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REPORTS OF ORIGINAL INVESTIGATIONS

Perioperative management and oncological outcomes following radical cystectomy for bladder cancer: a matched retrospective cohort study

Prise en charge périopératoire et devenirs oncologiques après une cystectomie radicale pour un cancer de la vessie: une étude rétrospective de cohorte appariée

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Abstract

Purpose *The immune system plays an important role in tumour progression. Systemic opioids are immunosuppressive; thus, theoretically they may promote tumour spread. Our primary aim was to test the hypothesis that general anesthesia (GA) with spinal analgesia (SA) in patients with bladder cancer undergoing radical cystectomy (RC) will both reduce systemic opioid use and improve oncological outcomes. Since blood transfusions also induce immunosuppression, a secondary aim was to evaluate the effect of perioperative transfusions on oncological outcomes.*

Methods *One hundred ninety-five patients who underwent RC with GA+SA from 1998-2007 were matched 1:1 to controls who underwent surgery with GA only using propensity scoring and tumour characteristics known to be highly associated with oncological outcomes. Medical records were reviewed for use of opioids and transfusions. Outcomes were tumour recurrence, cancer-specific mortality, and all-cause mortality. Survival was estimated using the Kaplan-Meier method, and associations of anesthetic technique and transfusions with outcomes were analyzed using stratified multivariable proportional hazard regression.*

Results *Systemic opioid use was reduced with GA+SA relative to GA ($P < 0.001$). There was no difference between groups with respect to all-cause mortality (hazard ratio [HR], 1.09; 95% confidence interval [CI], 0.77 to 1.53; $P = 0.636$), bladder cancer mortality (HR, 1.03; 95% CI, 0.66 to 1.61; $P = 0.893$), or cancer recurrence (HR, 1.32; 95% CI, 0.86 to 2.02; $P = 0.205$). Nevertheless, patients who were perioperatively transfused had an increased all-cause mortality (HR, 2.21; 95% CI, 1.11 to 4.40; $P = 0.025$), and cancer-specific mortality (HR, 2.61; 95% CI, 1.05 to 6.48; $P = 0.039$).*

Conclusions *In patients undergoing RC, the opioid-sparing effect with SA was not associated with improved oncological outcomes, while blood transfusion was associated with increased mortality.*

Résumé

Objectif *Le système immunitaire joue un rôle important dans la progression des tumeurs. Les opioïdes systémiques sont immunosuppressifs, ils pourraient donc, en théorie, promouvoir la propagation des tumeurs. Notre objectif principal était de tester l'hypothèse qu'en ajoutant une analgésie rachidienne (AR) à l'anesthésie générale (AG) chez les patients atteints d'un cancer de la vessie et*

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subissant une cystectomie radicale (CR), on réduirait l'utilisation d'opioïdes systémiques tout en améliorant les devenirs oncologiques. Étant donné que les transfusions sanguines induisent également une immunosuppression, l'un de nos objectifs secondaires était d'évaluer l'effet de transfusions périopératoires sur les devenirs oncologiques.

Méthode *Cent quatre-vingt-quinze patients ayant subi une CR avec AG+AR entre 1998 et 2007 ont été appariés à 1:1 à des patients témoins ayant subi une chirurgie avec AG seulement à l'aide des scores de propension et des caractéristiques tumorales connues comme étant fortement associées aux devenirs oncologiques. Les dossiers médicaux ont été passés en revue pour documenter l'utilisation d'opioïdes et les transfusions. Les critères d'évaluation étaient la récurrence de la tumeur, la mortalité liée spécifiquement au cancer et la mortalité toutes causes confondues. La survie a été estimée à l'aide de la méthode de Kaplan-Meier, et les associations entre technique anesthésique / transfusions et critères d'évaluation ont été analysées à l'aide d'un modèle de régression à risque proportionnel multivariable stratifié.*

Résultats *L'utilisation d'opioïdes systémiques a été réduite avec une technique AG+AR par rapport à une AG seule ($P < 0{,}001$). Aucune différence n'a été observée entre les groupes en matière de mortalité toutes causes confondues (rapport de risque [RR], 1,09; intervalle de confiance [IC] 95 %, 0,77 à 1,53; $P = 0{,}636$), de mortalité liée au cancer de la vessie (RR, 1,03; IC 95 %, 0,66 à 1,61; $P = 0{,}893$) ou de récurrence du cancer (RR, 1,32; IC 95 %, 0,86 à 2,02; $P = 0{,}205$). Toutefois, les patients transfusés en période périopératoire ont affiché une augmentation de mortalité toutes causes confondues (RR, 2,21; IC 95 %, 1,11 à 4,40; $P = 0{,}025$) et de la mortalité spécifiquement liée au cancer (RR, 2,61; IC 95 %, 1,05 à 6,48; $P = 0{,}039$).*

Conclusion *Chez les patients subissant une CR, l'effet d'épargne opioïde de l'AR n'a pas été associé à de meilleurs devenirs oncologiques, alors que la transfusion sanguine a été associée à une mortalité accrue.*

Radical cystectomy (RC) and urinary diversion is the mainstay treatment for muscle-invasive bladder cancer, but tumour recurrence is frequent.[1] The five-year survival rate for patients with pathologically organ-confined bladder cancer is 68%, but for those with extravesicular extension or lymph node involvement, the range is 25-30%.[1] These poor outcomes have created the rationale for investigating multimodal management approaches for these patients.

