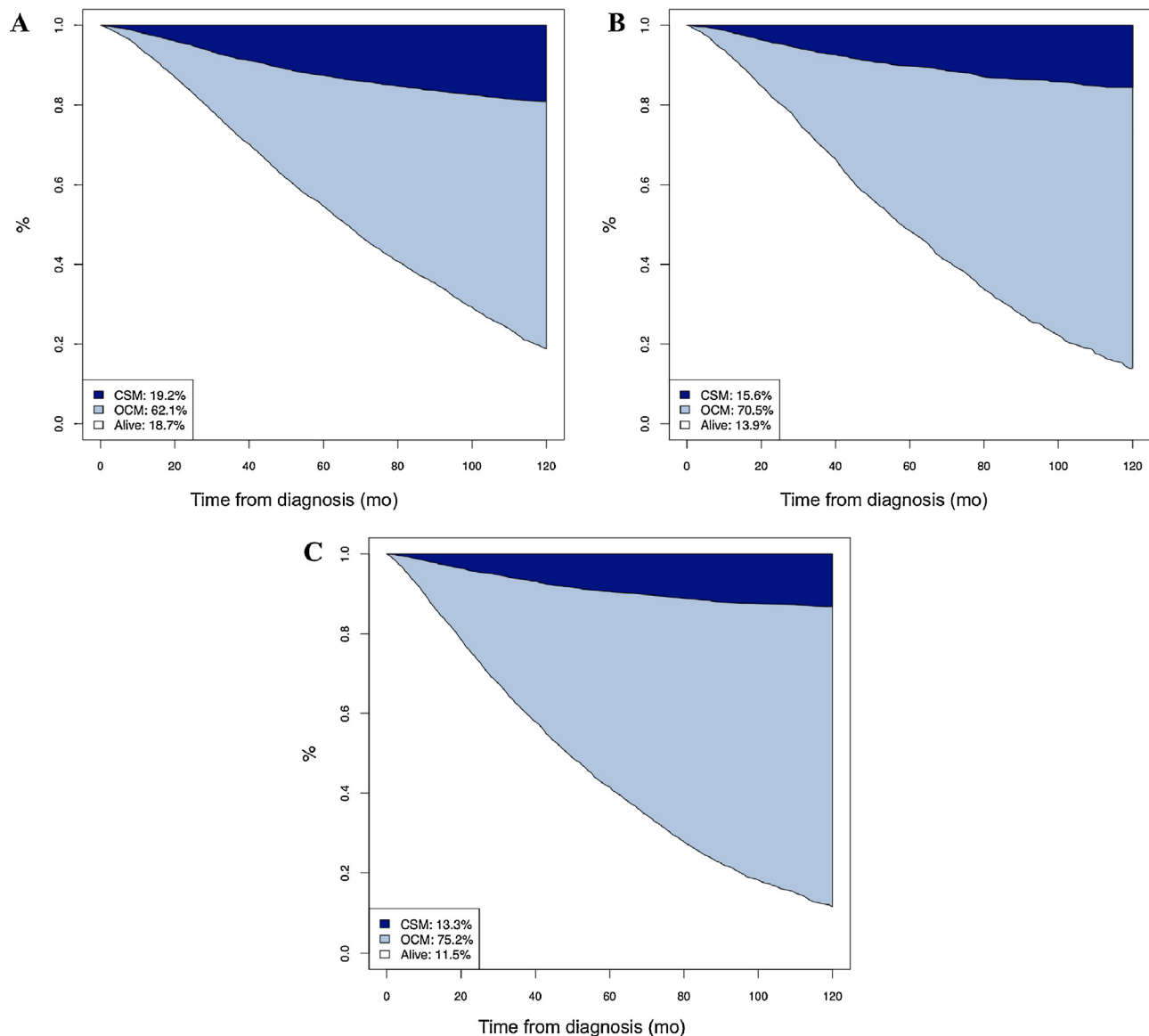


Fig. 3 – Cumulative incidence plots depicting cancer-specific mortality (CSM) and other-cause mortality (OCM) rates up to 10 years in patients with CCI = 0 (A), CCI = 1 (B) and CCI = 2 or more (C) exposed to primary androgen deprivation therapy for organ-confined prostate cancer. legend. CSM = cancer-specific mortality; OCM = other cause mortality.

published report of poor OS in PCa patients aged 80 yr or more. Moreover, they suggest substantial PADT overuse in such individuals. However, they also confirm the suspicion and/or practical experience of many clinicians with this group of individuals.

