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Survival after radical cystectomy during holiday periods

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ABSTRACT

Objective: For patients undergoing radical cystectomy for bladder cancer, a procedure requiring complex urinary tract reconstruction prone to major postoperative complications, the timing and quality of the surgery have been associated with outcomes.

Patients and methods: This study investigated if radical cystectomy for bladder cancer performed during holiday periods had worse disease-specific (DSS) and overall survival (OS), higher 90-day mortality and risk of readmissions. All patients operated on with radical cystectomy for primary bladder cancer during 1997–2014 with holiday periods as exposure (with one narrow (7 weeks) and one wider (14 weeks) definition) in the Swedish population-based bladder cancer research-database (BladderBaSe) were studied. DSS and OS after radical cystectomy during holiday periods were analysed with Cox regression models adjusted for sex, age, comorbidity, marital status, T-stage and nodal metastases, neoadjuvant chemotherapy, hospital volume and year of cystectomy.

Results: Surgery during the holiday periods (narrow and wide definitions) were not associated with DSS (Hazard ratio [HR] = 1.05, 95% confidence interval [95% CI] = 0.90–1.21 and HR = 1.04, 95% CI = 0.91–1.17), respectively. HRs for OS were similar, and no associations between radical cystectomy during any of the holiday period definitions and 90-day mortality and readmission were found.

Conclusion: Survival after radical cystectomy in Sweden is similar during holiday and non-holiday periods.

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Introduction

Worse long-term all-cause and disease-specific survival have been associated with cancer surgeries performed during holiday periods for several cancer forms including kidney- and urinary bladder cancer [1]. A seasonal variation of in-hospital mortality has also been noticed following lung cancer surgery [2], but not after colorectal cancer surgery [3]. In Sweden the holiday periods are mid-June to mid-August, and with a wider definition also end of August and mid-December to mid-January, are associated with a reduction of elective healthcare and number of available hospital beds [4].

The aim of the current study was to investigate survival after radical cystectomy for bladder cancer within holiday

periods, as compared to outside holiday periods among all bladder cancer patients subjected to primary radical cystectomy in the Bladder cancer Database Sweden (BladderBaSe) from 1997 to 2014 [5]. In addition, we investigated risk of postoperative mortality and hospital readmissions after radical cystectomy performed within as compared to outside holiday periods.

Patients and methods

The principles of data extraction applied and linkages of the current study are described in detail in the BladderBaSe cohort profile [5]. The study included all individuals diagnosed with bladder cancer with tumor stages Ta–T4, with

primary treatment radical cystectomy. Patients with missing data for at least one of the following; marital status, tumor stage, or hospital volume were excluded. The exposure was radical cystectomy within holiday periods using a wide definition of holiday period (16 June to 31 August and 16 December to 7 January) and a narrow definition (25 June to 15 August) similar to the previous hypothesis-generating findings by Lagergren et al. [1]. The wider definition represents the period corresponding to reduced elective health-care capacity in Sweden [4]. The outcomes investigated were disease-specific survival (DSS) and overall survival (OS), 90-day mortality, and readmission within 90 days (only in individuals receiving an ileal conduit, as all individuals with continent reconstructions have planned readmissions when commencing to use their reconstructed urinary tract). Date and cause of death were obtained in national registries and death from bladder cancer was defined as ICD-10 code C67 as underlying cause of death. To explore possible selection mechanisms by vacation period, we investigated monthly fluctuations in tumor stage at diagnosis and use of radical cystectomy and curative external beam irradiation, the number of patients diagnosed with tumor stage categories (Carcinoma *in situ* (Tis)/Ta/T1 vs T2 vs T3/T4), treated with radical cystectomy, and starting curative external beam irradiation were divided into months, and also computed as quantity by number of days in the month.