The immune system plays a prominent role in the host defenses against local or systemic tumour progression. It is important to preserve the function of natural killer (NK) cells, a subset of lymphocytes that spontaneously recognize and kill tumour cells.[2,3] Several perioperative factors may impair immunologic defenses. Specifically, surgical manipulation disseminates malignant cells into the bloodstream,[4] surgical stress promotes metastatic growth by affecting immunosuppression through neuroendocrine pathways,[2,3] and the use of systemic opioids directly inhibits NK cell activity.[5-9] Finally, blood transfusion induces immunosuppression.[10]

While systemic morphine reduces the NK cell activity, the addition of spinal blockade to general anesthesia in a murine model attenuated the propagation of metastases by surgery.[2] Neuraxially administered hydrophilic opioids (e.g., morphine, hydromorphone) have low systemic absorption; therefore, they reside within the injected neuraxial compartment with negligible systemic uptake. Furthermore, spinal analgesia uses a fraction of the opioid amount compared with the equianalgesic effect of the same drug given systemically. As a result, substantial systemic opioid-sparing is achieved, which may minimize the immunosuppressive effects from systemic opioids.[9,11] It has been shown that intrathecal morphine does not affect peripheral lymphocyte (NK cells) function.[12,13] This entire concept may have clinical implications for oncological patients undergoing surgery with regional anesthesia.[14,15] These effects are the basis for ongoing research that examines the role of opioid-sparing anesthetic techniques on oncological outcomes.[16] Nevertheless, there is substantial challenge to such translational work, and clinical studies have not found a consistent association between opioid-sparing and oncological outcomes.[17-27] One challenge with contemporary anesthetic practices is the impracticality of accomplishing acceptable analgesia without some perioperative opioids. This reality impedes definitive prospective research on whether complete avoidance of perioperative opioids modifies oncological outcomes. The second challenge is the creation of active and control study groups that are well balanced on important oncological prognosticating factors, especially when some factors can be determined only at the time of surgery. Finally, lengthy longitudinal assessments of oncological outcomes, measured in years, are needed in order to accomplish such a study.

There is a lack of studies examining the effect of opioid-sparing regional anesthetic techniques regarding oncological outcomes after RC for bladder cancer. We used the Mayo Clinic Radical Cystectomy Registry (MCRCR) to examine the outcomes associated with anesthetic and perioperative management. In this study, we tested the primary hypothesis that adding opioid-sparing spinal analgesia to general anesthesia improves oncological outcomes in these patients. Since blood transfusion is also associated with immunosuppression, as a secondary aim, we examined the hypothesis that

outcomes are worse in patients who receive perioperative blood transfusion.

Methods

This study was approved by the Institutional Review Board (IRB) of Mayo Clinic, Rochester, MN, USA. Consistent with Minnesota Statute 144.295, we included data only for those patients who provided written authorization to use their medical records for research.

We used the MCRCR, the anesthesia database, and electronic medical records to identify patients who underwent RC for muscle-invasive bladder cancer from January 1, 1998 to December 31, 2007.

Management of anesthesia and analgesia

We used the anesthesia database to review the anesthetic technique for RC. During the study period, *general anesthesia (only)* (GA) was usually induced with propofol or sodium thiopental, fentanyl, midazolam, and succinylcholine or vecuronium. Anesthesia was then maintained with isoflurane, desflurane, or sevoflurane, with or without nitrous oxide. Most typical intraoperative opioids were morphine, hydromorphone, and oxymorphone. When GA was supplemented by *spinal analgesia* (SA), a single dose of hydrophilic intrathecal opioid was administered—i.e., morphine (0.3-0.6 mg) or hydromorphone (50-60 μg), before induction of GA.

Study groups

All patients who received GA + SA or GA only during the study period were identified using the electronic anesthesia records. We chose to use a matched study design since many patient and tumour pathology characteristics are known to be associated with the outcomes of interest. Using this pool of patients from the cystectomy registry, we calculated a propensity score for each patient from logistic regression analysis with SA as a dependent variable. All patient characteristics listed in Table 1 were included as explanatory variables, with the exception of invasive disease focality, which was missing for many subjects. The C-statistic for our propensity model was 0.641. Since patient's age, nodal stage, and TNM classification (i.e., cancer staging notation system) are known to be highly associated with oncological outcomes and overall survival, we also used these variables, along with date of surgery, to identify matched sets. Each patient

Table 1 Demographics and cancer characteristics of cystectomy registry patients who received general anesthesia only or general + spinal anesthesia (1998-2007)*

Characteristics	Anesthesia Management		
	General only (*n*=1,166)	General + spinal (*n*=207)	*P* Value
Age (yr)	67.9 (10.6)	67.8 (10.3)	0.92
Sex			0.30
Male	933 (80)	172 (83)	
Female	233 (20)	35 (17)	
Number of Lymph Nodes Removed (*n*=1,253)	9 (0, 62)	8 (0, 55)	0.15
Charlson Comorbidity Index (*n*=1,217)			0.77
0-2	474 (47)	96 (48)	
≥3	542 (53)	105 (52)	
ECOG status (*n*=1,247)			0.32
0-1	989 (95)	199 (97)	
≥2	52 (5)	7 (3)	
Preoperative hydronephrosis (*n*=1,265)			0.49
Absent	761 (72)	144 (70)	
Present	297 (28)	63 (30)	
Primary tumour stage (*n*=1,258)			0.35
pT1 or less	478 (45)	83 (40)	
pT2	185 (18)	34 (16)	
pT3a	204 (19)	49 (24)	
pT3b	115 (11)	29 (14)	
pT4	69 (7)	12 (6)	
Nodal stage (*n*=1,248)			0.03
pN0	745 (71)	163 (79)	
pNX or pN+	297 (29)	43 (21)	
Invasive disease focality (*n*=818)			0.71
Unifocal	593 (89)	138 (90)	
Multifocal	72 (11)	15 (10)	
Lymphovascular invasion (*n*=1,265)			0.10
Absent	817 (77)	149 (72)	
Present	241 (23)	58 (28)	
Adjuvant chemotherapy (*n*=1,265)			0.32
Not received	912 (86)	173 (84)	
Received	146 (14)	34 (16)	

