Cancer Epidemiology 59 (2019) 135–142

Contents lists available at ScienceDirect

Cancer Epidemiology

journal homepage: www.elsevier.com/locate/canep

Contemporary trends of pelvic lymph node dissection at radical cystectomy for urothelial carcinoma of urinary bladder and associated cancer specific mortality and complications: comparison between octogenarian versus younger patients

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ARTICLE INFO

Keywords:
Urinary bladder neoplasms
Cystectomy
Lymph node excision
Adverse effects
Mortality
Octogenarians

ABSTRACT

Background: We analysed contemporary pelvic lymph node dissection (PLND) trend during radical cystectomy (RC) for urothelial carcinoma of urinary bladder (UCUB), as well as PLND association with cancer specific mortality (CSM) and complications after stratification according to octogenarian vs. younger age.

Materials and methods: Within the SEER and NIS databases, respectively 10,427 (T2 and T3 stages) and 19,203 (all T-stages) RC patients (2004–2015) for UCUB were identified. Univariable and multivariable analyses focused on PLND rates, CSM after inverse probability of treatment weighting (IPTW) adjustment, complication rates, length of stay (LOS) and total hospital charge (THC).

Results: Within the SEER database, RC and PLND was performed in 9,406 patients (87.4%), 981 (10.4%) octogenarians and 8,227 younger patients (at, respectively, 83 and 89% PLND). PLND rates increased over time in both patients groups ($p < 0.05$). PLND was independently associated with lower CSM in both age groups (octogenarians: hazard ratio [HR] 0.51, $p < 0.001$; younger patients: HR 0.56, $p < 0.001$). Within the NIS database, PLND was marginally higher associated with overall complications in octogenarians than in younger patients (odd ratio [OR]: 1.32 vs. 1.23, both $p < 0.001$), with longer LOS (OR: 1.20 vs. 1.08, both $p < 0.001$), higher THC (relative increase: 6933 vs. 4484, both $p < 0.001$), but not with higher in-hospital mortality.

Conclusions: PLND is associated with lower CSM, but its rate lags in octogenarian vs. younger patients. In both age groups, PLND leads to marginally higher complications, longer LOS and higher THC, but not to higher in-hospital mortality.

Abbreviation: CSM, Cancer specific mortality; EAPC, Estimating annual percentage changes; HR, Hazard ratio; ICD-O, International Classification of Disease for Oncology; IPTW, Inverse probability of treatment weighting; LOS, Length of stay; NIS, National Inpatient Sample database; OR, Odd ratio; PLND, Pelvic lymph node dissection; RC, Radical cystectomy; SEER, Surveillance, Epidemiology, and End Results; THC, Total hospital charge; UCUB, Urothelial carcinoma of urinary bladder

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https://doi.org/10.1016/j.canep.2019.02.002
Received 26 November 2018; Received in revised form 31 January 2019; Accepted 3 February 2019
Available online 13 February 2019
1877-7821/

1. Introduction

The National Comprehensive Cancer Network (NCCN) and the European Association of Urology (EAU) guidelines recommend PLND in all patients treated with radical cystectomy (RC) for urothelial carcinoma of urinary bladder (UCUB) with curative intent [1,2]. Unfortunately, guidelines adherence to this recommendation is yet not perfect [3–9]. However, previous reports documented increasing trends of PLND at RC over time [3,7,4–9].

Despite data that suggested a survival benefit related to PLND at RC vs. RC alone, the adherence to PLND guidelines recommendation was particularly poor in octogenarian patients, where as many as 31% did not benefit of PLND at RC [10]. This proportion sharply contrasts with the most contemporary adherence rates (81.9%), that were based on all RC patients across all ages [9].

Based on these observations, our objective was to examine the most contemporary PLND rates within the Surveillance, Epidemiology and End Results (SEER) database, and to stratify the results according to octogenarian vs. younger patients. Additionally, we postulated that the non-adherence rates in octogenarians have improved overtime. Moreover, we hypothesised that PLND is still associated with improved cancer specific mortality (CSM) in both octogenarian and younger patients. We tested the effect of PLND in both patients' groups on CSM, after detailed adjustment using the Inverse Probability of Treatment Weighting (IPTW).

Finally, we postulated that contemporary PLND in octogenarian patients is not associated with a significantly higher rate of complications, in-hospital mortality, longer length of stay (LOS) and total hospital charges (THC) than in younger patients. To test this hypothesis, we relied on the National Inpatient Sample (NIS) database.

2. Materials and methods

2.1. Data sources

The SEER database covers approximately 27.8% of the United States population and is considered representative of that population regarding demographics, cancer incidence and mortality [11]. The SEER database was used to examine all the cancer related endpoints, namely PLND, and CSM rates.

The NIS database is composed of longitudinal hospital inpatient databases that form the Healthcare Cost and Utilization Project family. The combined database includes 20% of the United States inpatient hospitalizations with discharge abstracts from 8 million hospital stays. It incorporates patient and hospital information, including Medicare, Medicaid, private insurance, and other insurance types [12]. All analyses focusing on complication rates, LOS, THC and in-hospital mortality relied on the NIS database.