Statistical analyses

The individual patient's date for radical cystectomy was used as the starting point for follow-up. Date of death, emigration, or 31 December 2014, was regarded as the end of follow-up, whatever happened first. Risk of the outcomes were calculated with hazard ratios (HR) using Cox regression analyses. Hospital volume was accounted for by period-specific mean annual volume (PSMAV) defined as the radical cystectomy volume per year for the 3 years preceding the individual patient's date of radical cystectomy [6]. The survival analyses were adjusted for the following covariates: gender, age, comorbidity (Charlson Comorbidity Index (CCI)), marital status (married/not married, divorced or widowed), tumor stage categories (Tis/Ta/T1 vs T2 vs T3/T4), nodal status (N0/N+), neoadjuvant chemotherapy, PSMAV (0–10), (10–25) and (25–86), and year of cystectomy (1997–2005 and 2006–2014) in the analyses. Risk of postoperative 90-day mortality and readmissions within 90 days were calculated with odds ratios (OR) using logistic regression models adjusting for the same covariates. Chi-square test were used to test for differences in stage groups, number of radical cystectomies and number of patients treated with curative external beam irradiation, separately across months. A *p*-value of <0.05 was considered statistically significant.

R statistical package, version 4.0.0 (R Core Team (2020)) was used for statistical analysis [7].

The study was approved by the Research Ethics Board of Uppsala University, Sweden (File no. 2015/277).

Results

The total number of patients with stage Ta–T4 undergoing radical cystectomy was 4,118. After exclusion of patients with missing values, our study population included 3,943 patients. Of them, 974 (25%) were females, and 2,659 (67%) received an ileal conduit. The median age at diagnosis was 67 (Inter Quartile Range [IQR] 62–74) years of age, and median time in follow-up was 29 (IQR = 13–72) months. Patient characteristics in relation to radical cystectomy performed during holiday periods are given in Table 1. There were modest fluctuations in the monthly use of radical cystectomy and curative external beam irradiation but with no systematic pattern in relation to vacation periods. The stage group distribution was similar over the years (Table 2).

Radical cystectomy performed during wide and narrow holiday periods was not associated with decreased DSS, HR = 1.04 (95% CI = 0.91–1.17) and HR = 1.05 (95% CI = 0.90–1.21), respectively, or decreased OS, HR = 0.98 (95% CI = 0.88–1.09) and HR = 1.00 (95% CI = 0.88–1.14), respectively (Table 3). The unadjusted HRs were similar to the adjusted figures given in Table 3.

Radical cystectomy during wide and narrow holiday periods was not associated with higher 90-day mortality, OR = 1.22 (95% CI = 0.89–1.68) and OR = 0.99 (95% CI = 0.64–1.53), or 30-day mortality, OR = 1.47 (95% CI = 0.81–2.64) and OR = 1.04 (95% CI = 0.47–2.32), respectively. Similarly, we found no increased risk of readmission among those patients that underwent urinary diversion with an ileal conduit was similar when the surgery was performed within or outside the holiday periods, wide and narrow periods, OR = 0.93 (95% CI = 0.76–1.13) and OR = 0.97 (95% CI = 0.76–1.24), respectively.

Discussion

Survival after radical cystectomy for primary bladder cancer was similar when performed within and outside during holiday periods, both using wide and narrow definitions. In addition, the short-term outcomes 90-day mortality and risk of readmission within 90 days of surgery were similar within and outside holiday periods.

To the best of our knowledge, there is only one previous study in this field, however that study reported an association between both surgery for renal cell carcinoma and bladder cancer with radical cystectomy during holidays and worse long-term outcome [1]. Unlike that study, the present study also adjusted the survival estimates for more detailed data of the bladder cancer (clinical T-stages and clinical nodal metastases defined separately instead of stratifying tumor stage into I–II vs III–IV). Additionally, the current study adjusted for marital status and neoadjuvant chemotherapy together with sex, age, comorbidity, hospital volume, and year of cystectomy, used as covariates in both studies. Thus, the differing results can potentially partly be explained by a more extensive adjustment for possible patient selection. In addition, the different clinical domain can partly explain the diverging results, where the inclusion of radiologically

Table 1. Distribution of descriptive data in all patients and within holiday periods using a narrow definition (25 June to 15 August) and a wider holiday definition (16 June to 31 August and 16 December to 7 January).