* Values are *n* (%) for categorical variables, mean (SD) for age, median (min, max) for number of lymph nodes removed. *P* values are Chi square for categorical variables and rank-sum or Student's *t* test as appropriate for continuous variables. ECOG = Eastern Cooperative Oncology Group

who received GA + SA was matched 1:1 with a patient who had GA only using the propensity score, pathologic TNM classification stage ($\leq$ T1 *vs* $\geq$ T2), nodal stage (NX *vs* N0 *vs* N1/N2/N3), age ($\pm$ seven years), and date of surgery ($\pm$ three years). Propensity score matching was performed using the optimal matching algorithm.[28,29]

Data collection

Data were abstracted from the paper and electronic medical records and entered manually into the web-based Research Electronic Data Capture (REDCap^{TM}) system (Version 3.6.7, Vanderbilt University, Nashville, Tennessee).[30] We recorded age, American Society of Anesthesiologists (ASA) physical status, and comorbidities, including coronary artery disease (prior coronary artery bypass grafting [CABG], stent, percutaneous transluminal coronary angioplasty [PTCA], angina, myocardial infarction, or medical treatment for coronary artery disease [CAD]), hypertension (treated), diabetes mellitus (treated), cerebrovascular disease (stroke, transient ischemic attacks), peripheral vascular disease, kidney disease (defined as serum creatinine $\geq$1.5 mg·dL^{-1}), and Charlson Comorbidity Index.[31]

Perioperative blood transfusion was defined as transfusion of allogeneic red blood cells, fresh frozen plasma, and/or platelets within the perioperative period (from the start of surgery until discharge from hospital).

Opioid use

Intrathecal opioid use was recorded but was not included in the calculation of systemic administration. For each patient, we recorded opioids administered in the operating room, recovery room, and for the 48 hr after discharge from the recovery room. All intraoperative and postoperative intravenous and oral opioids given within the first 48 hr were converted to intravenous morphine equivalents.[32,33]

Mayo Clinic Radical Cystectomy Registry

The clinicopathologic variables recorded in the database included age, sex, Eastern Cooperative Oncology Group (ECOG) performance status, surgical margin status, pathologic tumour stage, tumour histology, lymph node involvement, total number of lymph nodes removed, type of urinary diversion, and receipt of perioperative (neoadjuvant/adjuvant) chemotherapy. A single urologic pathologist re-reviewed all pathologic specimens for histologic classification. Tumour staging followed the American Joint Committee on Cancer/Union Internationale Contre le Cancer TNM classification, 7th edition.[34] Pathologic grade, assigned according to the 2004 World Health Organization criteria, was not reported separately as the majority of patients had high-grade disease. Because of the retrospective nature of this study, postoperative follow-up was not standardized. Nevertheless, at our institution, follow-up after RC is recommended quarterly for the first two years postoperatively, semiannually for the next two years, and annually thereafter for patients without evidence of recurrent disease. The registry collects information regarding local recurrence and systemic progression. Oncological evaluation includes history and physical examination, urine cytology, and imaging of the chest, abdomen, and pelvis. For evaluation of survival end points, vital status was identified from death certificates or physician correspondence. For patients followed elsewhere, the MCRCR monitors outcomes annually by correspondence with the patient and the local treating physician.

Follow-up and outcomes

Outcomes measured included *all-cause mortality, cancer-specific mortality*, *and tumour recurrence*. In general, vital status was determined from death certificates and/or from yearly correspondence with patients' personal physicians. Death was assigned to bladder cancer when medical records or the death certificate listed bladder cancer as a primary cause. In addition, the cystectomy registry considers death within 30 days after cystectomy as "bladder cancer death" because it resulted from the treatment (i.e., cystectomy impacted the pre-existing cardiovascular disease which led to death).

Statistical power/sample size considerations

The decision to use 1:1 matching was made based on the resource requirements for manual review of medical records. A formal statistical power analysis was not performed. Nevertheless, under the assumption that approximately 250 events would be observed, a proportional hazard analysis would have statistical power (two-tailed, alpha = 0.05) of 80% to detect a hazard ratio of 1.42.

Statistical analysis

Characteristics of GA only and GA + SA patients were summarized using descriptive statistics and compared using a two-sample Student's *t* test, rank-sum test, or Chi square test. Cumulative event rates for all-cause mortality, cancer-specific mortality, and cancer recurrence were

estimated using the Kaplan-Meier method. These outcomes were analyzed using stratified multivariable proportional hazard regression taking into account the 1:1 matched study design. In addition to anesthesia technique, perioperative blood transfusion was included as an explanatory variable in the model to test our secondary hypothesis that the use of blood products during RC increases the risk for adverse outcomes. Additional covariates included in the model were the Charlson Comorbidity Index, ECOG classification, number of lymph nodes removed, lymphovascular invasion, use of adjuvant chemotherapy, preoperative hydronephrosis, and preoperative hemoglobin concentrations. The assumption of proportional hazards was assessed using weighted Schoenfeld residuals.[35] Results are presented as point estimates and 95% confidence intervals (CIs). All reported *P* values are two sided. Statistical analyses were done using SAS® statistical software version 9.3 (SAS Institute, Cary, NC, USA).

