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ORIGINAL ARTICLE

Current impact of age and comorbidity assessment on prostate cancer treatment choice and over/undertreatment risk

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Abstract
Purpose We evaluated the influence of age and comorbidity (Charlson score assessment) on localized prostate cancer therapeutic management and the risk of prostate cancer over- and under-treatment.
Methods Among the 2571 prostate cancer cases diagnosed in 2011, a subset of 633 patients was randomly selected from the prospectively accrued cohort of the Regional Cancer Registry, among the 17 participating institutions. Treatment distributions were examined for patients at each individual prostate cancer risk, age and comorbidity level and analyzed by multivariate logistic regression analysis.
Results Treatments with curative intent were observed less often when age increased ($p < 0.001$). We found no impact of the Charlson score on the selection of a curative treatment [HR 0.89, 95 % CI (0.70–1.15)]. A 20 % overtreatment rate was reported in low-risk prostate cancer patients. For younger patients (65–75 years) with high comorbidity score, a 14 % overtreatment rate was observed. Conversely, a 16 % undertreatment rate was reported in older patients >75 years without any significant comorbidity.
Conclusion A better consideration of comorbidities could significantly reduce overtreatment in patients <75 year and promote curative treatment in aggressive prostate cancer for older patients without any significant comorbidity.

Keywords Prostate cancer · Comorbidity · Charlson score · Overtreatment · Undertreatment

Introduction

The objectives of modern screening and diagnostic strategies in prostate cancer (PCa) are to detect disease within the window of curability and avoid over- and under-treatment [1, 2]. While there is ample literature on the risks and harms of overdiagnosis and overtreatment, limited data are available regarding undertreatment. Given the demographics of PCa, which mostly impact elderly patients with competitive morbidities, undertreatment might typically be observed in fit patients diagnosed with cancers showing aggressive features. Individualization in care is therefore promoted by the recent updates in guidelines of the American Urological Association (AUA) [3, 4] and the European Association of Urology (EAU) [5], which both emphasize the value of considering simultaneously cancer characteristics and patients' life expectancy or comorbidities. Several studies have yet identified evidence of considering age-adjusted life expectancy with comorbidity assessment [6–8]. However, in a recent study using data from the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) registry, Cooperberg et al. [9] showed regional practice-level variation not explained by disease case-mix variability.

We analyzed a large regional registry to determine the influence of age and comorbidities on localized PCa therapeutic management and to evaluate the risk of PCa over- and under-treatment according to these factors.

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Materials and methods

PCa cases detected in 2011 were identified within the Midi-Pyrénées regional cancer registry that covers PCa treated within seventeen institutions of various patients' volumes (1 Teaching hospital, 2 Non-teaching government hospitals, 14 Private hospitals). The study population was randomly selected (1:3) from the database after stratification to take into account centers' Pca patient volumes (Fig. 1). Randomization was made to reduce selection bias and differences in PCa management resulting in centers' activity. Indeed, the number of PCa cases managed by each center over a year is extremely different, reaching from >150 to <10 cases. Figure 1 shows that patients' selection was stratified according to centers activity, to obtain a coherent and statistically equivalent repartition of selected cases from each patient volume center category (<150, 50–149, 11–49) and to exclude centers with very low patient volume (>10 cases). After randomization, 33 patients were excluded because of unavailable file, lost follow-up or PCa recidive. Finally, 633 patients were randomly selected and analyzed.

Patients' files were reviewed on site by trained research assistants to document patients demographics, cancer and treatment characteristics. Following AUA/EAU guidelines, cancers were stratified as of low, intermediate and high risk according to d'Amico [10]. Treatments were classified as with curative intent (TCI: Radical Prostatectomy—RP or External-Beam Radiation Therapy—EBRT or Brachytherapy) or with non-curative intent (TnCI: surveillance/watchful waiting/primary androgen deprivation therapy—ADT). Treatment distributions according to d'Amico risk

