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Predicting survival in node-positive prostate cancer after open, laparoscopic or robotic radical prostatectomy: A competing risk analysis of a multi-institutional database

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Abbreviations & Acronyms
aADT = adjuvant androgen deprivation therapy
aRT = adjuvant radiotherapy
BS = bone scan
CECT = contrast-enhanced abdominal computed tomography
CI = confidence interval
CSM = cancer-specific mortality
CSS = cancer-specific survival
ePLND = extended pelvic lymph node dissection
HR = hazard ratio
IQR = interquartile range
LN = lymph node
LNI = lymph node invasion
LNM = lymph node metastases
OCM = other-cause mortality
PCa = prostate cancer
PET/CT = positron emission tomography/computer tomography
PSA = prostate-specific antigen
RP = radical prostatectomy

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Objectives: To investigate cancer-specific mortality and other-cause mortality in prostate cancer patients with nodal metastases.

Methods: The study included 411 patients treated with radical prostatectomy and pelvic lymph node dissection for prostate cancer with lymph node metastases at 10 tertiary care centers between 1995 and 2014. Kaplan–Meier analyses were used to assess cancer-specific mortality-free survival rates at 8 years' follow up in the overall population, and after stratifying patients according to clinical and pathological parameters. Uni- and multivariable competing risk Cox regression analyses were used to assess cancer-specific mortality and other-cause mortality. Finally, cumulative-incidence plots were generated for cancer-specific mortality and other-cause mortality after stratifying patients according to the number of positive lymph nodes and the median age at surgery, according to the competing risks method.

Results: Men with prostate-specific antigen ≤40 ng/mL and those with one to three positive lymph nodes showed higher cancer-specific mortality-free survival estimates as compared with their counterparts with prostate-specific antigen >40 ng/mL and >3 metastatic lymph nodes, respectively (all $P < 0.001$). At multivariable Cox regression analyses, preoperative prostate-specific antigen >40 ng/mL, >3 lymph node metastases and pathological Gleason score 8–10 were all independent predictors of cancer-specific mortality (all *P*-values ≤0.001). On competing risk analysis, when patients were stratified according to the number of positive lymph nodes (namely, ≤3 *vs* >3), the 8-year cancer-specific mortality rates were 27.4% versus 44.8% for patients aged <65 years, and 15.2% versus 52.6% for patients aged ≥65 years, respectively.

Conclusions: Three positive lymph nodes represent the best prognostic cut-off in node-positive prostate cancer patients. In those individuals with >3 positive lymph nodes, the overall mortality rate is completely related to prostate cancer in young patients.

Key words: cancer-specific mortality, competing risk analysis, lymph node metastases, other-cause mortality, radical prostatectomy.

Introduction

In the PSA-era, approximately 10% of patients with clinically localized PCa after RP and PLND have LNM at final pathology.[1–7] Unlike other types of cancer, in the current TNM classification[8] all PCa patients with nodal metastases are classified in a single-risk group,[9] and

are considered as affected by systemic disease.[10] However, recent studies showed that outcomes of surgically-treated patients with positive LNs are not invariably poor;[6,7,11–14] indeed, patients with lower volumes of LNM have higher survival rates than those patients with a higher nodal burden.[7,15] In this contest, contemporary retrospective analyses suggest that RP in PCa patients with LNM might have a survival benefit after controlling for lymph node tumor burden.[16,17] Indeed, despite the evidence supporting the use of adjuvant aADT in patients with LNM,[18] recent evidence suggests that patients treated with aRT plus aADT had more favorable CSM-free rates than patients treated with aADT alone.[19,20] However, the optimal care of those patients is still debated. Indeed, data investigating the competing risk of mortality in node-positive PCa patients treated with adjuvant therapy are still limited. Assessing these aspects would be important to improve postoperative patients' counseling, to help the physician in order to identify patients at high risk of dying as a result of PCa and to plan the optimal postoperative treatment strategy. To address this void, we assessed the long-term CSM and OCM rate in a multi-institutional series of surgically-treated PCa patients with LNM, after stratifying patients according to clinical and pathological characteristics.