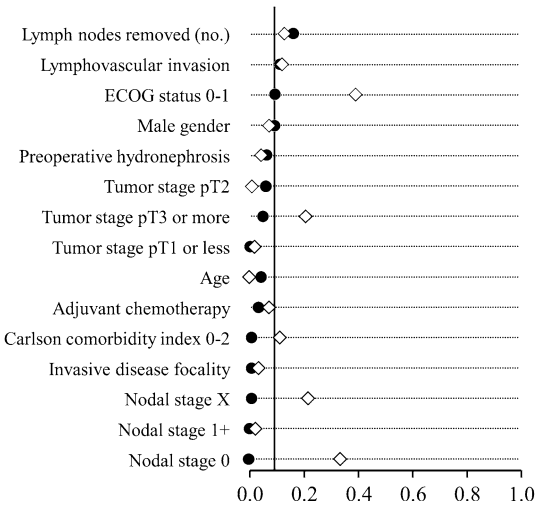

Fig. 1 Standardized differences between anesthesia groups (GA *vs* GA+SA) for the entire sample (open diamonds) and the 195 matched sets (solid circles). ECOG = Eastern Cooperative Oncology Group

Results

We identified 207 patients who underwent RC with GA+SA during 1998-2007. The majority of these patients (> 90%) received morphine as the intrathecal opioid.

Table 1 shows the demographic and tumour characteristics obtained from the cystectomy registry for the 207 GA+SA patients as well as all the patients who underwent cystectomy with GA only during the study period. Patients receiving GA only were more likely than the GA+SA patients to have a higher pNX or pN+ nodal stage (29% *vs* 21%, respectively; $P = 0.025$). Matches could not be identified for 12 of the 207 GA+SA patients. Fig. 1 shows the standardized differences between anesthesia groups in the entire sample and the 195 matched sets. In the matched sets, the standardized difference was < 0.2 for all characteristics and < 0.1 for all characteristics with the exception of the number of lymph nodes removed and lymphovascular invasion.

Demographic and comorbid characteristics for the 195 matched sets are shown in Table 2, while the clinicopathologic tumour characteristics are presented in Table 3. Preoperative comorbidities and cancer-specific characteristics did not differ between groups, with the exception of the number of lymph nodes removed, which was lower in the GA+SA patients than in the GA only patients (median 8 *vs* 10, respectively; $P = 0.028$).

Table 4 summarizes the duration of anesthesia, perioperative use of systemic opioids (expressed in intravenous morphine equivalents), and transfusion during hospitalization. Importantly, the Appendix includes details regarding the timing and type of blood product

Table 2 Demographics and comorbidities in two study groups

Characteristics	Anesthesia Management		*P* Value
	General only (*n*=195)	General + spinal (*n*=195)	
Age	68.2 (10.0)	67.8 (10.4)	0.65
Sex			0.36
Male	155 (79)	162 (83)	
Female	40 (21)	33 (17)	
ASA physical status			0.84
II	86 (44)	88 (45)	
III-IV	109 (56)	107 (55)	
Charlson Comorbidity Index			0.92
0-2	95 (49)	94 (48)	
≥3	100 (51)	101 (52)	
Coronary artery disease	55 (28)	59 (30)	0.66
Hypertension (treated)	85 (44)	96 (49)	0.26
Stroke/Transitory ischemic attack	11 (6)	7 (4)	0.33
Peripheral vascular disease	20 (10)	16 (8)	0.48
Kidney disease*	24 (13)	20 (11)	0.58
Diabetes mellitus (treated)	22 (11)	24 (12)	0.75
Preoperative anemia†	5 (3)	9 (5)	0.28

Values are *n* (%) for categorical variables, mean (SD) for age. *P* values are Chi square for categorical variables and rank-sum or Student's *t* test as appropriate for continuous variables

* Serum creatinine ≥1.5 mg·dL^{-1}; †Hemoglobin concentration ≤ 10 g·dL^{-1}.[56]

ASA = American Society of Anesthesiologists

Table 3 Cancer characteristics in two study groups*

Characteristics	Anesthesia Management		*P* Value
	General only (*n* = 195)	General + spinal (*n* = 195)	
ECOG status			0.36
0-1	191 (98)	188 (96)	
≥2	4 (2)	7 (4)	
Preoperative hydronephrosis			0.50
Absent	141 (72)	135 (69)	
Present	54 (28)	60 (31)	
Primary tumour stage			0.84
pT1 or less	75 (38)	75 (38)	
pT2	39 (20)	34 (17)	
pT3a	48 (25)	47 (24)	
pT3b	21 (11)	28 (14)	
pT4	12 (6)	11 (6)	
Nodal stage			1.00
pN0	153 (78)	153 (78)	
pNX or pN+	42 (22)	42 (22)	
Invasive disease focality (*n*=278)			0.94
Unifocal	118 (90)	132 (90)	
Multifocal	13 (10)	15 (10)	
Lymphovascular invasion			0.25
Absent	149 (76)	139 (71)	
Present	46 (24)	56 (29)	
Number of lymph nodes removed	10 (0, 43)	8 (0, 55)	0.03
Adjuvant chemotherapy			0.68
Not received	166 (85)	163 (84)	
Received	29 (15)	32 (16)	

*Values are *n* (%) for categorical variables, median (min, max) for number of lymph nodes removed. *P* values are Chi square for categorical variables and rank-sum or Student's *t* test as appropriate for continuous variables. ECOG = Eastern Cooperative Oncology Group

administration. As expected, systemic opioid use was reduced (on average 54%), albeit not eliminated, in GA+SA patients compared with GA patients ($P < 0.001$).