2.2. Study Population and definition of variables for analyses

Within the SEER databases (2004–2015), we identified 10,427 patients treated with RC with or without PLND for pT2-T3 stage non-metastatic UCUB (International Classification of Disease for Oncology [ICD-O-3] site code C67.0 to C67.9). Exclusions consisted of unknown PLND status, since the PLND status represented the predictor variable of interest. The outcomes examined consisted of PLND rates and CSM rates. Covariates consisted of T-stage (T2, T3), tumour grade (low, high or unknown), year of surgery, age at surgery (younger vs. older than 80 years), gender (male vs. female), race (Caucasian, African-American or other), marital status (married, never married, previously married and unknown) and socioeconomic status (SES, low or high).

Within the NIS databases (2004–2015), 19,203 patients treated with RC with or without PLND for non-metastatic UCUB were identified. PLND represented the risk variable of interest. The outcomes examined consisted of complication rates, in-hospital mortality, length of stay (LOS) and THC. Within complications, we examined overall complications and eight specific complications' subgroups: medical miscellaneous, surgical miscellaneous, genitourinary, vascular, cardiac, pulmonary, infectious and wound [13].

2.3. Statistical analyses

Within the SEER database, we first evaluated the overall PLND rates at RC. Subsequently, estimated annual percentage changes (EAPC) tested for statistically significant annual PLND rate differences. Univariable and multivariable logistic regression models focused on predictors of PLND rates. In all three steps, analyses were stratified according to octogenarian vs. younger patients.

Subsequently, we focused on CSM. Here, IPTW was used to minimize potential differences that might exist in patients' characteristics, according PLND status [14]. First, IPTW adjusted Kaplan-Meier plots graphically depicted the relationship between PLND status and CSM in octogenarian vs. younger patients, according to T-stage subgroups: T2 vs. T3. Second, univariable and multivariable Cox regression models tested the effect of PLND status on CSM, according to stratification between octogenarian vs. younger patients. Third, all models were separately refitted in both age groups according to T-stage subgroups: T2 vs. T3. In order to adjust for other-cause mortality, competing risks regression models were used to test the effect of PLND status on CSM after adjustment for other-cause mortality, as well as after propensity score matching (ratio 1:1) that relied on the following variables: T-stage, tumour grade, race, year of surgery, and marital status. Competing risks regression models were fitted after stratification according to octogenarian vs. younger patients. Competing risks regression models were subsequently refitted in both age groups after further stratification between T2 vs. T3 stage. In all multivariable regression models (logistic, Cox and competing risks), covariates consisted of year of diagnosis (continuously coded), race, marital status, T-stage, N-stage and grade. Lastly, in separate subgroups of octogenarian vs. younger PLND patients, two separate multivariable Cox regression models respectively tested for the effect of number of removed nodes (continuously coded) on CSM.

Within the NIS database, we tested the effect of PLND on complication rates, LOS, THC and in-hospital mortality, after stratification between octogenarian vs. younger patients. Specifically, separate multivariable logistic regression models adjusted for clustering focused on the following endpoints: 1) in-hospital mortality, 2) LOS, 3) THC, 4) overall complications and eight additional specific complications 5–13) (medical miscellaneous, surgical miscellaneous, genitourinary, vascular, cardiac, pulmonary, infectious and wound). All multivariable analyses predicting THC were adjusted for overall complications and LOS.

All statistical tests were two-sided with a level of significance set at $p < 0.05$. Analyses were performed using the R software environment for statistical computing and graphics (version3.4.1; http://www.r-project.org/). The retrospective and anonymously coded study design was approved by the Institutional Review Board of the Centre Hospitalier de l'Université de Montreal.

3. Results

Within the SEER database, RC and PLND was performed in 9,406 patients (87.4%), 981 (10.4%) octogenarians and 8,227 younger patients (at, respectively, 83 and 89% PLND rate) (Table 1). In octogenarians, PLND was more frequently performed in T3 stage ($p < 0.001$). However, no significant differences were identified in PLND rates according to tumour-grade, year of diagnosis, gender, SES, race or marital status. Conversely, in younger patients PLND was more frequently performed in T2 stage ($p < 0.001$), in patients with high-grade tumour ($p = 0.02$), in race other than Caucasian or African-American ($p = 0.01$), in the lowest SES ($p < 0.01$) and in most contemporary study years ($p < 0.001$).

Table 1
Descriptive characteristics of 10,427 patients with non-metastatic T2-T3 stage urothelial carcinoma of urinary bladder treated with radical cystectomy, with or without pelvic lymph node dissection (PLND). Patients were stratified according to age: octogenarian vs. younger patients.