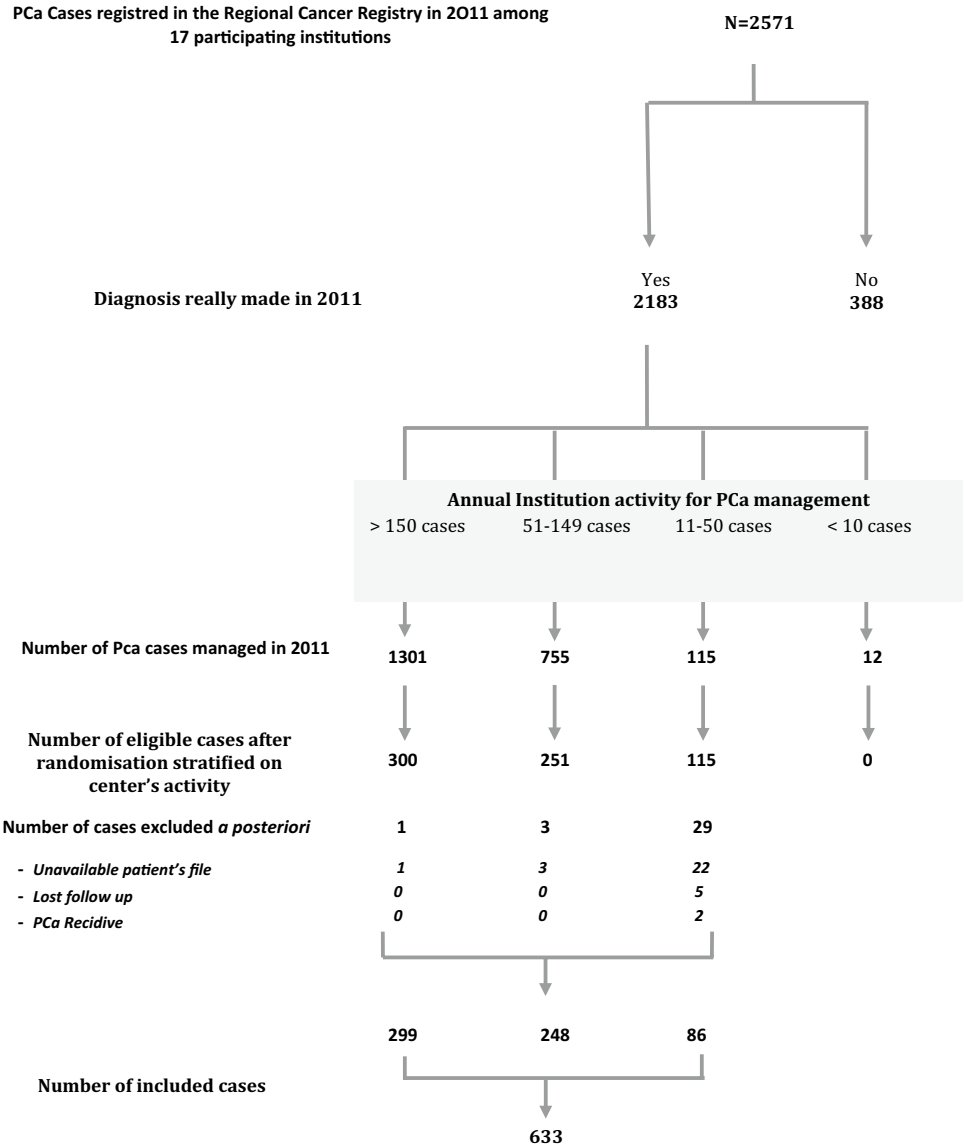

Fig. 1 Selection of the population study

Table 1 Evaluation criteria for overtreatment and undertreatment

	D'Amico's risk group	Patient's characteristics	Adapted from
Overtreatment	Any	Age <75 + CCI ≥ 2	[11–14]
		Age >75 + CCI ≥ 1	(High probability of comorbidity-related death)
	Low risk	Age 65–75 + CCI ≤ 1	[4–6]
			(Low probability of Overall Death)
Undertreatment	Intermediate or	Age <75 + CCI ≤ 1	[11–14]
	High risk	Age 75–85 + CCI 0	(Low probability of comorbidity-related death)

stratification, age and comorbidity assessment (Charlson Comorbidity Index, CCI) [11] were then obtained.