The median follow-up after RC was 5.2 yr for GA+SA patients and 5.9 yr for GA patients. During follow-up, 261 patients died; 130 of these patients received GA only and 131 received GA+SA. Moreover, of 147 patients who died of bladder cancer, 67 patients received GA only and 80 received GA+SA.

From proportional hazard regression, there was no difference between the GA+SA and GA only anesthesia groups with respect to all-cause mortality (hazard ratio [HR], 1.09; 95% CI, 0.77 to 1.53; $P = 0.636$; Fig. 2 A), bladder cancer mortality (HR, 1.03; 95% CI, 0.66 to 1.61; $P = 0.893$; Fig. 2 B), or cancer recurrence (HR, 1.32; 95% CI, 0.86 to 2.02; $P = 0.205$; Fig. 2 C).

As expected, patients who received perioperative transfusion (≥ 1 unit) had lower mean (SD) preoperative hemoglobin levels compared with non-transfused patients [12.7 (1.8) $g{\cdot}dL^{-1}$ *vs* 14.2 (1.4) $g{\cdot}dL^{-1}$; $P < 0.001$). Accordingly, preoperative hemoglobin was included as a covariate in the proportional hazards regression analysis. For our secondary hypothesis, i.e., assessing the potential association of blood transfusion with outcomes, we found evidence that the assumption of proportional hazards was violated ($P = 0.058$, $P = 0.044$, and $P = 0.048$ for overall mortality, bladder cancer mortality, and tumour recurrence, respectively). For this reason, the analysis was restricted to the first five years following RC. From these analyses, patients who received blood transfusions during hospitalization were found to have significantly increased all-cause mortality (HR, 2.21; 95% CI, 1.11 to 4.40; $P = 0.025$; Fig. 3 A), and bladder cancer mortality (HR, 2.61; 95% CI, 1.05 to 6.48; $P = 0.039$; Fig. 3 B); however, the difference in the rate of cancer recurrence was not statistically significant between groups (HR, 1.69; 95% CI, 0.80 to 3.58; $P = 0.171$; Fig. 3 C).

Discussion

The main finding of this study was that spinal analgesia with hydrophilic opioids induced an opioid-sparing effect in patients undergoing RC for bladder cancer. Nevertheless, the magnitude of this opioid-sparing was not associated with improved oncological outcomes. After accounting for the major factors important for prognosis, the use of blood transfusion was associated with worse all-cause and cancer-specific survival.

Opioid-sparing anesthesia and oncological outcomes

Surgical stress and systemic opioids impair immunologic host defenses, and the systemic use of morphine within the range of analgesic doses causes suppression of cellular immune system.[3,6-8] A reduction in systemic opioids has been associated with a reduction in both the recurrence and the progression of cancer in a murine model.[2] Nevertheless, conducting clinical studies that examine the effects of opioid-sparing anesthetic techniques on oncological outcomes is a complex undertaking. First, despite the use of regional anesthesia, it may be difficult to achieve a true opioid-sparing effect in the perioperative period after major oncological operations. Second, tumours are heterogeneous in their malignant potentials (e.g., pancreas *vs* prostate),

Table 4 Duration of anesthesia, perioperative systemic opioid use and perioperative transfusion*

Characteristics	Anesthesia Management		*P* Value
	General only (*n*=195)	General + spinal (*n*=195)	
Duration of Anesthesia (hr)	5.7 [5.1-6.6]	5.7 [5.1-6.8]	0.40
Systemic opioid, morphine equivalents (mg)†			
Operating room	45 [39-53]	25 [15-33]	<0.001
Recovery room	5 [0-10]	0 [0-4]	<0.001
Post-recovery room, 48 hr	40 [18-67]	9 [0-25)	<0.001
Total 48 hr	93 [63-127]	39 [25-60]	<0.001
Any perioperative transfusion‡	73 (37)	78 (40)	0.60
Timing of transfusion§			0.19
Intraoperative only¥	41 (56)	33 (42)	
Intraoperative¥ and postoperative	13 (18)	15 (19)	
Postoperative only	19 (26)	30 (38)	

* Values are median (interquartile range [IQR]) for duration of anesthesia and morphine equivalents, *n* (%) for transfusion variables. *P* values are Chi square for categorical variables and rank-sum test for continuous variables. †Perioperative systemic opioids used included morphine, fentanyl, hydrocodone, hydromorphone, meperidine, oxycodone, oxymorphone, propoxyphene, and sufentanil. ‡All 151 patients who received transfusions received packed red blood cells (PRBC), five patients received non-PRBC products (two received PRBC + fresh frozen plasma, two received PRBC + platelets, and one received PRBC + fresh frozen plasma + platelets).§Analysis was restricted to patients who received transfusion. ¥ Includes transfusions received in recovery room

and this characteristic may negate identification of effects based on opioid-sparing.[24] Third, the proper selection of neuraxial opioid is important; some investigators used fentanyl as part of neuraxial analgesia[25,26]; however, this lipophilic opioid given epidurally is promptly systemically absorbed and does not provide a systemic opioid-sparing effect.[26,36]

In the present study, we used SA with morphine, and despite achieving an opioid-sparing effect, the oncological outcomes were not improved. This is in contrast with our previous report where neuraxial anesthetic with morphine and hydromorphone improved oncological outcomes after radical prostatectomy.[27] A possibility for this discrepancy may exist because bladder cancer is more aggressive than prostate adenocarcinoma, which may render it unresponsive to immunomodulatory effects mediated through opioid-sparing. Also RC is a more extensive operation, and the single administration of opioid in the intrathecal space reduces but does not entirely eliminate the perioperative use of systemic opioids. Nevertheless, even with the level of opioid sparing achieved in our study, there was no evidence for a trend of improved outcome. It is unknown whether there exists a dose threshold for systemic opioids beyond which their use adversely affects the immune response. Alternatively, bladder cancer may be less sensitive to the immunomodulation of systemic opioids.