		Patients younger than 80 years				**Octogenarian patients**			
		Overall cohort (n 9,248) ‡	**Patients not treated with PLND (n 1,021; 11%)** ‡	**Patients treated with PLND (n 8,227; 89%)** ‡	**Statistical significance of group differences expressed according to t-test or Chi-square test (p value)**	**Overall cohort (n 1,179)** ‡	**Patients not treated with PLND (n 198; 17%)** ‡	**Patients treated with PLND (n 981; 83%)** ‡	**Statistical significance of group differences expressed according to t-test or Chi-square test (p value)**
Year intervals of surgery	2004-2009	4,333 (46.9)	550 (53.9)	3,783 (46)	< **0.001**	549 (46.6)	101 (51)	448 (45.7)	0.2
	2010-2015	4,915 (53.1)	471 (46.1)	4,444 (54)		630 (53.4)	97 (49)	533 (54.3)	
T-stage	T2	5,339 (57.7)	774 (75.8)	4,565 (55.5)	< **0.001**	562 (47.7)	129 (65.2)	433 (44.1)	< **0.001**
	T3	3,909 (42.3)	247 (24.2)	3,662 (44.5)		617 (52.3)	69 (34.8)	548 (55.9)	
Tumour grade	Low grade	249 (2.7)	32 (3.1)	217 (2.6)	**0.02**	33 (2.8)	4 (2)	29 (3)	0.4
	High grade	8,588 (92.9)	927 (90.8)	7,661 (93.1)		1102 (93.5)	184 (92.9)	918 (93.6)	
	Unknown	411 (4.4)	62 (6.1)	349 (4.2)		44 (3.7)	10 (5.1)	34 (3.5)	
Race	Caucasian	8,289 (89.6)	922 (90.3)	7,367 (89.5)	**0.01**	1079 (91.5)	188 (94.9)	891 (90.8)	0.1
	African-American	537 (5.8)	69 (6.8)	468 (5.7)		44 (3.7)	7 (3.5)	37 (3.8)	
	Other	422 (4.6)	30 (2.9)	392 (4.8)		56 (4.7)	3 (1.5)	53 (5.4)	
Socio-economic status Low vs. High	1st quartile	2,359 (25.5)	226 (22.1)	2,133 (25.9)	< **0.01**	814 (69)	137 (69.2)	677 (69)	1.0
	2nd to 4th	6,888 (74.5)	795 (77.9)	6,093 (74.1)		365 (31)	61 (30.8)	304 (31)	
Marital status	Married	5,969 (64.5)	665 (65.1)	5,304 (64.5)	0.6	689 (58.4)	109 (55.1)	580 (59.1)	0.7
	Never Married	1,057 (11.4)	104 (10.2)	953 (11.6)		54 (4.6)	9 (4.5)	45 (4.6)	
	Previously Married	1,878 (20.3)	213 (20.9)	1,665 (20.2)		403 (34.2)	75 (37.9)	328 (33.4)	
	Unknown	344 (3.7)	39 (3.8)	305 (3.7)		33 (2.8)	5 (2.5)	28 (2.9)	
Gender	Male	7,051 (76.2)	777 (76.1)	6,274 (76.3)	0.9	248 (21)	33 (16.7)	215 (21.9)	0.1
	Female	2,197 (23.8)	244 (23.9)	1,953 (23.7)		931 (79)	165 (83.3)	766 (78.1)	

Analyses focused on cancer control outcomes and relied on the Surveillance, Epidemiology, and End Results (SEER) database (2004–2015).
Abbreviation: pelvic lymph node dissection (PLND).
‡ Column percentage.