We considered age, tumor stage and grade, and comorbidity-adjusted life expectancy to define over- and undertreatments per protocol, using a threshold value of 10 years for life expectancy. Individual 10-year life expectancies were estimated from age using French National Demographic statistics [12] and from CCI using the current literature [13–16]. Briefly, patients of any age with CCI ≥ 2 or older than 85 years of age were assumed to have a life expectancy <10 years, while patients younger than 85 years of age and with CCI ≤ 1 belonged to a group whose mean life expectancy reached or exceeded 10 years.

Overtreatment was characterized in patients who underwent curative treatment despite a high probability of comorbidity-related death within 10 years following diagnosis. To be even more restrictive with patients > 75 years, we only considered for overtreatment those with CCI ≥ 1 and not ≥ 2:

Regardless disease stage or grade

- Age <75 + CCI ≥ 2.
- Age >75 + CCI ≥ 1.

Furthermore, there is a matter of judgment between active surveillance and curative treatment for young fit patients with low-risk PCa. Following actual recommendations, we deemed that patients <65 years treated with curative intent could not be considered as overtreated. That's why we put aside a 3rd category of «potential overtreatment», defined by:

- Age 65–75 + CCI ≤ 1 + low-risk PCa.

Undertreatment was characterized in patients with aggressive PCa features (intermediate or high-risk PCa) who received TnCI despite >10 years comorbidity-adjusted life expectancy (low probability of comorbidity-related death within 10 years). To be even more restrictive with patients 75–85 years, we only considered for undertreatment the fittest one (those with CCI = 0 and not ≤ 1):

Only intermediate or high-risk PCa

- Age <75 + CCI ≤ 1.
- Age 75–85 + CCI = 0.

Table 1 explains definitions of over- and under-treatment.

Demographic and clinical data are summarized using descriptive statistics. For qualitative data, comparison between groups was made using the Pearson's correlation coefficient (r) and the nonparametric Mann–Whitney test. The Kruskal–Wallis test was used for quantitative variables. All tests were two-sided using Stata version 11.0 (College Station, Texas: Stata Corporation).

Results

Out of the 2571 new cases of PCa registered in 2011, 666 were randomly selected. Thirty-three patients with missing data or lost to follow-up were not considered for analysis (Fig. 1). Patients' age, CCI and cancer characteristics are presented in Table 2. More aggressive localized PCa in the d'Amico risk stratification were observed with increment in age ($p < 0.001$) and CCI ($p = 0.016$).

Localized prostate cancer, as defined by a clinical stage < T3bN0M0, was evidenced in 511/633 patients (80.7 %), 440/633 (69.5 %) elected TCI. Univariate analysis showed that TCI was positively impacted by younger age ($p < 0.001$) and by d'Amico risk stratification ($p < 0.001$), while CCI was of no influence on treatment decision (Table 3). On multivariate analysis, TCI was less frequently selected with increasing age, as shown by a 12 % decrease in 5-year increments (HR 0.88, 95 % CI 0.85–0.91), and confirmed to be independent of CCI (HR 0.89, 95 % CI 0.70–1.15). Subgroup analyses (<65, 65–75, >75 years of age) confirmed that whatever the age, comorbidity evaluation was not taken into account in the decision process. Compared to low risk patients, TCI was three times more likely to be selected in patients showing intermediate-risk PCa (HR 3.02 (95 % CI, $p < 0.001$). A nonsignificant trend toward higher use of TCI was also observed in high-risk PCa patients (HR 1.47, 95 % CI, $p = 0.23$, n.s.)