Methods

Study population

We reviewed 4815 PCa patients treated with RP and PLND between 1995 and 2014 at 10 tertiary European care centers. In order to evaluate the survival outcomes of node-positive PCa patients, we included 511 individuals (10.6%) with LNM at final pathology in our analysis. Among these 511 patients, 100 (19.6%) with incomplete clinical, pathological and follow-up data, and with <10 LNs retrieved were excluded, resulting in a final population of 411 individuals. All patients were preoperatively staged with CECT or BS or, more recently, with 11C-choline PET/computed tomography scan according to local protocol. Men with clinically localized or locally advanced PCa were referred for surgery. No patient had evidence of distant metastatic disease at preoperative imaging; however, selected cases with clinically suspicious of low-volume nodal involvement at preoperative imaging (2.3%) were included. During the study period, surgical procedures were carried out with a retropubic, laparoscopic or robot-assisted approach according to surgeon preference by expert urologists who completed the learning curve of the specific techniques. Routine PLND at the time of RP in all the 10 centers was carried out in the presence of high-risk PCa and intermediate-risk PCa with an estimated risk for positive lymph nodes >5%; indeed, PLND was carried out in low-risk PCa patients according to the surgeon's attitude. The template of the course of lymph node dissection included the fibrofatty tissue along the external iliac vein, with the distal limit of the deep circumflex vein and the femoral canal; proximally, the dissection was carried out up to and including the bifurcation of the common iliac artery. All fibrofatty tissue within the obturator fossa was removed to completely skeletonize the obturator nerve. The lateral limit consisted of the pelvic sidewall, and the medial dissection limit was defined by perivesical fat.[21] According to the surgeon's attitude, high-risk patients were submitted to extended PLND including bilateral common iliac lymph nodes, in selected cases, up to aortic bifurcation. Within all centers, one experienced genitourinary pathologist reviewed all surgical specimens.

Covariates and follow up

All patients had complete data including preoperative PSA, biopsy Gleason score, pathological stage and Gleason score, margin status, number of nodes removed, and number of positive nodes. All patients received postoperative therapy including aADT alone or aRT in combination with aADT. Regarding postoperative treatments, aADT consisted of hormone deprivation therapy initiated within 90 days from RP. Furthermore, aRT consisted of whole-pelvis irradiation targeted to the prostatic and seminal vesicles bed (66 Gy) and pelvic lymph nodes (54 Gy), including the bilateral obturator, and external, internal and common iliac lymphatic chain, and was started within 90 days of RP,[17] according to local protocol and the treating physician's preference.

Outcomes

The outcomes of the study were CSM, namely death due to PCa and death due to any other cause (OCM). Vital status and cause of death were identified from death certificates or physician correspondence. On death certificates, PCa was considered as the cause of death when it was registered as the first cause, otherwise OCM was considered as the cause of death.

Statistical analysis

Median and interquartile ranges were reported for continuous variables. Frequencies and proportions were reported for categorical variables. The Mann–Whitney *U*-test and χ^2-tests were used to compare the statistical significance of differences in medians and proportions, respectively. Our statistical analyses consisted of several steps. First, Kaplan–Meier analyses were used to assess CSM-free survival rates at 5- and 8-year follow up in the overall population, and after stratifying patients according to clinical and pathological parameters (namely, preoperative PSA, number of positive LNs and adjuvant treatments). The number of positive LNs and preoperative PSA were dichotomized according to the most informative cut-off predicting CSM-free survival. This was obtained applying the χ^2-test for every possible cut-off value and choosing the lowest *P*-value.

Second, uni- and multivariate logistic regression analysis were used to test the association between preoperative patients' characteristics (namely, age, preoperative PSA; clinical stage, biopsy Gleason score and number of LNs retrieved) and the risk of >3 lymph node metastases after RP and PLND. Third, uni- and multivariable competing risks Cox regression models were used to identify predictors of CSM and OCM. Covariates consisted of age at surgery, pathological Gleason score, pathological stage, surgical margins status,

number of LNs metastases and adjuvant therapies. Finally, cumulative incidence plots were generated for CSM and OCM according to the competing risks method, after stratifying patients according to the number of LNs metastases and median age at surgery.[22] All statistical tests were carried out using the R statistical package (R Foundation for Statistical Computing, Vienna, Austria), with a two-sided significance level set at $P < 0.05$. The local institutional ethical committee approved the study (approval code STUD-OF by the S. Orsola-Malpighi Hospital, IRB 11 September 2012).

Results

Overall, 411 node-positive PCa patients composed the final population. Overall, 352 (85.6%) patients underwent open RP, whereas 16 (3.9%) had laparoscopic and 43 (10.5%) had the robotic-assisted approach. Table 1 shows the baseline characteristics of all patients included in the study, stratifying patients according to the number of positive LNs at final pathology. The median number of lymph nodes removed was 15 (IQR 11–20). The median number of positive lymph nodes was two (IQR 1–4): 308 (74.9%) patients showed ≤3 positive LNs, whereas 103 (25.1%) individuals had >3 positive LNs at final pathology. Of all patients, 228 (55.5%) were referred for aRT with aADT, whereas 183 (44.5%) received aADT alone. When patients were stratified according to the number of positive LNs (≤3 positive LNs *vs* >3 positive LNs), significant differences were recorded with regard to the clinical and pathological Gleason score, number of LNs retrieved, positive LNs, lymph node density and surgical technique (all $P \leq 0.04$; Table 1). At multivariable logistic regression, the number of LNs retrieved resulted in the only significant predictor of more extended LNs involvement (namely, >3 positive LNs; Table 2).