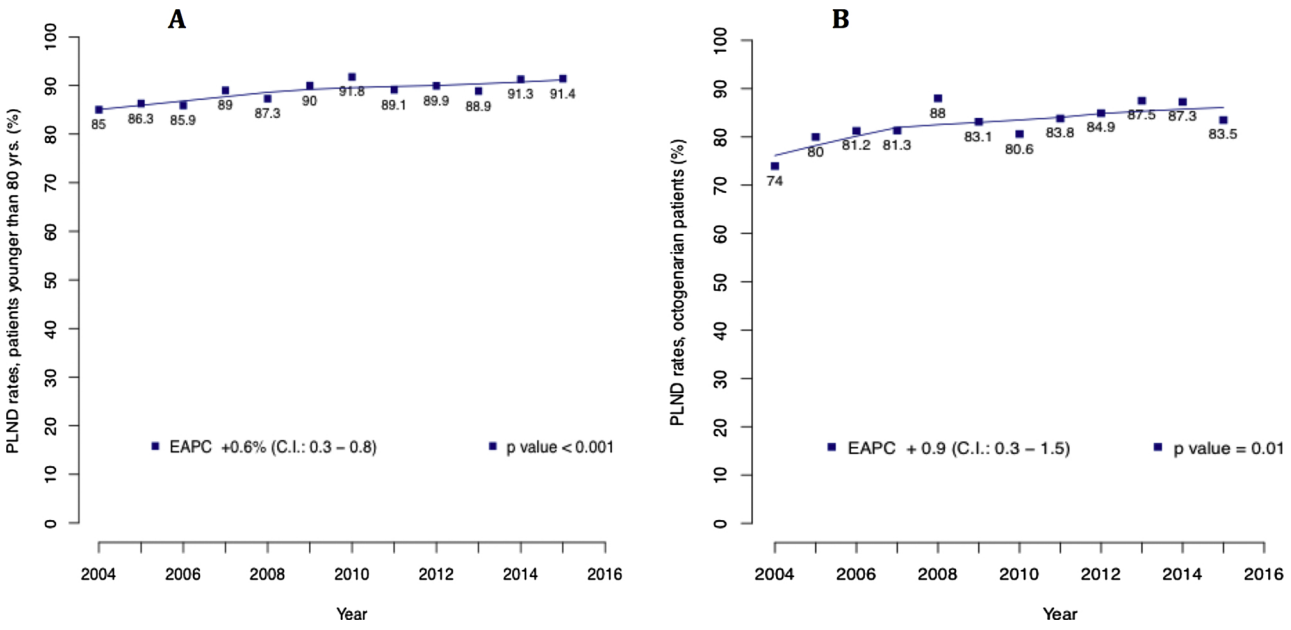

Fig. 1. Annual trends (2004–2015) of pelvic lymph node dissection (PLND) at radical cystectomy in patients with non-metastatic T2-T3 stage urothelial carcinoma of urinary bladder, within the Surveillance, Epidemiology, and End Results (SEER) database. Each square represents the annual rate of PLND. Panel A) represents annual rates and the estimated annual proportion change (EAPC) in patients younger then 80 years. Panel B) represents annual rates and the estimated annual proportion change (EAPC) in octogenarian patients.

In octogenarians, a statistically significant increase from 74 to 83.5% in annual PLND rates was recorded over the study span (EAPC: +0.9%; p = 0. 01) (Fig. 1). In younger patients, higher annual PLND rates were recorded and these rates increased from 85 to 92%, in a statistically significant fashion over the study span (EAPC: +0.6%; p < 0.001).

In multivariable logistic regression analyses focusing on octogenarians, stage T3 (odd ratio [OR]: 2.41, p < 0.001), year of surgery (OR 1.05; p = 0.02) and other racial origin than Caucasian or African-American (OR: 3.72, p = 0.03) were independent predictors of higher PLND rates. The same independent predictors of higher PLND rate, stage T3 (OR: 2.53, p < 0.001), year of surgery (OR 1.06; p < 0.001) and race other than Caucasian or Afro-American (OR: 1.65, p < 0.001) were also identified in younger patients. Conversely, higher SES quartiles predicted lower PLND rate (OR: 0.81, p < 0.01) (Supplementary Table 1).

In IPTW adjusted Kaplan-Meier analyses focusing on octogenarian patients, five-year CSM rates were respectively 22.3 vs. 39.6% (log-rank p = 0.01), when PLND was or was not performed for T2 patients, and 47.2 vs. 55.7% (log-rank p = 0.02) for T3 patients (Fig. 2). In IPTW adjusted Kaplan-Meier analyses focusing on younger patients, five-year CSM rates were respectively 20.9 vs. 29.6% (log-rank p < 0.001), when PLND was or was not performed in T2 patients and 45.9 vs. 55.5% (log-rank p = 0.02) in T3 patients (Fig. 2).

In multivariable IPTW adjusted Cox regression models focusing on octogenarians (Table 2), PLND represented an independent predictor of lower CSM (hazard ratio [HR] 0.51, p < 0.001). When multivariable IPTW adjusted Cox regression models focusing on octogenarians were refitted after stratification according to T2 (HR 0.50; p < 0.001) vs. T3 (HR 0.44; p < 0.001) stage, PLND also represented an independent predictor of lower CSM in both T-stages. In multivariable IPTW adjusted Cox regression models focusing on younger patients (Table 2), PLND represented an independent predictor of lower CSM (HR 0.56, p < 0.001). When multivariable IPTW adjusted Cox regression models focusing on younger patients were refitted after stratification according to T2 (HR 0.58; p < 0.001) vs. T3 (HR 0.51; p < 0.001) stage, PLND also represented an independent predictor of lower CSM in both T-stages. Moreover, it is noteworthy that the number of removed nodes was identified as an independent predictor of lower CSM (HR: 0.99; p = 0.01) in patients younger than 80 years. However, the number of removed nodes was not an independent predictor of lower CSM (HR 0.99; p = 0.4) in octogenarians.

When competing risks regression models were used to test the effect of PLND on CSM after adjustment for other-cause mortality, as well as after propensity score matching, virtually the same results were recorded as in IPTW-adjusted Cox regression models. The only exception consisted of non-significant findings in T3 stage patients older than 80 years (HR 0.62; p = 0.9), instead of statistically significant findings in IPTW-adjusted Cox regression models (HR 0.44; p < 0.001).

When multivariable Cox regression models tested the effect of number of removed nodes on CSM in respectively the subgroups of younger, as well as octogenarian PLND patients, independent predictor status was confirmed in younger (HR: 0.99; p < 0.001), but not in octogenarian (HR: 0.99; p = 0.2) patients.

Within the NIS database, PLND was significantly (all p values < 0.05) associated with higher absolute rate of overall complications (+6.4%), medical miscellaneous (+11.6%), infectious (+4.0%), pulmonary (+3.4%), wound (+2.7%), and vascular complications (+1.7%) in octogenarian patients. Additionally, PLND in octogenarians was associated with significantly longer hospital stay (LOS: 9 vs. 7 days; p < 0.001) and with higher median THCs (28136 vs. 20418 $; p < 0.001). Lastly, PLND was not associated with higher rate of in-hospital mortality, surgical miscellaneous, cardiac and genitourinary complications (Table 3). In younger patients, PLND was also significantly (all p values < 0.05) associated with higher absolute rate of overall complications (+4.6%), medical miscellaneous (+4.6%) and vascular complications (+0.7%). Additionally, PLND was significantly associated with longer hospital stay (LOS: 8 vs. 7 days; p < 0.001) and with higher median THCs (26,735 vs. 20,948 $; p < 0.001). Conversely, PLND was associated with lower absolute rate of surgical miscellaneous (-1.9%), cardiac complications (-1.0%) and lower in-hospital mortality (-0.5%) (all p values < 0.05). Lastly, PLND was not associated with wound, pulmonary, infectious and genitourinary complications (Table 3).