Table 2 Population characteristics

Patients	Cancer characteristics (D'Amico risk)					
	Total	Low	Intermediate	High	Locally advanced	Metastatic
N (%)	633	146 (23 %)	289 (46 %)	116(18 %)	48 (8 %)	34 (5 %)
Age		$p < 0.001$				
0–54	28 (4 %)	9 (32 %)	14 (50 %)	2 (7 %)	2 (7 %)	1 (4 %)
55–59	57 (9 %)	13 (23 %)	32 (56 %)	9 (16 %)	0 (0 %)	3 (5 %)
60–64	122 (19 %)	39 (32 %)	54 (44 %)	16 (13 %)	5 (4 %)	8 (7 %)
65–69	124 (19 %)	39 (31.5 %)	49 (40 %)	19 (15 %)	8 (6.5 %)	9 (7 %)
70–74	111 (18 %)	17 (15 %)	68 (61.5 %)	16 (14.5 %)	6 (5 %)	4 (4 %)
75–79	114 (18 %)	28 (24 %)	49 (43 %)	25 (22 %)	10 (9 %)	2 (2 %)
80–84	55 (9 %)	1 (2 %)	21 (38 %)	24 (44 %)	7 (13 %)	2 (3 %)
≥85	22 (4 %)	0 (0 %)	2 (9 %)	5 (23 %)	10 (45 %)	5 (23 %)
CCI		$p = 0.016$				
0	414 (66 %)	104 (25 %)	192 (46.5 %)	68 (16.5 %)	30 (7 %)	20 (5 %)
1	115 (18 %)	21 (18 %)	55 (48 %)	27 (24 %)	6 (5 %)	6 (5 %)
2	65 (10 %)	17 (26 %)	30 (46 %)	11 (17 %)	4 (6 %)	3 (5 %)
≥3	39 (6 %)	4 (10 %)	12 (31 %)	10 (26 %)	8 (20 %)	5 (13 %)

Table 3 Treatment modality

	Patients $n = 551$	TnCI $n = 111$	TCI $n = 440$		RP $n = 285$	Irradiation $n = 152$	
CCI							
0	364 (66 %)	67 (18 %)	297 (82 %)	$p = 0.213$	205 (69 %)	92 (31 %)	$p = 0.011$
1	103 (19 %)	20 (19 %)	83 (81 %)		43 (52 %)	40 (48 %)	
2	58 (10.5 %)	17 (29 %)	41 (71 %)		28 (68 %)	13 (32 %)	
3	26 (4.5 %)	7 (27 %)	19 (73 %)		9 (47 %)	10 (53 %)	
Age							
0–54	25 (5 %)	1 (4 %)	24 (96 %)	$p < 0.001$	21 (87.5 %)	3 (12.5 %)	$p < 0.001$
55–59	54 (10 %)	4 (7 %)	50 (93 %)		43 (86 %)	7 (14 %)	
60–64	109 (20 %)	15 (14 %)	94 (86 %)		76 (81 %)	18 (19 %)	
65–69	107 (19 %)	17 (16 %)	90 (84 %)		72 (80 %)	18 (20 %)	
70–74	101 (18 %)	9 (9 %)	92 (91 %)		53 (58 %)	39 (42 %)	
75–79	102 (19 %)	24 (23.5 %)	78 (76.5 %)		19 (24 %)	59 (76 %)	
80–84	46 (8 %)	34 (74 %)	12 (26 %)		1 (8 %)	11 (92 %)	
>85	7 (1 %)	7 (100 %)	0 (0 %)		0 (0 %)	0 (0 %)	
PCa risk stratification							
Low	146 (27 %)	35 (24 %)	111 (76 %)	$p = 0.001$	80 (72 %)	31 (28 %)	$p = 0.026$
Intermediate	289 (52 %)	39 (13.5 %)	250 (86.5 %)		163 (65 %)	87 (35 %)	
High	116 (21 %)	37 (32 %)	79 (68 %)		42 (53 %)	37 (47 %)	

On the other hand, CCI had a significant impact on the choice of treatment modalities in patients electing TCI as showed by a 60 % reduction in the proportion of surgical treatment observed with increasing CCI scores (HR 0.384, 95 % CI 0.15–0.95) when radiation therapy was taken as reference.