The median follow up for RP for survivors was 55 months (IQR 34–86). During this period, there were 74 (18%) cancer-specific deaths. Overall, the CSM-free survival estimates at 5- and 8-year follow up were 84.5% and 71.1%, respectively (Fig. 1). The best cut-off for PSA and LNM was 40 ng/mL and three positive LNs, respectively. After stratifying patients according to preoperative PSA value, men with PSA ≤20 ng/mL and those with PSA between 21 and 40 ng/mL had higher CSM-free survival estimates as compared with those patients with PSA >40 ng/mL (87.5% and 84.8% *vs* 69.5% at 5-year follow up, respectively; 72.6% and 84.8% *vs* 45.8% at 8-year follow up, respectively, $P < 0.001$; Fig. 2). Considering LNM, men with ≤3 positive LNs showed higher CSM-free survival estimates as compared with those individuals with >3 positive LNs (87.1% *vs* 76.4% at 5-year follow up, respectively; 77.1% *vs* 52.1% at 8-year follow up, respectively, $P < 0.001$; Fig. 3). After stratifying patients according to postoperative treatments, men submitted to aRT with aADT tended to show better CSM-free survival estimates as compared with those patients submitted to aADT alone, despite any statistical significance (88.0% *vs* 80.4% and 70.4 *vs* 70.8 at 5- and 8-year follow up, respectively; Fig. 4).

At multivariable Cox regression analyses (Table 3), preoperative PSA >40 ng/mL (HR 1.97), >3 positive LNs (HR 2.16) and pathological Gleason score 8–10 (HR 2.07)

Table 1 Patient characteristics and descriptive statistics

Variable	Overall	≤3 positive LNs	>3 positive LNs	*P*-value
No. patients (%)	411 (100)	308 (74.9)	103 (25.1)	–
Age (years)				
Median	65	65	65	0.8
IQR	60–70	61–70	60–70	
PSA (ng/mL)				
Median	15.5	15.3	16	0.4
IQR	8.2–30	8.1–28.1	8.8–36	
PSA (ng/mL)				
≤20	258 (62.8)	195 (63.3)	63 (61.2)	0.08
21–40	95 (23.1)	76 (24.7)	19 (18.4)	
>40	58 (14.1)	37 (12)	21 (20.4)	
Biopsy Gleason score (%)				
<7	71 (17.4)	57 (18.6)	14 (13.7)	0.01
7	174 (42.5)	136 (44.3)	38 (37.3)	
8–10	164 (40.1)	114 (37.1)	50 (49)	
Clinical stage (%)				
T1a	2 (0.5)	1 (0.3)	1 (1)	0.3
T1b	3 (0.7)	3 (1)	0 (0)	
T1c	40 (9.7)	34 (11)	6 (5.8)	
T2a	101 (24.6)	73 (23.7)	28 (27.2)	
T2b	42 (10.2)	30 (9.7)	12 (11.7)	
T2c	63 (15.3)	45 (14.6)	18 (17.5)	
T3a	82 (20)	60 (19.4)	22 (21.4)	
T3b	47 (11.4)	34 (11)	13 (12.6)	
D'Amico risk group (%)				
Low risk PCa	24 (5.8)	20 (6.5)	4 (3.9)	0.6
Intermediate risk PCa	120 (29.2)	88 (28.6)	32 (31.1)	
High risk PCa	267 (65)	200 (64.9)	67 (65)	
Pathological Gleason score (%)				
≤7	208 (50.6)	164 (53.2)	44 (42.7)	0.04
8–10	203 (49.4)	144 (46.8)	59 (57.3)	
Pathological stage (%)				
pT2	35 (8.5)	28 (9.1)	7 (6.8)	0.5
pT3a	100 (24.3)	79 (25.6)	21 (20.4)	
pT3b	244 (59.4)	179 (25.1)	65 (63.1)	
pT4	32 (7.8)	22 (7.1)	10 (9.7)	
Surgical margins status (%)				
Negative	157 (38.4)	120 (39)	39 (37.9)	0.5
Positive	252 (61.6)	188 (61)	68 (62.1)	
No. LNs removed				
Median	15	14	16	0.003
IQR	11–20	10–19	12–23	
No. positive LNs				
Median	2	1	6	<0.001
IQR	1–4	1–2	5–8	
LN density				
Median	12.5	10	40	<0.001
IQR	7.1–25	6.4–15.3	26.3–54.5	
Years of surgery				
1995–2000	37 (9)	29 (9.4)	8 (7.8)	0.4
2001–2005	88 (21.4)	66 (21.4)	22 (21.4)	
2006–2010	188 (45.7)	126 (47.4)	42 (40.8)	
2011–2014	98 (23.8)	67 (21.8)	32 (30.1)	
Surgical technique				
Open	352 (85.6)	273 (88.6)	79 (76.7)	0.01
Laparoscopic	16 (3.9)	10 (3.2)	6 (5.8)	
Robotic	43 (10.5)	25 (8.1)	18 (17.5)	
Adjuvant treatments				
aADT alone	183 (44.5)	139 (45.1)	44 (42.7)	0.4
aRT with aADT	228 (55.5)	169 (54.9)	59 (57.3)	

Patients were stratified according to the number of positive LNs (namely, men with ≤3 LNs and those with >3 LNs) at final pathology.