In multivariable logistic regression models that focused on overall complications, specific complications, LOS and in-hospital mortality in

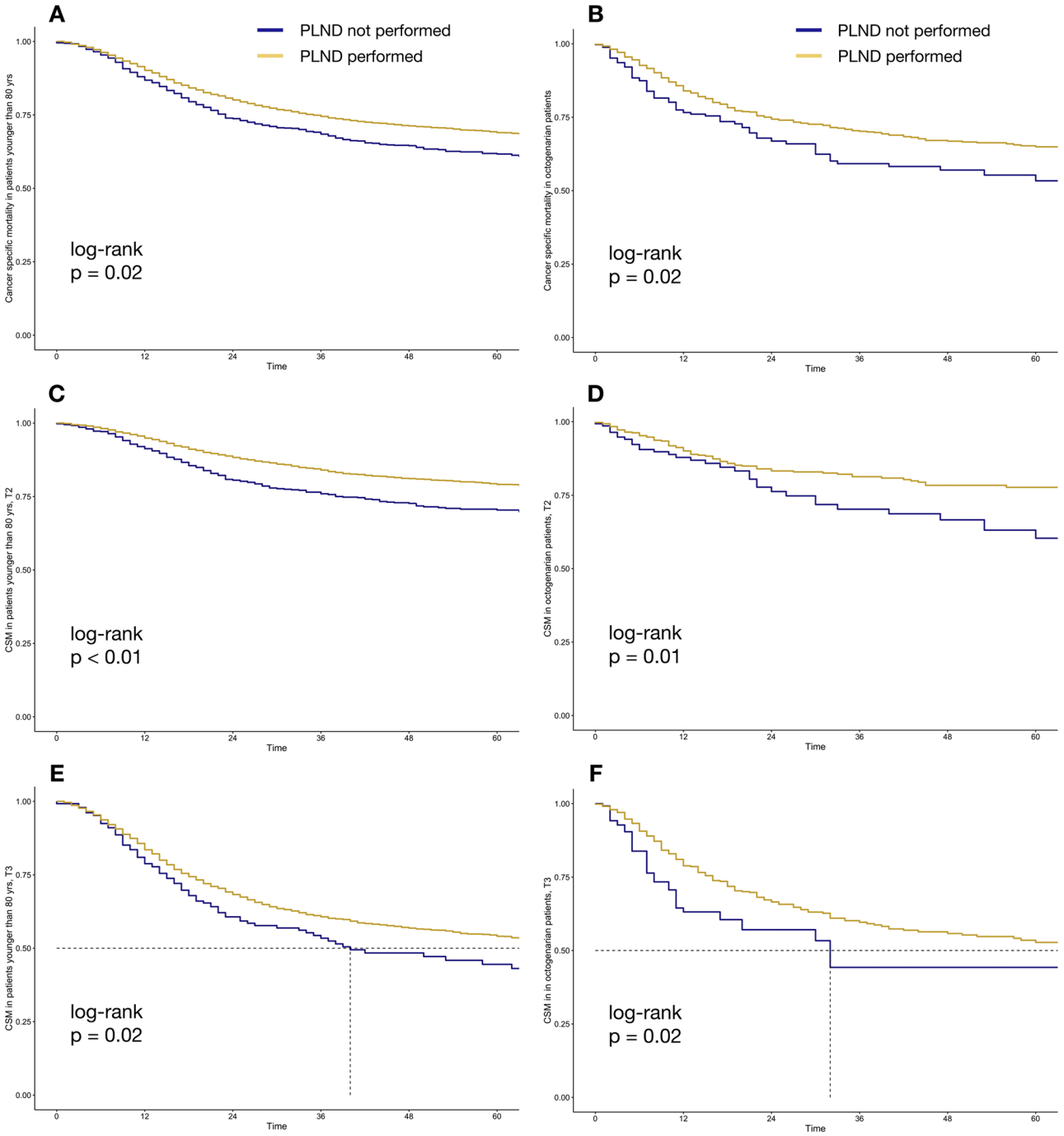

Fig. 2. Kaplan-Meier plots illustrating cancer specific mortality (CSM) according to performance (yellow) or not (blue) of pelvic lymph node dissection (PLND). The analyses relied on the Surveillance, Epidemiology, and End Results (SEER) database (2004–2015). Panel A) represents the CSM in the entire cohort of patients younger than 80 years. Panel B) represents the CSM in the entire cohort of octogenarian patients. Panel C) represents the CSM in stage T2 younger than 80 years patients. Panel D) represents the CSM in stage T2 octogenarian patients. Panel E) represents the CSM in stage T3 younger than 80 years patients. Panel F) represents the CSM in stage T3 octogenarian patients (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