Table 4 reports overtreatment and undertreatment according to the PCa risk group, age and the comorbidity status. Among the 440 patients who underwent TCI, 76 presented high probability of non-specific PCa (comorbidity related) death. Furthermore, 36 young patients with low-risk PCa, eligible to active surveillance, were also overtreated. Globally, 112 patients (25.5 %) were in a situation of overtreatment. Conversely, a 37.8 % undertreatment rate (42/111) was observed among patients who underwent TnCI.

Table 4 Rates of over- and under-treatment according to PCa group risks, age and comorbidity status

Treatment modality	D'Amico's risk group	Patient's characteristics	*N* (%)	Total (%)
Overtreatment				
TCI $n = 440$	Any	Age <75 + CCI ≥ 2	44[a]	112 (25.5 %)
		Age >75 + CCI ≥ 1	32	
	Low risk	Age 65–75 + CCI ≤ 1	36	
Undertreatment				
TnCI $n = 111$	Intermediate or	Age <75 + CCI ≤ 1	17	42 (37.8 %)
	High Risk	Age 75–85 + CCI 0	25	

[a] Of whom, 15 were < 65 years

Discussion

The National Comprehensive Cancer Network guidelines for prostate cancer suggest that curative treatment should be proposed only for men whose overall life expectancy is over 10 years [17]. According to these guidelines, urologists have to make decisions based on both patient's life expectancy and PCa characteristics. In this prospectively accrued cohort of men with PCa, we observed that the comorbidity status as defined by the Charlson score only marginally modified curative treatment decision-making. Thus, overtreatment rate remains non-negligible for patients with high comorbidity score and who had a great risk of death not attributable to PCa. Conversely, a non-negligible proportion of men with intermediate or high-risk PCa did not receive curative treatment in spite of a clinically localized disease and a low comorbidity burden. The potential undertreatment rate appears to be a growing concern, estimated in this study at almost 37.8 %.

Previous findings demonstrated that management of localized PCa shows substantial variations in practice patterns across clinicians and clinical sites [9, 18]. A growing body of evidence suggests that individual comorbidity assessment is a key factor to reduce overdiagnosis and overtreatment. In the large series of Guzzo [15], Albertsen [17] and Daskivich [19], men with CCI ≥ 2 have a subsequent risk of non-specific PCa death compared to those with CCI ≤ 1 with a relative risk of 2, and life expectancy was <10 years regardless age or progression risk according to d'Amico. Conversely, men less than 80 years old with CCI ≤ 1 had a 52 % of at least 10 years overall survival [16].

Randomly selected population was made to reduce selection bias. This population was representative in terms of age, tumor grade and stage, and comorbidity level compared to non-selected population. Furthermore, we compared our population with those of precedent large European and American studies. Thus, the rate of patients with CCI 0 was similar in our study (65.4 %) and in those of Delpierre et al. [20] carried out in France in 2001 (64.5 %) and Vulto et al. [21] in the Netherlands in 2006 (60 %). The proportion of patients with CCI ≥ 3 in our study (6.16 %) corresponded to those found in studies of Mohan and Daskivich (4.4 and 11 %, respectively) [22, 23].

In this study, 70 % of patients underwent curative treatment. As expected, the PCa risk was strongly correlated with curative treatment decision. Multivariate analysis showed that the type of chosen curative treatment modality was influenced by both age and comorbidities, as shown by a significant reduction in RP practice compared to EBRT or Brachytherapy when age and comorbidities increased. These trends are explained by the will to avoid surgical complications for unfit patients [24]. Therefore, comparing Pca overall survival following RP or EBRT remains difficult. Retrospective studies might lead to biased conclusions when not considering comorbidity burden [25].