Second, our analyses not only show poor OS, but also confirm that 80% of deaths observed during the study period were related to non-PCa causes. In the overall analyses, the OCM rate was 68% at 10-yr follow-up. This finding was also confirmed in the “best-case scenario” where the rate of OCM should be at its lowest, namely in younger and healthier individuals. Here, the 10-yr OCM rate was 65% in younger (age 80–84 yr) versus 62% in healthier (CCI = 0) versus 57% in the combined categories of younger and healthier patients. Taken together, these findings indicate that OCM was overwhelmingly the leading cause of death in

elderly patients with organ-confined PCa treated with PADT.

Third, it is of interest to note that 20% of deaths during the study period were related to PCa. Assessment of time of PCa death revealed that 16% of PCa events occurred within 10 yr. Such elevated rates are surprising in the context of organ-confined PCa patients and might be indicative of a stage misclassification bias. Specifically, patients with locally advanced disease might have been included in the category of localized PCa. For example, patients treated with active surveillance exhibited CSM of 1.9% at 10 yr [23]. Similarly, patients treated with RT and ADT for locally advanced high-risk PCa exhibited CSM of 10.3% at 10 yr [18]. Our CSM rate of 16% at 10 yr appears to be substantially higher than expected for organ-confined PCa disease. This observation questions the elevated CSM rate in our cohort

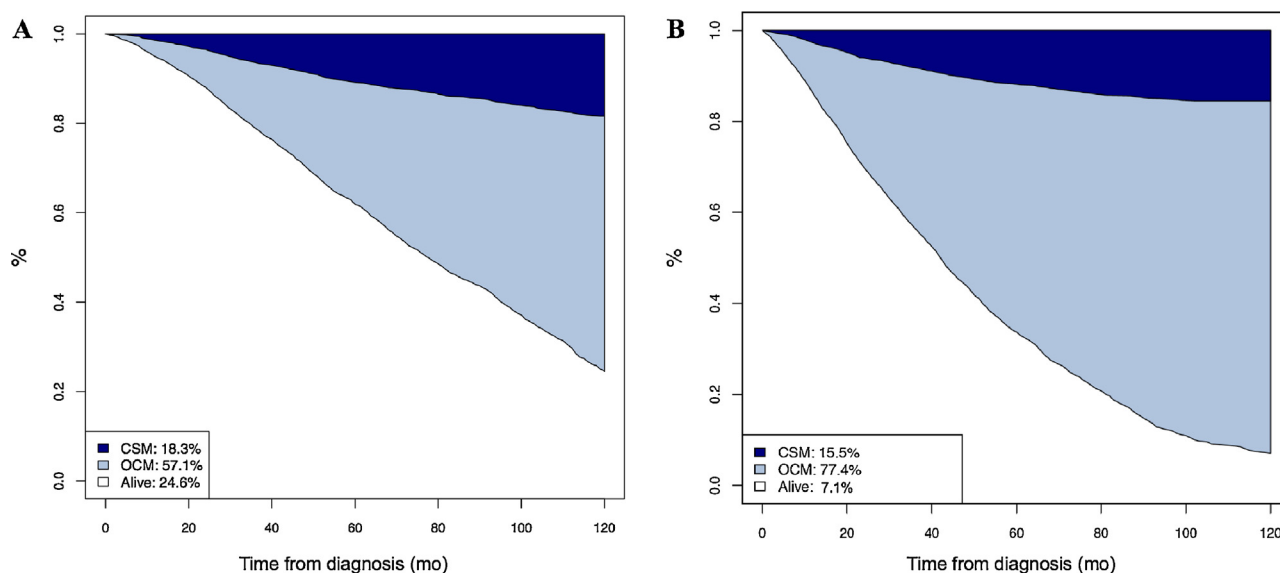


Fig. 4 – Cumulative incidence plots depicting cancer-specific mortality (CSM) and other-cause mortality (OCM) rates up to 10 years in (A) younger and healthier patients (patients aged 80–84 + CCI = 0) vs. (B) older and sicker patients (patients aged 85 or more + CCI = 1 or more) exposed to primary androgen deprivation therapy for organ-confined prostate cancer. legend. CSM = cancer-specific mortality; OCM = other cause mortality.

and supports the hypothesis of stage misclassification bias, whereby men with higher PCa stages were included in the current cohort of patients with organ-confined disease. The same misclassification bias appears operational in the cohort of patients studied by Lu-Yao et al. [24], in which 10-yr CSM rates between 17% and 20% were recorded. The similarity of these rates was expected given the same origin of data, namely the SEER-Medicare database. It is noteworthy that our study and the previous SEER-based analysis performed by Lu-Yao et al. failed to reveal a minimal benefit of PADT in an organ-confined setting, despite the presence of such a misclassification bias.