octogenarians, PLND was an independent predictor of overall (OR 1.32), medical miscellaneous (OR 1.60), vascular (OR 1.52), wound (OR 1.51), pulmonary (OR 1.41), infectious complications (OR 1.75) (all $p < 0.05$), longer LOS (OR 1.20, $p < 0.001$) and higher THCs (relative increase 6933 $, $p < 0.001$), but not with higher in-hospital mortality (Table 4). In multivariable logistic regression models that focused on overall complications, specific complications, LOS and in-hospital mortality in younger patients, PLND was an independent predictor of overall (OR 1.23), vascular (OR 1.30) and medical miscellaneous complications (OR 1.28) (all $p < 0.05$), longer LOS (relative risk 1.08, $p < 0.001$) and higher THCs (relative increase 4,484, $p < 0.001$), but not with higher in-hospital mortality rate (Table 4). Conversely, PLND was associated with lower surgical miscellaneous complication rates (OR 0.79; $p < 0.001$).

4. Discussion

Although, United States and European guidelines recommend PLND in all UCUB patients who undergo a RC [1,2], previous reports examining PLND rates at RC failed to identify perfect guidelines

Table 2
Univariable and multivariable Cox regression models predicting cancer specific mortality (CSM) according to pelvic lymph node dissection (PLND) status (performed vs. not performed) at radical cystectomy, stratified according to age: octogenarian vs. younger patients. Same analyses were reported after stratification according to T-stage: T2 vs. T3.

		Univariable HR	95% C.I.	P value	Multivariable HR	95% C.I.	p value
	Patients younger than 80 years						
PLND							
	noPLND	Ref.			Ref.		
	PLND	0.87	(0.77–0.98)	**0.02**	0.56	(0.51–0.61)	< **0.001**
Stratified analyses according to T-stage in patients younger than 80 years							
	T2 cohort						
PLND							
	noPLND	Ref.			Ref.		
	PLND	0.63	(0.54–0.74)	< **0.001**	0.52	(0.45–0.59)	< **0.001**
	T3 cohort						
PLND							
	noPLND	Ref.			Ref.		
	PLND	0.78	(0.63–0.96)	**0.02**	0.58	(0.51–0.65)	< **0.001**
	Octogenarian patients						
PLND							
	noPLND	Ref.			Ref.		
	PLND	0.77	(0.58–1.03)	0.07	0.51	(0.39–0.65)	< **0.001**
Stratified analyses according to T-stage in octogenarian patients							
	T2 cohort						
PLND							
	noPLND	Ref.			Ref.		
	PLND	0.59	(0.39–0.90)	**0.01**	0.50	(0.33–0.74)	< **0.001**
	T3 cohort						
PLND							
	noPLND	Ref.			Ref.		
	PLND	0.62	(0.40–0.95)	**0.03**	0.44	(0.32–0.62)	< **0.001**

All analyses were adjusted for the following covariates: T-stage, N-stage, tumour grade, socio-economic status, race and marital status.
Abbreviations: pelvic lymph node dissection (PLND), hazard ratio (HR), confidence intervals (C.I.), reference (Ref.).

adherence rates [4–7], especially in octogenarian patients [10]. Based on these observations, we hypothesised that PLND rates may have increased within the SEER database in both octogenarians, as well as in younger patients, and postulated that PLND may have a beneficial role on CSM, regardless of age including octogenarian patients. Last but not least, we also relied on a second population-based data depository, namely the NIS, to examine complications, LOS, THC and in-hospital mortality rates, according to PLND status, with further stratification according to octogenarian vs. younger patients age. Our analyses focused on three specific objectives: 1) rates of PLND, 2) effect of PLND on CSM and 3) effect of PLND on complications, LOS, THC and in-hospital mortality. We identified several noteworthy findings.

First, PLND rates in octogenarians within the SEER database was lower (83% vs. 89%; $p < 0.001$) than in the younger patients. However, our findings regarding both octogenarian and younger patients' PLND rates were higher compared to the most contemporary adherence rates reported by Zaffuto et al. (81.9%), where no stratification was made according to octogenarian vs. younger patient age [9]. Previous population-based analyses showed annual PLND rates that ranged from 63 to 85.9% [3,5,9,10]. However, only one performed a

Table 3
Descriptive characteristics of 19,203 non-metastatic bladder cancer patients treated with radical cystectomy, with or without pelvic lymph node dissection (PLND). Patients were stratified according age: octogenarian vs. younger patients. Analyses focused on complications rate, length of stay, total hospital charges and in-hospital mortality rate and relied on the National Inpatient Sample (NIS) database (2004–2015).