Conversely, even after age adjustment in multivariable analyses, no statistically significant impact of CCI was found on treatment decision-making regarding TCI versus TnCI. Thus, age remains the main treatment decision-making factor. These findings emphasized that the comorbidity is not sufficiently taken into account in pre-treatment life-expectancy assessment. These results are similar to those found in recent series of Daskivich et al. [19], Berglund et al. [26] and Loeb et al. [27]. Although guidelines recommend the use of population-based scales such as mortality tables to estimate life expectancy, chronological age should not be considered as the main decisive factor. These measures do not consider individual health status and may overestimate life expectancy for patients with competitive morbidities [17, 28]. Similarly, it may also be underestimated for patients without comorbidity whose life expectancy is greater than general population. It therefore appears that the lack of individual comorbidities assessment may expose to overtreatment or undertreatment risks.

Using criteria adapted from literature's data [13–16], regardless of PCa risk, we observed a 16.4 % rate (72/440) of overtreatment in patients with a high probability of comorbidity-related 10-year death. Considering the subgroup of 65–75 years fit patients with low CCI and low-risk

PCa, potential overtreatment concerned 36 of them. Even for those patients, limit between overtreatment and appropriate management can be discussed. Indeed, patients detected with low-risk PCa are both eligible to initial curative treatment and active surveillance as recommended options. Klotz et al [29] in a recent updated long-term follow-up of a large active surveillance cohort showed a 9.2:1 cumulative hazard ratio for non-prostate-to-prostate cancer mortality, suggesting a potential overtreatment of this selected population. That's why we considered these patients as «potentially overtreated». Daskivich et al. [22] found an overtreatment rate of 48 % in their retrospective series from 1991 to 2007, with the same endpoints. In a French cohort of patients in 2001, Delpierre et al. [20] reported an overtreatment rate of 34.6 % for patients with localized PCa and a CCI > 2. The 25.5 % overtreatment rate found in our cohort seems to show an improvement in treatment decision-making over time. Conversely, our results did not show any correlation between comorbidity score and curative treatment selection. This contradiction might be explained by an efficient upstream diagnosis to a selected fit population, as shown by an overall 84 % of men presenting CCI $\leq$ 1 (Table 2).

Overall, 37.8 % (42/111) of the TnCI decisions were potentially undertreatment situations when considering comorbidity-adjusted life expectancy in this study. In a recent large nationwide register study, Bratt et al. [16] observed a 10 % rate of men aged 75–80 year with Charlson score 0 receiving radical treatment, compared with approximately half of the men younger than 70 year with a similar life expectancy. Similarly, in our series, 16 % (25/156) of patients aged 75–85 year had untreated intermediate or high-risk disease and no comorbidity and were therefore in a potential undertreatment situation. Moreover, undertreatment concept is only here developed in terms of specific survival but could also usefully be analyzed in terms of disease-free survival or life quality-adjusted survival. Using theses endpoints, a greater rate of potential undertreatment should be retrieved.

Compared to the literature, results found in our cohort seem to show a decrement in overtreatment, whereas undertreatment is a growing concern for elderly patients. "Preference-Sensitive" management tends to select aggressive treatments when PCa risk increases in younger patients, and surveillance, watchful waiting or ADT for older patients. We deem these trends should be better controlled with earlier consideration of comorbidity assessment in therapeutic decisions [16, 30].

Conclusion

Overtreatment of low-risk PCa is a major public health issue. Nevertheless, the present series confirms a continuous decrease in overtreatment rate over time. Age remains the main factor affecting the treatment choice, whereas the comorbidity does not significantly influence overall curative treatment decision-making. However, a better consideration of comorbidities could significantly reduce overtreatment in patients <75 year and promote curative treatment in aggressive PCa for older patients without any significant comorbidity. A life-expectancy evaluation based on both age and comorbidity status should help physician to improve management at an individual patient basis.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Informed consent was obtained from all individual participants included in the study.

Authors' contribution Lunardi P.: Data collection or management, Data analysis, Manuscript writing/editing, Ploussard G.: Content's review, Grosclaude P.: Data analysis, Roumiguié M.: Protocol/project development, Soulié M.: Protocol/project development, Beauval JB.: Protocol/project development, Content's review. Malavaud B.: Protocol/project development, Manuscript writing, Content's review.

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