Bladder cancer has a high potential for recurrence,[37] and the main predictors of death are tumours with an advanced pathologic stage, the presence of extranodal extension, and lymphovascular invasion of disease.[38-41] All these risk factors were well balanced between our two study groups, as they were either matched or adjusted; therefore, the comparison between groups accounted for the most important elements that determine the prognosis. Despite that, we failed to find an association between the use of opioid-sparing SA and bladder cancer oncological outcomes.

Perioperative transfusion and oncological outcomes

In our study, perioperative administration of blood was associated with worse survival in models that accounted for prognostically important factors. The potential explanations for the association between blood transfusions and adverse outcomes may be either causative or affected by the presence of unmeasured confounding factors (i.e., transfusion may be a surrogate marker for increased comorbidity, more complex surgery, etc.). It is thought that the "adverse" effects of allogeneic blood transfusions are mediated through mechanisms based on immunosuppression.[42-44] Nevertheless, autologous or leukocyte-depleted transfusions did not improve outcomes for colorectal cancer patients,[45,46] suggesting that other non-immune-mediated factors may be responsible for poor outcomes.[47,48] Based on the information available in the present study, it is not possible to determine whether some unmeasured confounders may have contributed to our findings. Nevertheless, the results of two recent studies showed that perioperative blood transfusions were associated with worse oncological outcomes in patients with bladder cancer, albeit only in univariable

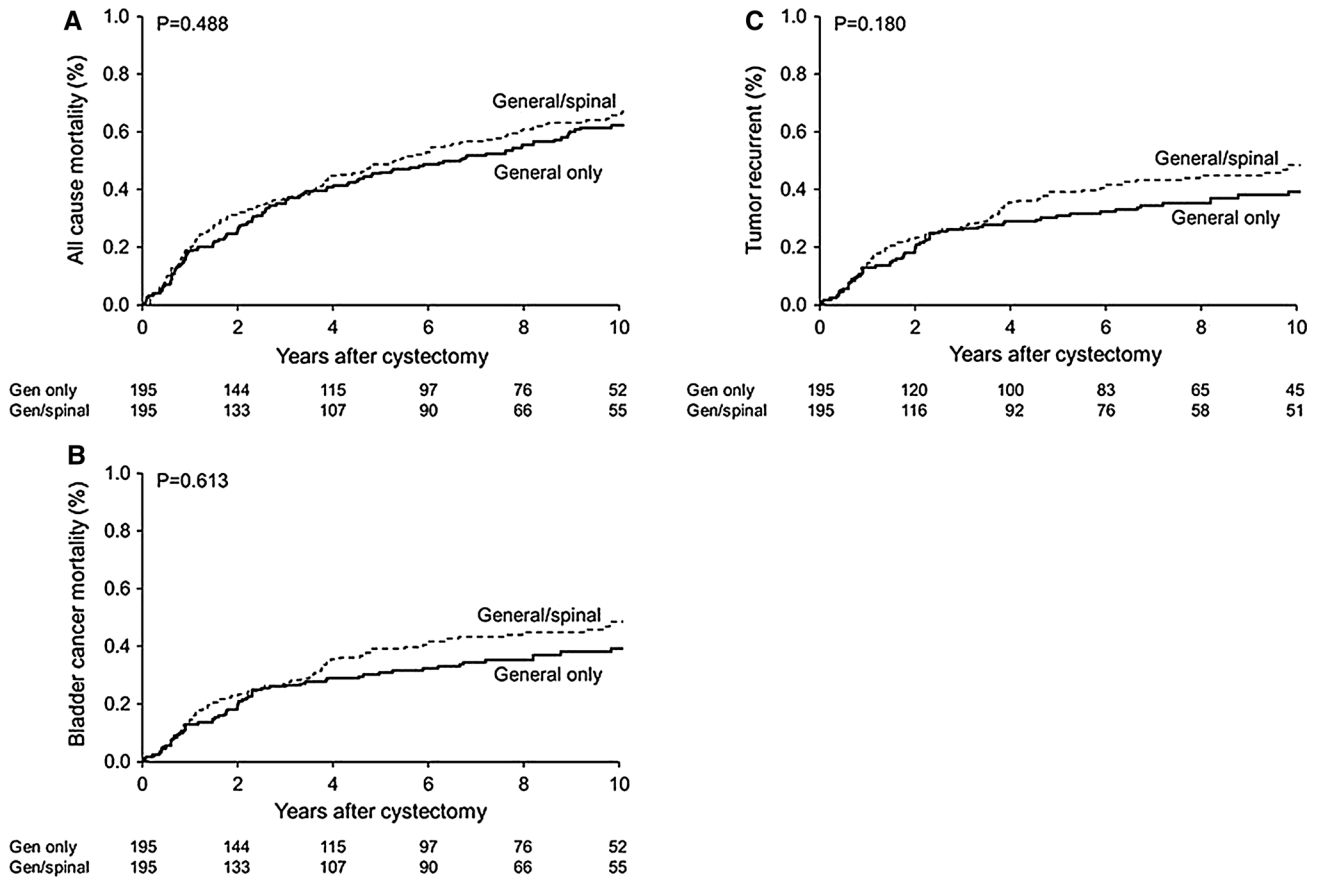

Fig. 2 Cumulative percentage of patients experiencing all-cause death (a), cancer-specific death (b), and cancer recurrence (c) in patients undergoing radical cystectomy with general anesthesia only (general only, solid line) and with general anesthesia supplemented with spinal analgesia (general + spinal analgesia, dashed line). Numbers of patients at risk are shown at zero, two, four, six, eight, and ten years after surgery. *P* values are from the stratified proportional hazards regression with covariates included for Charlson Comorbidity Index, Eastern Cooperative Oncology Group classification, number of lymph nodes removed, lymphovascular invasion, use of adjuvant chemotherapy, and preoperative hydronephrosis