		Patients younger than 80 years: PLND performed (n 12,229; 75%)‡	**Patients younger than 80 years: PLND not performed (n** 4,040; **25%)**‡	**p value**	**Octogenarian patients: PLND performed (n** 1,827; **62%)**‡	**Octogenarian patients: PLND not performed (n** 1,107; **38%)**‡	**p value**
Overall complications	n (%)	7,465 (61.0)	2,279 (56.4)	< **0.001**	1,252 (68.5)	688 (62.1)	< **0.001**
Medical miscellaneous complications	n (%)	4,345 (35.5)	1,249 (30.9)	< **0.001**	804 (44)	359 (32.4)	< **0.001**
Surgical miscellaneous complications	n (%)	798 (6.5)	341 (8.4)	< **0.001**	157 (8.6)	102 (9.2)	0.6
Vascular complication	n (%)	411 (3.4)	109 (2.7)	**0.04**	98 (5.4)	41 (3.7)	< **0.05**
Wound complication	n (%)	782 (6.4)	237 (5.9)	0.2	144 (7.9)	58 (5.2)	< **0.01**
Cardiac complication	n (%)	827 (6.8)	316 (7.8)	**0.02**	218 (11.9)	150 (13.6)	0.2
Pulmonary complication	n (%)	1,296 (10.6)	447 (11.1)	0.4	296 (16.2)	142 (12.8)	**0.02**
Genitourinary complication	n (%)	1,975 (16.2)	701 (17.4)	0.1	326 (17.8)	190 (17.2)	0.7
Infectious complication	n (%)	757 (6.2)	241 (6)	0.6	169 (9.3)	59 (5.3)	< **0.001**
In hospital mortality	n (%)	147 (1.2)	68 (1.7)	**0.02**	62 (3.4)	43 (3.9)	0.6
Length of stay	Median	8	7	< **0.001**	9	7	< **0.001**
	IQR	6-11	5-10		7-13	5-11	
Total hospital charges ($)	Median	26,735	20,948	< **0.001**	28,136	20,418	< **0.001**
	IQR	19,948 -37,235	13,358-32,871		20,290-40,750	12,749-32,545	

Abbreviation: pelvic lymph node dissection (PLND), interquartile rage (IQR).
‡ Column percentage.

Table 4
Univariable and multivariable logistic regression models predicting complications rate, length of stay, total hospital charges, and in-hospital mortality according to pelvic lymph node dissection status (performed vs. not performed) at radical cystectomy, stratified according to age: octogenarian vs. younger patients. The analyses relied on National Inpatients Sample (NIS) database (2004–2015).

Type of complication	Univariable OR	C.I. 2.5%	C.I. 97.5%	P value	Multivariable OR	C.I. 2.5%	C.I. 97.5%	P value
Patients younger than 80 years								
Overall complications	1.21	1.13	1.30	< **0.001**	1.23	1.14	1.32	< **0.001**
Medical miscellaneous	1.23	1.14	1.33	< **0.001**	1.28	1.18	1.38	< **0.001**
Surgical miscellaneous	0.76	0.66	0.87	< **0.001**	0.79	0.69	0.91	< **0.001**
Vascular	1.25	1.02	1.56	**0.04**	1.30	1.05	1.62	**0.02**
Wound	1.09	0.95	1.28	0.2	1.13	0.97	1.32	0.1
Infectious	1.04	0.90	1.21	0.6	1.08	0.92	1.25	0.4
Pulmonary	0.95	0.85	1.07	0.4	1.02	0.91	1.15	0.7
Cardiac	0.85	0.75	0.98	**0.02**	0.93	0.81	1.06	0.3
Genitourinary	0.92	0.83	1.01	0.1	0.93	0.84	1.02	0.1
In hospital mortality	0.71	0.53	0.95	**0.02**	0.83	0.62	1.12	0.2
Length of stay †	1.06	1.05	1.07	< **0.001**	1.08	1.07	1.10	< **0.001**
Total hospital charges ($)*	4832	3854	5810	< **0.001**	4484	3233	5735	< **0.001**
Octogenarian patients								
Overall complications	1.33	1.13	1.55	< **0.001**	1.32	1.12	1.55	< **0.001**
Medical miscellaneous	1.64	1.40	1.91	< **0.001**	1.60	1.36	1.88	< **0.001**
Surgical miscellaneous	0.93	0.71	1.21	0.6	0.90	0.69	1.18	0.4
Vascular	1.47	1.02	2.16	**0.04**	1.52	1.04	2.25	**0.03**
Wound	1.55	1.14	2.13	< **0.01**	1.51	1.10	2.11	**0.01**
Infectious	1.81	1.34	2.48	< **0.001**	1.75	1.28	2.42	< **0.001**
Pulmonary	1.31	1.06	1.63	**0.01**	1.41	1.13	1.77	< **0.01**
Cardiac	0.86	0.69	1.08	0.2	0.96	0.76	1.21	0.7
Genitourinary	1.05	0.86	1.28	0.6	1.07	0.87	1.31	0.5
In-hospital mortality	0.87	0.59	1.30	0.5	0.95	0.63	1.45	0.8
Length of stay †	1.19	1.17	1.22	< **0.001**	1.20	1.17	1.23	< **0.001**
Total hospital charges ($)*	7666	5517	9814	< **0.001**	6933	4663	9204	< **0.001**

All analyses were adjusted for the following covariates: age, year of surgery, type of surgery (minimally invasive vs. open), Charlson-Comorbidity Index score, gender, race, type of insurance, region.
Abbreviation: odds ratio (OR), confidence intervals (C.I.).
† Reported as relative risk.
* Reported as relative increase.

stratification according to octogenarian vs. younger patient age [10]. In this study, the adherence to PLND in octogenarians was 69.2% [10].Taken together, our study showed higher rates of PLND in octogenarians than previously reported. Nonetheless, the rates are not optimal yet. In consequence, efforts aimed at sensitising the urologic community about the importance of PLND at RC need to be maintained.