	Study population (%)	Patients operated outside narrow holiday period (%)	Patients operated within narrow holiday period (%)	Patients operated outside wide holiday period (%)	Patients operated within wide holiday period (%)
Sex					
Male	2,969 (75)	2,624 (76)	345 (73)	2,327 (75)	642 (75)
Female	974 (25)	847 (24)	127 (27)	758 (25)	216 (25)
Age					
<65	1,292 (33)	1,150 (33)	142 (30)	1,016 (33)	276 (32)
65+	2,651 (67)	2,321 (67)	330 (70)	2,069 (67)	582 (68)
CCI					
CCI = 0	2,812 (71)	2,471 (71)	341 (72)	2,198 (71)	614 (72)
CCI > 0	1,131 (29)	1,000 (29)	131 (28)	887 (29)	244 (28)
Marital status					
Not married, divorced or widowed	1,470 (37)	1,285 (37)	185 (39)	1,148 (37)	322 (38)
Married	2,473 (63)	2,186 (63)	287 (61)	1,937 (63)	536 (63)
T stage category					
Tis/Ta/T1	699 (18)	626 (18)	73 (16)	544 (18)	155 (18)
T2	2,340 (59)	2,065 (60)	275 (58)	1,830 (59)	510 (59)
T3/T4	904 (23)	780 (23)	124 (26)	711 (23)	193 (23)
Nodal metastases					
No	3,535 (90)	3,120 (90)	415 (88)	2,766 (90)	769 (90)
Yes	408 (10)	351 (10)	57 (12)	319 (10)	89 (10)
Neoadjuvant treatment					
No	3,487 (88)	3,078 (89)	415 (87)	2,742 (89)	745 (87)
Yes	456 (12)	393 (11)	63 (13)	343 (11)	113 (13)
Period-specific mean annual volume (PSMAV)					
0–10	1,201 (31)	1,060 (31)	141 (30)	939 (30)	262 (31)
10–25	1,546 (39)	1,360 (39)	186 (39)	1,214 (39)	332 (39)
25–75	1,196 (30)	1,051 (30)	145 (31)	932 (30)	264 (31)
Year of cystectomy					
1997–2005	1,514 (38)	1,322 (38)	192 (41)	1,183 (38)	331 (39)
2006–2014	2,429 (62)	2,149 (62)	280 (59)	1,902 (62)	527 (61)

The proportion of patients operated on in low (0–10), median (10–25) and high-volume hospitals (25–75) are given based on the period-specific mean annual volume (PSMAV) during the 3 preceding years. CCI, Charlson Comorbidity Index.

Table 2. Distribution of stage groups per month ($p = 0.2$), total number of patients in relation to starting date for patients subjected to curative external beam irradiation for bladder cancer per month in the study, and mean number of patients per day for each month ($p = 0.04$), and total number of patients subjected to radical cystectomy per month in the study, and mean number of radical cystectomies per day for each month ($p = 0.02$) (p -values from Chi-square tests).

Month	Non-muscle invasive disease	cT2	cT3/T4	Total number of patients subjects to curative external beam radiation	Mean numbers/day	Total number of patients subjected to radical cystectomy	Mean numbers/day
January	55 (17%)	198 (60%)	75 (23%)	44	1.4	346	11.2
February	49 (16%)	185 (62%)	66 (22%)	23	0.8	312	11.0
March	78 (20%)	216 (57%)	88 (23%)	24	0.8	397	12.8
April	42 (13%)	193 (61%)	82 (26%)	36	1.2	336	11.2
May	82 (22%)	203 (55%)	81 (22%)	38	1.2	386	12.5
June	41 (13%)	213 (66%)	67 (21%)	41	1.4	334	11.1
July	63 (20%)	176 (56%)	74 (24%)	31	1.0	325	10.5
August	55 (18%)	168 (56%)	78 (26%)	46	1.5	314	10.1
September	54 (17%)	194 (60%)	75 (23%)	49	1.6	335	11.2
October	64 (18%)	205 (59%)	78 (22%)	46	1.5	357	11.5
November	53 (17%)	189 (62%)	63 (21%)	38	1.3	325	10.8
December	63 (19%)	200 (59%)	77 (23%)	37	1.2	351	11.3

detected small renal cell carcinomas is a critical point. In Sweden the proportion of incidentally detected renal cell carcinomas is currently 66% of all renal cell carcinomas [8]. For these small renal tumors for which surgery can be safely postponed until after the holiday period, a selection of preferentially more severe renal tumors for surgery during the holiday periods is likely, which thus contributes to a worse long-term survival for the whole group [1].