Table 2 Uni- and multivariate logistic regression analysis testing the association between preoperative patients' characteristics and the risk of >3 lymph node metastases after RP in node-positive patients

	Univariate		Multivariate	
Variables	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age at surgery (years)	0.99 (0.96–1.03)	0.7	1.00 (0.96–1.03)	0.9
Preoperative PSA	1.00 (0.98–1.01)	0.6	1.00 (0.99–1.01)	0.9
Clinical stage				
T1	Reference		Reference	
T2	2.13 (0.90–5.04)	0.09	2.06 (0.86–4.97)	0.1
T3	2.02 (0.83–4.95)	0.1	1.76 (0.69–4.45)	0.2
Biopsy Gleason score				
<7	Reference		Reference	
7	1.14 (0.57–2.26)	0.7	1.06 (0.52–2.16)	0.9
8–10	1.79 (0.91–3.50)	0.09	1.42 (0.70–2.89)	0.3
No. LNs retrieved	1.04 (1.01–1.06)	0.002	1.04 (1.01–1.07)	0.003

were all independent predictors of CSM (all *P*-values ≤0.01).

To investigate the competing causes of mortality prevalent in node-positive PCa, a competing risks analysis was carried out to estimate the real risk of death from PCa rather than any causes, considering the most informative threshold for LNM and median age at surgery as confounders. When patients were stratified according to LNM (namely, ≤3 *vs* >3), the 8-year CSM rates were 27.4% versus 44.8% for patients aged <65 years at surgery, and 15.2% versus 52.6% for patients aged ≥65 years at surgery, respectively. Furthermore, considering individuals with ≤3 LNM, the 8-year OCM rates were 16.2% and 23.2% for patients aged <65 years and those aged ≥65 years at surgery, respectively. Considering patients with >3 LNM, every cause of mortality was due to PCa in men aged <65 years, whereas the 8-year OCM rate was 2.6% in their older counterparts (Fig. 5).

Discussion

Despite node-positive PCa patients experiencing worse oncological outcomes,[7,11,15,23] previous studies showed that patients with LNM represent a highly heterogeneous category.[7,11–13,15,24] Indeed several long-term data show excellent cancer control outcomes for patients with LNM and with favorable pathological aspects, suggesting the potential overtreatment with indiscriminate use of postoperative hormonal therapies.[25,26] However, the best treatment modality, as well as the correct timing, remains unclear.

To address these issues, we collected one of the largest cohorts of node-positive PCa patients submitted to RP and PLND at multi-institutional European centers, and we carried out a competing risk analysis to test the predictive value of clinical and pathological variables on the risk of dying from PCa rather than other causes. Such predictive tools could be useful for many reasons: (i) to offer a prognostic stratification of node-positive patients after surgery for proper counseling and follow-up planning; (ii) to investigate the real risk of dying from PCa, according to age and the tumor's characteristics; and (iii) to propose selection criteria for future prospective randomized trials exploring the role of emerging treatments in PCa patients with LNI.

Several findings of the present study were remarkable. First, our analyses confirmed that node-positive PCa patients

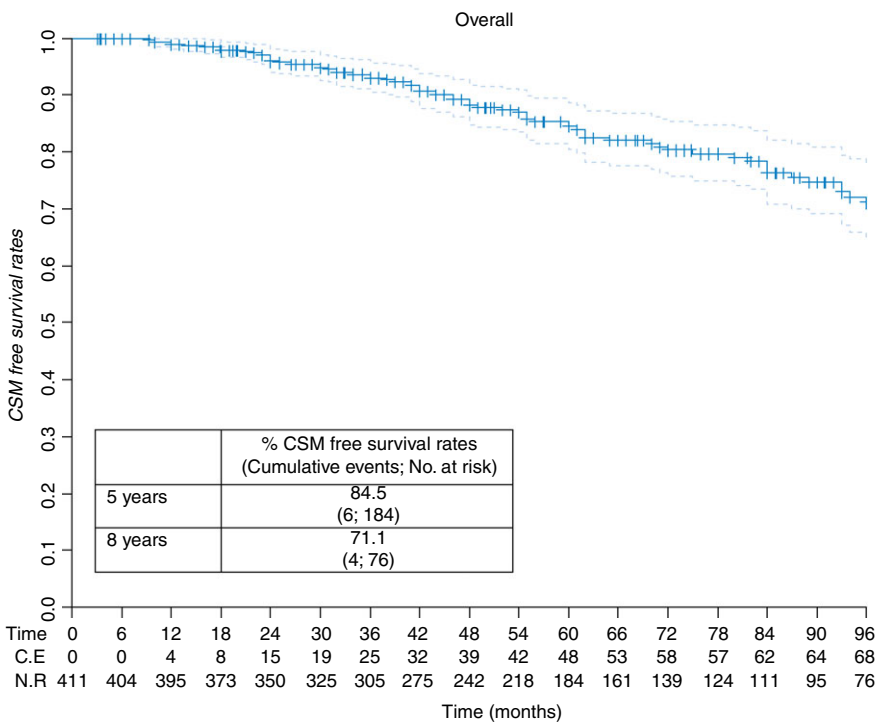

Fig. 1 Kaplan–Meier curve showing CSM-free survival rates in the overall patient population (n = 411).