analyses.[49,50] Further, findings in another large study (n = 2,060) from MCRCR showed that the increased number of blood units transfused was associated with reduced cancer-specific survival and all-cause mortality.[51] The timespan of that study (1980-2005)[51] partially overlaps with the present report (1997-2007); however, we reconfirmed a strong association between blood transfusion and adverse oncological outcomes on a substantially smaller patient cohort. Therefore, under the assumption that transfusion *per se* is associated with worse oncological outcomes, efforts should be undertaken to reduce blood transfusions by considering correcting the anemia preoperatively,[52,53] tolerating lower intraoperative hemoglobin levels, and utilizing techniques that have the potential to reduce intraoperative bleeding.[54,55]

Strengths and limitations

Important strengths of this study include utilizing a well-structured RC registry with patients who are receiving longitudinal assessments of oncological outcomes. Nevertheless, this report has all the inherent limitations of an observational retrospective study design. Even the use of propensity matching does not guarantee a balance of unmeasured confounders, and unmeasured or residual confounding by treatment assignment may still persist. Furthermore, non-randomized administration of intrathecal opioid cannot exclude a potential for patient selection bias. Nevertheless, these effects were minimized by our case matching using the most important oncological prognosticating factors. The analysis may not have been sufficiently powered to detect small effects related to the found magnitude of opioid-sparing; however, outcomes in patients who received spinal analgesia were in the "non-protective" direction. Another limitation was the use of our propensity matching based on the use of regional anesthesia to assess for potential associations between blood transfusions and outcomes. Furthermore, administration of blood products was based on the discretion of the treating physicians. This report