Fourth, it is of note that CSM did not vary significantly according to age and comorbidities. For example, CSM rates were 18% in younger and healthier patients (age 80–84 yr and CCI = 0) versus 16% in older and sicker individuals (age 85–89 yr and CCI ≥ 1). This implies that in organ-confined PCa patients exposed to ADT, age and CCI have a marginal effect on CSM. Conversely, age and CCI even in the current population of octo- and nonagenarians have a tremendous effect on OS. For example, the OS rate was 25% in younger and healthier patients (age 80–84 yr and CCI = 0) versus 7% in older and sicker patients (age 85–89 yr and CCI ≥ 1). Finally, when comorbidities and age were considered in multivariable analyses, these variables represented independent predictors of worse OS. Consequently, age and comorbidity should be considered in the decision-making for PADT in elderly patients.

Our study may be compared with previous reports by Lu-Yao et al. [7,24]. In these analyses, the authors focused on PADT efficacy in SEER-Medicare patients aged >65 yr. Their findings failed to support PADT efficacy in these individuals. We relied on a different approach to demonstrate the futility of PADT for SEER-Medicare patients. First, we focused on the most elderly patients, namely, those aged over 80 yr, in whom short LE may not warrant ADT use, in

the light of organ-confined disease, advanced age, and the presence of comorbidities. Moreover, we did not attempt a comparison hinging on cancer control between PADT-treated and untreated individuals. Instead, we showed very short OS (15%) in those exposed to PADT. Moreover, we demonstrated that the overwhelming majority of deaths in these individuals are unrelated to PCa (80%). Hopefully, these arguments will add to those of Lu-Yao et al. and more conclusively discourage the use of PADT, specifically in elderly PCa patients. It is of note that the lack of indications for PADT based on the poor LE of elderly patients is further compounded by a myriad of side effects that these agents are known for [25–28].

Although our findings are noteworthy, they must be interpreted in the context of the study design. First, our findings are limited by their retrospective nature. Second, our results are not applicable to patients younger than 80 yr. Third, our results cannot be applied to all contemporary patients because we focused only on patients treated until 2009. Fourth, similar to other retrospective studies [29], several limitations of the SEER-Medicare database likely also biased our findings, such as uncovered problems with prostate-specific antigen (PSA) values announced by SEER on April 15, 2015 [30] that did not allow further stratification according to PSA, the absence of information regarding the type and dose of ADT, and changes in PCa grading over the study period. Last but not least, the pattern of ADT use and the LE of our patients could be different from other insurance coverage groups.

Despite their limitations, our results showed that octo- and nonagenarians with organ-confined PCa who are exposed to PADT have poor LE at 10-yr follow-up. Moreover, the leading cause of death recorded at 10-yr follow-up was not attributable to PCa. Last but not least, the rate of PCa death was overestimated due to a potential misclassification bias. This very fact strongly questions the validity of

PADT in this patient population. Consequently, use of PADT may represent a poor choice in these individuals. Instead, delayed ADT might represent a more cost-conscious option, especially in light of the absence of a cancer control benefit of PADT except for patients with more aggressive disease [10].

5. Conclusions

Fifteen percent of elderly patients treated with PADT for organ-confined PCa survive at 10-yr follow-up. Mortality related to non-cancer causes is the leading cause of death in the same follow-up period. These figures question the rationale for PADT in elderly men with organ-confined PCa.

Author contribution: Paolo Dell'Oglio had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Dell'Oglio, Bishr, Karakiewicz.

Acquisition of data: Dell'Oglio, Bishr, Trudeau.

Analysis and interpretation of data: Dell'Oglio, Bishr, Karakiewicz, Boehm.

Drafting of the manuscript: Dell'Oglio, Bishr, Karakiewicz.

Critical revision of the manuscript for important intellectual content: Dell'Oglio, Bishr, Boehm, Trudeau, Larcher, Tian, Sosa, Moschini, Saad, Capitanio, Briganti, Graefen, Montorsi, Karakiewicz.

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Other: None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.euf.2017.01.017>.