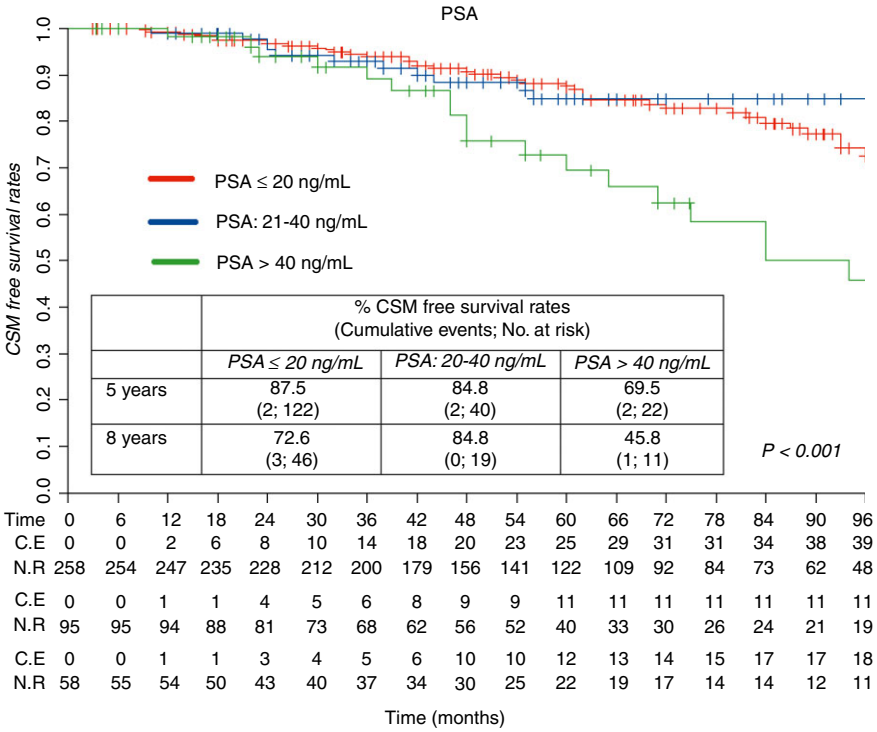

Fig. 2 Kaplan–Meier curve showing CSM-free survival rates in the overall patient population (n = 411) after stratifying according to preoperative PSA levels, (namely, PSA ≤20 ng/mL *vs* PSA = 21–40 ng/mL *vs* PSA >40 ng/mL; P < 0.001).

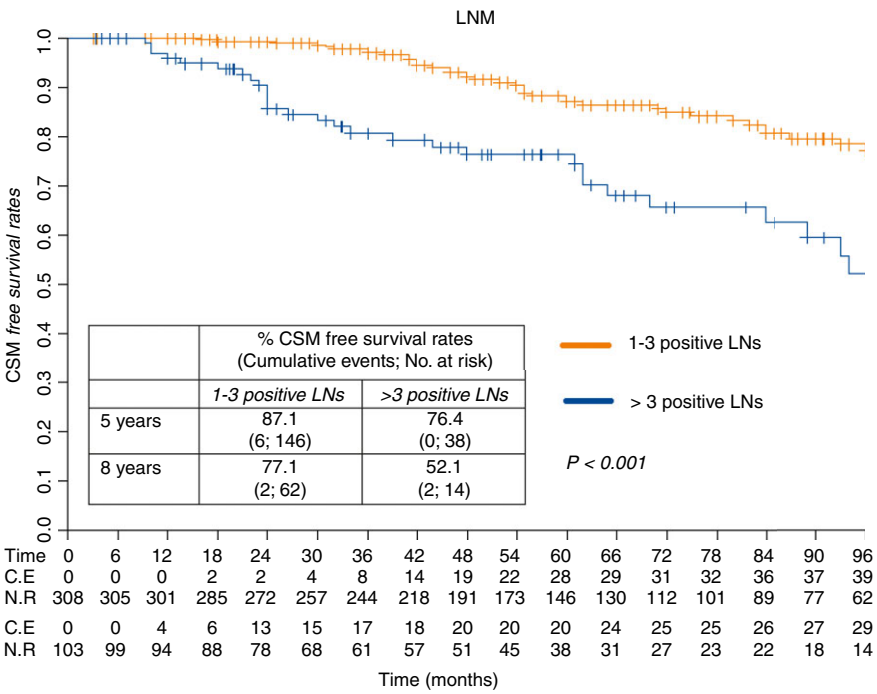

Fig. 3 Kaplan–Meier curve showing CSM-free survival rates in the overall patient population (n = 411) after stratifying according to LNM, (namely, LNM = 1–3 *vs* LNM >3; P < 0.001).

after surgery showed favorable oncological outcomes, despite LNM, as others authors previously reported.[11,13,17] In this contest, the 5- and 8-year CSM-free survival rates in the overall population were 84.5% and 71.1%, respectively.