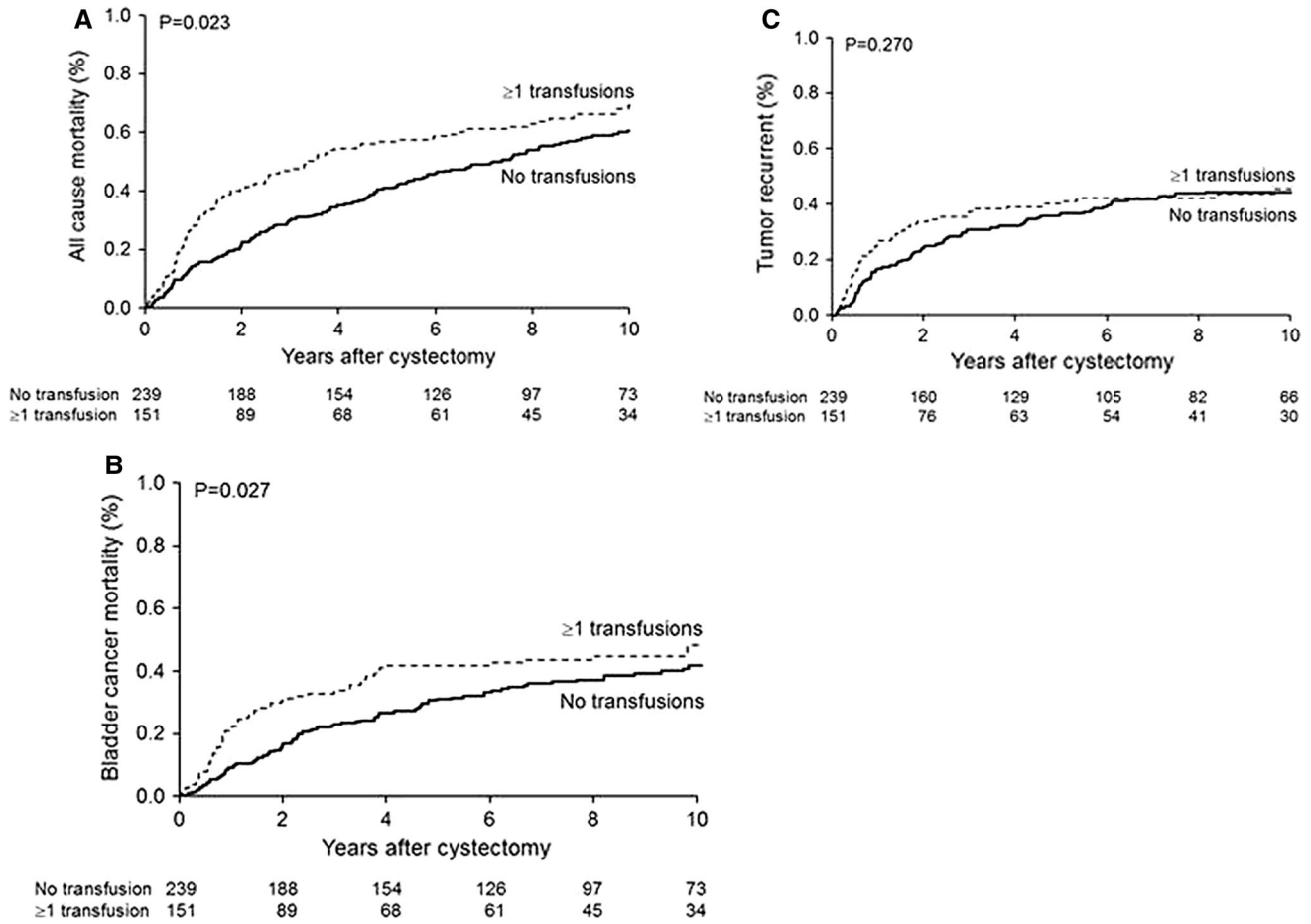

Fig. 3 Cumulative percentage of patients experiencing all-cause death (a), cancer-specific death (b), and cancer recurrence (c) in patients undergoing radical cystectomy stratified by receipt of perioperative blood transfusion: no transfusion received (solid line) and ≥ 1 blood transfusion received (dashed line). Numbers of patients at risk are shown at zero, two, four, six, eight, and ten years after surgery. *P* values are from the stratified proportional hazards regression with covariates included for the use of spinal analgesia, Charlson Comorbidity Index, preoperative hemoglobin, Eastern Cooperative Oncology Group classification, number of lymph nodes removed, lymphovascular invasion, use of adjuvant chemotherapy, and preoperative hydronephrosis. Due to a violation of the proportional hazards assumption when all follow-up was used, the analysis was performed using only follow-up through the first five years following cystectomy

identified a significant association between transfusion and increased cancer mortality (HR, 2.61; $P = 0.039$), but this association was not statistically significant for cancer recurrence (HR, 1.69; $P = 0.171$). This may be explained by the compliance with follow-up and the timing of follow-up visits, which are important for identifying recurrence and assigning a date of recurrence. These issues are especially important given the referral nature of our institution. At the same time, determining the date and cause of death is not dependent on how frequently a patient returns for a follow-up visit, as this information is obtained from death certificates.

In conclusion, a reduction in perioperative systemic opioid use achieved with intrathecal morphine analgesia was not associated with improved oncological outcomes following RC for bladder cancer when compared with perioperative analgesia provided by systemic opioids. At the same time, perioperative transfusion was associated with worse survival. In view of these results, future studies are needed to address whether correction of anemia before surgery and implementation of other strategies to avoid perioperative transfusions could improve long-term oncological outcomes.

Author contributions: *Juraj Sprung*, *Darrell R. Schroeder,* and *Toby N. Weingarten* had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Toby N. Weingarten*, *Igor Frank*, *Stephen A. Boorjian*, *Darrell R. Schroeder,* and *Juraj Sprung* were involved in the study conception and design. *Samuel T. Ahle*, *Kelsey R. Dietz, Shaun S. Dowd, and Ashley M. Taccolini*, were involved in the acquisition of data. *Samuel T. Ahle*, *Kelsey R. Dietz*, *Shaun S. Dowd*, *Ashley M. Taccolini, Toby N. Weingarten,* and *Juraj Sprung* were involved in the analysis and interpretation of data. *Stephen A. Boorjian*, *Darrell*

R. Schroeder, *Toby N. Weingarten*, *Igor Frank*, *Samuel T. Ahle*, *Kelsey R. Dietz*, *Shaun S. Dowd, Ashley M. Taccolini*, and *Juraj Sprung* were involved in drafting the manuscript. *Igor Frank*, *Toby N. Weingarten*, *Darrell R. Schroeder, Juraj Sprung*, *Samuel T. Ahle*, *Kelsey R. Dietz,* and *Shaun S. Dowd, Ashley M. Taccolini* were involved in the critical revision of the manuscript for important intellectual content. *Toby N. Weingarten*, *Darrell R. Schroeder*, *Prabin Thapa, Andrew C. Hanson,* and *Juraj Sprung* were involved in the statistical analysis. *Juraj Sprung* and *Toby N. Weingarten* were involved in obtaining funding.

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Conflicts of interest None declared.

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Appendix

Transfusion units of blood products transfused in our patients

Transfusion type and timing	General only (*n*=195)		General/spinal (*n*=195)	
Intraoperative (OR/PACU)				
PRBC units				
0	141	(72%)	147	(75%)
1	12	(6%)	17	(9%)
2	27	(14%)	19	(10%)
3	8	(4%)	6	(3%)
4	3	(2%)	3	(2%)
5	4	(2%)	2	(1%)
8	0	(0%)	1	(1%)
FFP units				
0	193	(99%)	195	(100%)
1	1	(1%)	0	(0%)
4	1	(1%)	0	(0%)
Platelet units				
0	194	(99%)	195	(100%)
2	1	(1%)	0	(0%)
Postoperative (after PACU discharge)				
PRBC units				
0	165	(85%)	150	(77%)
1	7	(4%)	11	(6%)
2	20	(10%)	29	(15%)
3	2	(1%)	2	(1%)
4	0	(0%)	3	(2%)
10	1	(1%)	0	(0%)
FFP units				
0	193	(99%)	195	(100%)
2	1	(1%)	0	(0%)
3	1	(1%)	0	(0%)
Platelet units				
0	193	(99%)	194	(99%)
1	0	(0%)	1	(1%)
2	1	(1%)	0	(0%)
3	1	(1%)	0	(0%)

Data are number and percentage (%)

FFP = fresh frozen plasma; OR = operating room; PACU = postoperative anesthesia care unit. OR+PACU was considered in the study as intraoperative blood administration. PRBC = packed red blood cells

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