A variation in survival by season of diagnosis for cancers that to a large proportion is detected in an asymptomatic

state is in line with what other publications have suggested, i.e., that a larger proportion of advanced breast and prostate cancers are diagnosed during vacation periods is the main driver behind worse DSS for patients diagnosed during vacation periods [9]. For these cancers less patients referred from screening programmes halted over the summer is an important determinant for an unfavourable stage distribution. This is in stark contrast to the common diagnostic pathways for bladder cancer, which almost always are initiated based on symptoms, of which gross haematuria is by far the

Table 3. Multivariate Cox regression (disease specific survival (DSS) and overall survival (OS)) for patients operated on within narrow (25 June to 15 August) and wide (16 June to 31 August and 16 December to 7 January) holiday periods compared to patients operated on outside the respective holiday period.

	Numbers of patients	HR (DSS)	95% CI	HR (OS)	95% CI
Radical cystectomy in relation to narrow holiday period					
Outside	3,471	1, ref		1, ref	
Within	472	1.05	0.90–1.21	1.00	0.88–1.14
Radical cystectomy in relation to wide holiday period					
Outside	3,085	1, ref		1, ref	
Within	858	1.04	0.91–1.17	0.98	0.88–1.09

Abbreviations: CCI, Charlson Comorbidity Index; CI, Confidence Interval; CIS, Carcinoma *In Situ*; DSS, Disease-Specific Survival; HR, Hazard Ratio; IQR, Inter Quartile Range; OS, Overall Survival; PSMASV, Period-Specific Mean Annual Volume.

HRs are adjusted for sex, age (stratified above and below 65 years of age), comorbidity (Charlson comorbidity index 0 or above), marital status, T-stage group stratified in non-muscle invasive disease (Tis/Ta/T1, stage T2, and stage T3/T4), nodal metastases, neoadjuvant chemotherapy, hospital volume of radical cystectomy (low [0–10], median [10–25], and high volume hospitals [25–75] based on the period-specific mean annual volume (PSMASV)), and year of cystectomy (1997–2005 vs 2006–2014). HR, Hazard Ratio; CI, Confidence interval; DSS, Disease-specific survival; OS, Overall survival.

most common [10]. This is reflected in this study as the stage group distribution did not change during holiday months.

Some aspects of the clinical infrastructure may have hidden an underlying worse prognosis after a cystectomy during vacation periods. First, allocation of patients from smaller units to high-volume units could have occurred during the holiday periods. If so, the benefit of being operated on in larger units with possible better long-term survival for these allocated patients might conceal actual worse outcomes at smaller units for patients operated on during holiday periods [6]. Similarly, such allocation to larger units might have affected the risk of readmission, as lower anaesthesiologist case volume for radical cystectomy have been associated with increased risk of readmission after radical cystectomy [11]. However, looking at the distribution of operations by PSMASV, this seems not to have happened in Sweden (Table 1). Secondly, there might be an increased propensity to refer patients suitable for radical cystectomy to curative radiation therapy during holiday periods with a selection of more advanced cases to irradiation. However, this possible selection bias is not evident from the seasonal distribution of treatment modalities offered (Table 2). Thirdly, operations of patients in the more advanced categories perceived to be more technically demanding could have been postponed until teams were fully manned after vacation periods. However, as pointed out above, the stage distribution over the year was similar. Fourthly, operations for patients with less advanced tumors may have been postponed during periods when expert teams were less manned, but also here the even stage distribution over the year (Table 2) and similar proportion node-positive disease operated within and outside holiday periods (Table 1) contradicts this possibility.

Strengths of the current study include access to several nationwide population-based registers with high quality data of diagnosis and treatment in patients with bladder cancer [5]. Data from these national registers from an entire country will entail some misclassification compared to a review of patients' charts, but we have no indications that misclassification is associated with vacation periods. As our results were observed in a nation-wide database over the course of 17 years during which the mortality for hospitalized care during holiday periods have been the same [12], it is less likely to be a reflection only of the specific organization of Swedish urological care.

Conclusion

Survival and short-time outcomes among bladder cancer patients subjected to radical cystectomy were similar within, as compared to outside vacation periods. Our findings raise the question if seasonal variations in outcome of cancer care are mostly related to stage distribution in cancers that are to a substantial proportion detected by organized screening, extensive use of early detection measures, or detected en passant in conjunction with other diagnostic pathways.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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