Second, even if in our population aRT was not an independent predictor of better survival (P > 0.05), on multivariable Cox analysis, those individuals treated with aRT with aADT experienced slightly better CSM-free survival rates than those referred for aADT alone (88% *vs* 80.4% at 5-year follow up, respectively). Recent literature suggests a beneficial impact of aRT on CSM-free survival, and aRT could help reaching an optimal local control improving cancer survival.[19,20] A possible explanation of the present result could be found in the relatively short follow-up period, and different timing, protocols and indications of radiotherapy between single centers through such a large timespan. It results in a potential

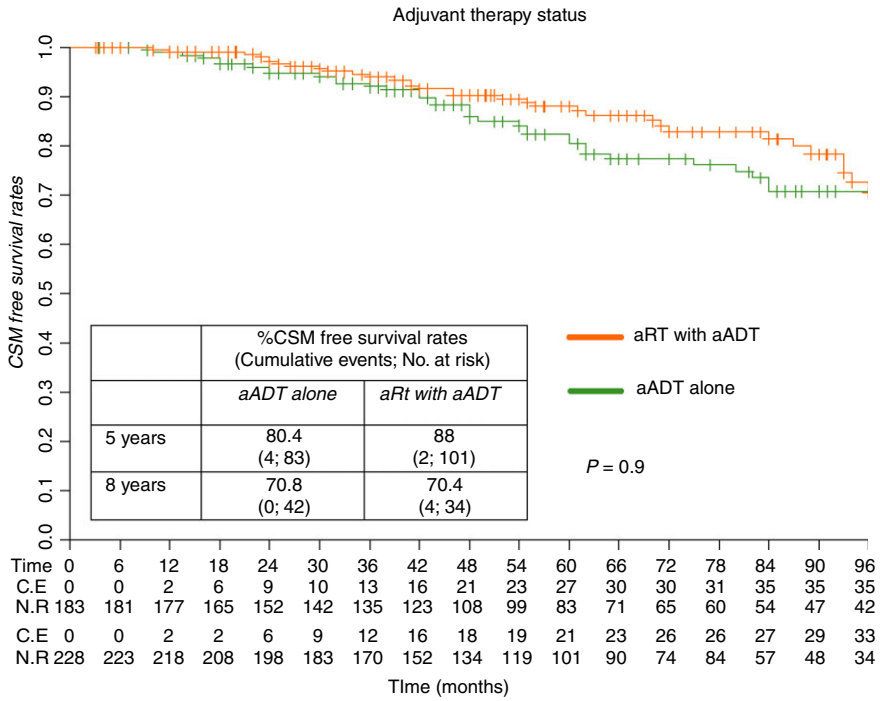

Fig. 4 Kaplan–Meier curve showing CSM-free survival rates in overall patient population (n = 411) after stratifying according to postoperative adjuvant treatments (namely, aRT with aADT *vs* aADT alone; P = 0.6).

Table 3 Univariable and multivariable competing risks regression models predicting CSM and OCM in the overall population (n = 411)

	CSM				OCM			
	Univariable analyses		Multivariable analyses		Univariable analyses		Multivariable analyses	
Variables	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age at surgery (years)	0.99 (0.95–1.03)	0.5	0.99 (0.96–1.03)	0.8	0.99 (0.92–1.06)	0.8	0.97 (0.91–1.04)	0.4
Preoperative PSA (ng/mL)								
≤20	Reference		Reference		Reference		Reference	
21–40	0.79 (0.41–1.51)	0.5	0.75 (0.38–1.49)	0.4	1.20 (0.38–3.78)	0.8	1.07 (0.32–3.53)	0.9
>40	2.29 (1.35–3.88)	0.002	1.97 (1.16–3.35)	0.01	1.22 (0.35–4.28)	0.8	1.3 (0.37–4.59)	0.7
Pathological stage								
pT2–pT3a	Reference		Reference		Reference		Reference	
pT3b–pT4	2.14 (1.20–3.80)	0.01	1.69 (0.91–3.15)	0.1	0.79 (0.30–2.10)	0.6	0.7 (0.25–1.97)	0.5
Pathological Gleason score								
pGs ≤7	Reference		Reference		Reference		Reference	
pGs 8–10	2.5 (1.55–4.04)	0.0002	2.07 (1.24–3.47)	0.007	1.18 (0.46–3.02)	0.7	1.44 (0.51–4.08)	0.5
Surgical margins status								
Negative	Reference		Reference		Reference		Reference	
Positive	1.29 (0.79–2.10)	0.3	1.13 (0.70–1.85)	0.6	1.36 (0.51–3.64)	0.5	1.74 (0.61–4.99)	0.3
LNI								
1–3 positive nodes	Reference		Reference		Reference		Reference	
>3 positive nodes	2.6 (1.63–4.16)	<0.001	2.16 (1.32–3.52)	0.002	0.63 (0.18–2.16)	0.5	0.6 (0.16–4.08)	0.4
Adjuvant treatment								
aADT alone	Reference		Reference		Reference		Reference	
aRT with aADT	0.92 (0.57–1.47)	0.7	0.78 (0.46–1.30)	0.3	0.42 (0.15–0.11)	0.1	0.34 (0.11–1.04)	0.06