References

- [1] Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. *CA Cancer J Clin* 63:2013:1130.
- [2] 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. *Lancet Oncol* 2014;15:e404–14.
- [3] Bian SX, Hoffman KE. Management of prostate cancer in elderly men. *Semin Radiat Oncol* 2013;23:198–205.
- [4] Shahinian VB, Kuo YF, Freeman JL, Orihuela E, Goodwin JS. Increasing use of gonadotropin-releasing hormone agonists for the treatment of localized prostate carcinoma. *Cancer* 2005;103:1615–24.
- [5] Cooperberg MR, Grossfeld GD, Lubeck DP, Carroll PR. National practice patterns and time trends in androgen ablation for localized prostate cancer. *J Natl Cancer Inst* 2003;95:981–9.
- [6] Kawakami J, Cowan JE, Elkin EP, Latini DM, DuChane J, Carroll PR. Androgen-deprivation therapy as primary treatment for localized prostate cancer: data from Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE). *Cancer* 2006;106:1708–14.
- [7] Lu-Yao GL, Albertsen PC, Moore DF, et al. Fifteen-year survival outcomes following primary androgen-deprivation therapy for localized prostate cancer. *JAMA Intern Med* 2014;174:1460–7.
- [8] Wong YN, Freedland SJ, Egleston B, Vapiwala N, Uzzo R, Armstrong K. The role of primary androgen deprivation therapy in localized prostate cancer. *Eur Urol* 2009;56:609–16.
- [9] Mottet N, Bellmunt J, Briers E, et al. Guidelines on prostate cancer. European Association of Urology; 2016 <http://uroweb.org/guideline/prostate-cancer/>
- [10] Studer UE, Collette L, Whelan P, et al. Using PSA to guide timing of androgen deprivation in patients with T0–4 N0–2 M0 prostate cancer not suitable for local curative treatment (EORTC 30891). *Eur Urol* 2008;53:941–9.
- [11] Warren JL, Klabunde CN, Schrag D, Bach PB, Riley GF. Overview of the SEER-Medicare data: content, research applications, and generalizability to the United States elderly population. *Med Care* 2002;40(8 Suppl), IV-3–18.
- [12] Du XL, Fang S, Coker AL, et al. Racial disparity and socioeconomic status in association with survival in older men with local/regional stage prostate carcinoma: findings from a large community-based cohort. *Cancer* 2006;106:1276–85.
- [13] Robert SA, Strombom I, Trentham-Dietz A, et al. Socioeconomic risk factors for breast cancer: distinguishing individual- and community-level effects. *Epidemiology* 2004;15:442–50.
- [14] Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol* 1992;45:613–9.
- [15] Hu CY, Xing Y, Cormier JN, Chang GJ. Assessing the utility of cancer-registry-processed cause of death in calculating cancer-specific survival. *Cancer* 2013;119:1900–7.
- [16] Dell'Oglio P, Karnes RJ, Joniau S, et al. Very long-term survival patterns of young patients treated with radical prostatectomy for high-risk prostate cancer. *Urol Oncol* 2016;34:234, e13–9.
- [17] Walsh PC. Immediate versus deferred treatment for advanced prostatic cancer: initial results of the Medical Research Council Trial. The Medical Research Council Prostate Cancer Working Party Investigators Group. *Br J Urol* 1997;79:235–46.
- [18] Bolla M, Van Tienhoven G, Warde P, et al. External irradiation with or without long-term androgen suppression for prostate cancer with high metastatic risk: 10-year results of an EORTC randomised study. *Lancet Oncol* 2010;11:1066–73.
- [19] Pilepich MV, Winter K, Lawton CA, et al. Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma—long-term results of phase III RTOG 85–31. *Int J Radiat Oncol Biol Phys* 2005;61:1285–90.
- [20] D'Amico AV, Manola J, Loffredo M, Renshaw AA, DellaCrocce A, Kantoff PW. 6-Month androgen suppression plus radiation therapy vs radiation therapy alone for patients with clinically localized prostate cancer: a randomized controlled trial. *JAMA* 2004;292:821–7.
- [21] Messing EM, Manola J, Sarosdy M, Wilding G, Crawford ED, Trump D. Immediate hormonal therapy compared with observation after radical prostatectomy and pelvic lymphadenectomy in men with node-positive prostate cancer. *N Engl J Med* 1999;341:1781–8.
- [22] Messing EM, Manola J, Yao J, et al. Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy. *Lancet Oncol* 2006;7:472–9.

-
- [23] Klotz L, Vesprini D, Sethukavalan P, et al. Long-term follow-up of a large active surveillance cohort of patients with prostate cancer. *J Clin Oncol* 2015;33:272–7.
 - [24] Lu-Yao GL, Albertsen PC, Moore DF, et al. Survival following primary androgen deprivation therapy among men with localized prostate cancer. *JAMA* 2008;300:173–81.
 - [25] Shahinian VB, Kuo YF, Freeman JL, Goodwin JS. Risk of fracture after androgen deprivation for prostate cancer. *N Engl J Med* 2005;352:154–64.
 - [26] Smith MR, Lee H, Nathan DM. Insulin sensitivity during combined androgen blockade for prostate cancer. *J Clin Endocrinol Metab* 2006;91:1305–8.
 - [27] Keating NL, O'Malley AJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. *J Clin Oncol* 2006;24:4448–56.
 - [28] Nguyen PL, Alibhai SM, Basaria S, et al. Adverse effects of androgen deprivation therapy and strategies to mitigate them. *Eur Urol* 2015;67:825–36.
 - [29] Bekelman JE, Mitra N, Handorf EA, et al. Effectiveness of androgen-deprivation therapy and radiotherapy for older men with locally advanced prostate cancer. *J Clin Oncol* 2015;33:716–22.
 - [30] Furlow B. US National Cancer Institute investigates PSA coding errors. *Lancet Oncol* 2015;16:614.