Second, our analyses demonstrated an increase in annual PLND rates at RC in octogenarians (EAPC: +0.9%; p = 0. 01), as well as in younger patients (EAPC: +0.6%; p < 0. 001). It is noteworthy that the absolute differences in rates over time were relatively small. Nonetheless, the rate of PLND in octogenarian patients does lag behind rates in young patients. These observations validate our recommendation about the need to maintain efforts aimed at sensitising the urologic community concerning the need about PLND, especially in elderly patients.

Third, our findings suggested a survival benefit when PLND at RC is performed vs. when it is omitted. Specifically, the CSM benefit was virtually the same in octogenarian (HR 0.51; p < 0.001) vs. younger patients (HR 0.56; p < 0.001), even in multivariable and IPTW adjusted analyses. These observations are novel with respect to more detailed adjustment according to PLND status, since IPTW analyses were never applied in previous reports. In consequence, the importance of PLND at RC is the same in octogenarians, as well as in younger patients. Therefore, PLND should be performed at the same rate regardless of age. Our results are in strong agreement with previous analyses reported by Abdollah et al. [10], where a 1.3-fold higher cancer specific rate was showed in both octogenarian and younger patients when PLND was omitted at RC (p < 0.001). In other analyses, no stratification was made according to age. Nonetheless, a CSM benefit was also suggested, when PLND at RC was performed [15,16]. To the best of our knowledge, no previous population-based analyses ever questioned the suggested CSM survival benefit of PLND at RC [3,5,6,8,9]. Our findings corroborate a strong protective effect of PLND on CSM, even in the most contemporary patients, in both octogenarian and younger ages. Moreover, it is also of note that the extent of lymphadenectomy had a protective effect on CSM. Unfortunately due to sample size limitations in octogenarian patients independent predictor status of this effect could not be demonstrated, but was shown in younger patients.

Fourth, we identified marginal, albeit statistically significant differences in complication rates, LOS and THCs, when PLND vs. no PLND status at RC was tested in octogenarian patients. Interestingly, analyses that focused on younger patients revealed very comparable findings in overall complications, LOS and THCs. In general, the magnitude of the increase was somewhat higher in octogenarians than in younger patients. Moreover, minor differences existed in the rates of the increase that was recorded for specific complications, when octogenarians were compared to younger patients. Examples are vascular, wound, pulmonary and infectious complications. Conversely, no statistically significant differences were described in both age groups terms of in-hospital mortality, when PLND vs. no PLND status was tested at RC. The absolute in-hospital mortality rate was slightly higher in young patients who underwent PLND, relative to no-PLND young patients, and no statistically significant difference was recoded in octogenarian patients between who did or did not undergo PLND. In general, the absolute in-hospital rate in both age categories was very low. In consequence, the clinical importance of the statistically significant difference in young population might be marginal at best.

Taken together, these observations indicate that complication rates, LOS and THCs are sensitive to whether or not PLND is performed. Moreover, when PLND is performed, all three indicators (complication rates, LOS and THCs) show marginal, albeit statistically significant increases in both octogenarian, as well as younger patients. This said, the differences in the rate of increase are not prohibitive in either patient group and are only marginally higher in octogenarians than in younger

patients. In consequence, our findings indicate that in general clinicians should not anticipate a sharp increase in complications, LOS or THC, when PLND is performed in octogenarians relative to younger patients.

Despite the novelty of our findings, important limitations need to be acknowledged. First, our data represent a retrospective analysis with high potential for selection biases. To maximally reduce biases, we relied on IPTW-based adjustment [14]. However, it is possible that residual difference persisted according to variables that are unavailable in retrospective databases, such as the SEER or the NIS database. Particularly, within the SEER database lack of central pathology, as well as of early cancer control endpoints, such as distant recurrence or metastatic progression, represent weaknesses. Moreover, the SEER database does not provide information regarding patients' performance status or Charlson comorbidity index. In consequence, it is possible that surgical selection bias could have partially affected our analyses.

Regarding complications, LOS, THCs and in-hospital mortality rates that are available in the NIS database are applicable to in-hospital stay. In consequence, additional complications, as well as additional mortality and THCs may arise after discharge and cannot be captured in the current database.

5. Conclusions

Even though within the SEER database, PLND was associated with lower CSM regardless age, PLND rates were lower in octogenarians, relative to younger patients. However, an increasing trend over the time was described in both groups that was of smaller magnitude in octogenarian than in younger patients. Within the NIS database, PLND was also associated with higher complication rates longer hospital stay, higher THCs, but not with higher in-hospital mortality rate in both octogenarian and younger patients. However, the difference in absolute complication rates, when PLND was performed at RC vs. omitted, was marginally higher in analyses focusing on octogenarians than in those addressing younger patients. This said, the differences were not prohibitive and should not be interpreted as a discouragement towards PLND at RC in octogenarians. In consequence, based on lower CSM and on a marginal lower increase in adverse outcomes, when PLND is performed, PLND should be strongly advocated at RC, especially in octogenarian patients.

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Conflict of interests

Authors declare no conflicts of interest, including specific financial interests or relationships or affiliations relevant to the subject matter or materials discussed in the manuscript.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.canep.2019.02.002.

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