underestimated beneficial impact of radiation therapy on cancer control in our population. Third, the present findings confirmed that the main clinical-pathological tumor characteristics were independent predictors of CSM at multivariable competing risk Cox regression analysis. For example, individuals with preoperative PSA >40 ng/mL had a 1.97-fold higher risk of dying from PCa as compared with those with a preoperative PSA level of ≤20 ng/mL. Similarly, men with a pathological Gleason score ≥8 had a 2.07-fold risk of experiencing unfavorable oncological outcomes as compared with those patients with a pathological Gleason score of ≤7. Our findings corroborate the results of previous reports and stress the necessity to stratify node-positive PCa, maybe thanks to a revision of the current TNM classification.

More importantly, in contrast to previous reports that proposed two positive LNs as a better prognostic cut-off, the

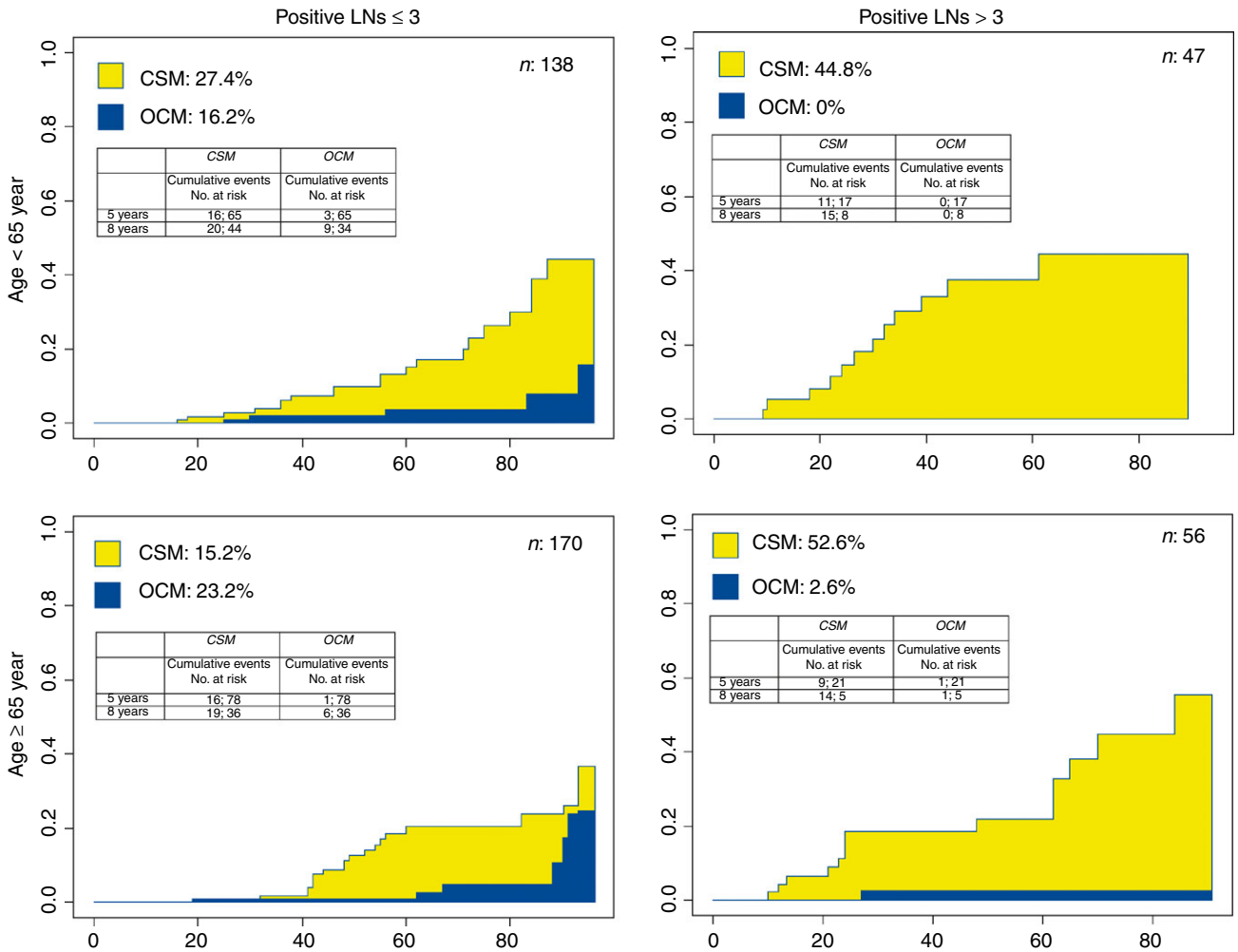

Fig. 5 Competing risks models showing 8-years CSM and OCM rates in 411 node-positive PCa patients referred for RP and PLND, and adjuvant treatments. Patients were stratified according to the number of positive LNs (namely, ≤3 *vs* >3) and age at surgery (namely, <65 years *vs* ≥65 years). White area, alive; blue area, OCM; yellow area, CSM.

best cut-off of positive LNs in predicting CSM in our population was three LNs.[6,27] Observing the multivariable competing risk Cox regression, patients with >3 LNs involved by PCa had a 2.16-fold risk of dying from PCa as compared with those with ≤3 positive LNs. Accordingly, the Kaplan–Maier curve showed that PCa patients with >3 positive LNs experienced statistically significant lower CSM-free survival rates, as compared with those individuals with ≤3 positive nodes. Thus, our data confirmed that not all node-positive PCa must be considered to be affected by systemic disease, and that even those with >1 (but <4) positive lymph node could experience good cancer control. As a consequence, RP and PLND with appropriate postoperative multimodal treatment could guarantee optimal oncological outcomes at long-term follow up in those individuals with less aggressive pathological characteristics.

Fourth, among our node-positive PCa patients at final pathological examination, the number of LNs retrieved was found to be the only predictor of more extended LNs involvement (namely, >3 positive LNs), whereas the other preoperative characteristics (PSA, clinical stage and Gleason score) did not (Table 2). As a consequence, in the PCa population with a higher risk of LNs metastases, a more extended PLND resulted in a proper selection of individuals with both higher and lower nodal burdens, which would experience different survival outcomes.

Finally, we plotted CSM and OCM rates using a competing risks methodology, stratifying patients according to the most informative threshold for LNI and median age at surgery as confounders. In patients with ≤3 positive LNs, we found that the proportion of individuals dying from PCa was higher than the proportion of those dying from all other causes, regardless of the age at surgery (Fig. 5). Conversely, in patients with >3 positive LNs, the overall mortality rate was completely related to PCa in men aged <65 years at surgery, whereas not in those aged ≥65 years at surgery. Interestingly, we observed that death from PCa was a competing cause of mortality in PCa patients with ≤3 positive LNs, regardless of age at surgery, and in older men with >3 LNs. The main implications of these findings consist of proper patient selection in order to identify which men are more likely to die from PCa rather than other causes. Younger

individuals, in particular those with a higher number of LNs involvement, are at higher risk of succumbing to PCa, and should be scheduled for more aggressive postoperative follow up in order to guarantee an earlier detection of recurrence and optimal salvage treatments options to reach cancer control. Indeed, despite older patients having a not negligible risk of dying from other causes, a considerable proportion of them could experience high PCa-related death; as a consequence, age should not be taken into account to spare an intensive follow-up schedule and aggressive treatments in order to obtain better oncological control of disease.

Despite several strengths, the present study was not devoid of limitations. First, our analyses were limited by their retrospective nature. For example, the exact timing of administration of postoperative therapies was left to the clinical decision of each treating physician. Second, the study covered a long period of time. Diagnostic, grading and therapeutic changes occurring over the past years might have influenced our analysis. Furthermore, although the extent of the nodal dissection was well standardized in all the treating centers, variability in surgeons' and pathologists' attitudes, as well as interindividual variability might have influenced the accuracy of nodal staging; furthermore, the dissection templates could have varied among years in each center, according to international guidelines modifications. Third, the inclusion of patients coming from different referral centers could have affected the results of our analyses, mainly due to possible different surgical approaches and treatment behaviors between single centres. Finally, a potential limitation of the study was the lack of comorbidity data, which are required to accurately predict OCM. Despite these limitations, our competing risk analyses represent a reliable tool aimed at predicting the long-term CSM rate after accounting for OCM rate, in a large multi-institutional cohort of node-positive PCa, and it could be useful to counsel patients correctly and to plan proper postoperative follow up in order to guarantee an earlier detection of recurrence and optimal salvage treatments options to reach cancer control. Currently, all node-positive PCa are classified in a single-risk group and are considered as affected by systemic disease. However, these patients might have optimal cancer control, especially when they show an organ-confined and well-differentiated disease with low PSA and a low number of positive LNs.

In the present study population, three positive LNs represent the best prognostic cut-off: in patients with ≤ 3 positive LNs, PCa is a competing cause of mortality, regardless of age at surgery; in those individuals with >3 positive LNs, the overall mortality rate is completely related to PCa in young patients, whereas PCa remains a competing cause of mortality in older patients. Indeed, despite older patients in the node-positive PCa population having a not negligible risk of dying from other causes, a considerable proportion of them could experience PCa-related death. However, although RP and PLND are not devoid of several side-effects, such aggressive treatment options are curative in more than half of node-positive PCa patients, regardless of age and nodal metastases volume. As a consequence, our risk stratification of node-positive PCa patients would help physicians to identify patients with higher risk of dying from PCa, suggesting that age should not be taken into account to spare more extensive, multimodal treatment modalities in order to obtain optimal cancer control.

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Conflict of interest

None declared.

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