Association Between Anesthetic Technique and Survival After Radical Nephroureterectomy: A Propensity Score-matching Study

YUDAI ISHIYAMA^{1,2}, TSUNENORI KONDO¹, HIDEKAZU TACHIBANA¹,
HIROKI ISHIHARA¹, HARUKA ITO NISHIOKI², KAZUHIKO YOSHIDA²,
JUNPEI IIZUKA², KAZUNARI TANABE² and TOSHIO TAKAGI²

¹Department of Urology, Tokyo Women's Medical University Medical Center East, Tokyo, Japan;

²Department of Urology, Tokyo Women's Medical University, Tokyo, Japan

Abstract. *Background/Aim:* Whether anesthesia can affect oncological outcomes in urothelial carcinoma of the upper urinary tract undergoing radical nephroureterectomy (RNU) is not clear. *Patients and Methods:* One-hundred and ninety-seven patients who underwent RNU were retrospectively recruited and divided into total intravenous (TIVA, n=90) and volatile inhalation anesthesia (VIA, n=107) groups. A 1:1 propensity score-matching method was employed to minimize selection bias (n=70 each). Cancer-specific (CSS), overall (OS) and metastasis-free (MFS) survival were compared between groups before and after matching. *Results:* For all survival endpoints, no significant differences were observed between the two study groups, both before (hazard ratio for TIVA: CSS: 0.70, OS: 0.75, MFS: 0.78) and after (hazard ratios for TIV: CSS: 1.21, OS: 0.82, MFS: 0.84) matching. *Conclusion:* With no survival difference observed according to anesthetic technique for RNU, the choice should be based on factors such as accessibility, prevention of side-effects, or costs.

With the growing number of cancer cases, the number of patients undergoing surgery under general anesthesia is also increasing (1). In recent years, hypotheses have emerged that the anesthetic technique during surgery may impact cancer recurrence or survival. Proposed mechanisms involve the

characteristics of agents used in volatile inhalation anesthesia (VIA) and total intravenous anesthesia (TIVA). According to previous studies, VIA agents can impair immune function enabling tumor cells to evade natural killer cells (2) and can up-regulate signaling pathways such as the hypoxia-inducible factor 1-alpha (HIF1 α) pathway, thereby promoting the proliferation of residual tumors (3). By contrast, propofol used in TIVA may protect from cancer recurrence through its anti-inflammatory and antioxidant potentials (4, 5).

However, the clinical evidence on this topic remains conflicting. Wigmore *et al.* reported based on a dataset of mixed malignancy types that the use of TIVA is associated with a lower overall risk of death compared to VIA (6). Several publications found similar results (7-9), but other studies showed no benefit of TIVA over VIA (10-12). For urothelial carcinoma (UC), Pfail *et al.* demonstrated that VIA is associated with an increased risk of recurrence compared to TIVA during robot-assisted radical cystectomy for bladder cancer (13). To date, there is no evidence whether the type of anesthetic technique impacts cancer recurrence or survival in patients with UC of the upper tract (UCUT) undergoing radical nephroureterectomy (RNU). As recurrences after RNU, especially in invasive cases, are not rare, understanding of this association is of clinical importance (14).

In this context, we aimed to evaluate cancer recurrence and survival of patients by anesthetic type, utilizing propensity score matching to adjust patient characteristics and minimize preoperative selection bias.

Patients and Methods

Patient selection and data collection. This retrospective study included 224 consecutive patients who underwent RNU for radiographically diagnosed non-metastatic UCUT at two tertiary institutions between January 2010 and December 2019. After excluding patients with non-UC pathology in surgical specimens (n=2), cases with less than 3 months of follow-up (n=8), patients

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Correspondence to: Tsunenori Kondo, Department of Urology, Tokyo Women's Medical University Medical Center East, 2-1-10 Nishiogu, Arakawa-ku, Tokyo 116-8567, Japan. Tel: +81 338108111, Fax: +81 338100705, e-mail: tsunenori.kondo@twmu.ac.jp

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who underwent concurrent or prior radical cystectomy (n=13), those on dialysis at the time of surgery (n=1), and patients who had insufficient clinical data (n=3), data for 197 patients were finally analyzed. Clinical and laboratory data were obtained from the institutions' electronic databases and medical records of the patients.

The Internal Ethics Review Board of Tokyo Women's Medical University approved this study (approval ID: 5761), which was performed in accordance with the Declaration of Helsinki. Due to the retrospective, observational nature of the study, the requirement for informed consent was waived.

Study design. Patients were classified into two groups based on the anesthetic they received during surgery, namely TIVA and VIA groups. In both institutions, the decision to utilize TIVA or VIA was solely based on the anesthesiologist's choice. Briefly, midazolam (3.0 to 4.0 mg/kg) or propofol (1.5 to 2.5 mg/kg) was used for induction, followed by rocuronium (0.6 to 1.0 mg/kg) prior to endotracheal intubation. TIVA was conducted with continuous propofol infusion, maintained at 2.0 to 4.0 mg/kg/h, and no volatile agents were administered. Patients managed with VIA received either sevoflurane (1.0 to 2.5%) or desflurane (3.0 to 5.0%) for maintenance. In the majority of cases of both TIVA and VIA groups, 0.25 to 0.5 µg/kg/min remifentanyl was used in conjunction with the above agents.

Outcomes of interest were cancer-specific survival (CSS), overall survival (OS), and metastasis-free survival (MFS) after RNU. CSS was defined as the time from surgery until death due to cancer-related events, and OS was defined as the time from surgery until death due to any cause. Patients lost to follow-up were censored at the time of the last confirmed survival. MFS was defined as the time from surgery until detection of distant lymph node or organ metastasis. Patients with no radiological or clinical distal metastasis at final follow-up were censored. To control for baseline patient characteristics, 1:1 propensity score matching was carried out using the following variables: age at surgery, sex, Eastern Cooperative Oncology Group performance status score (≤ 1 or ≥ 2), Charlson Comorbidity Index score (≤ 2 or ≥ 3), site of cancer, tumor size, preoperative T-stage, surgical approach (open or retroperitoneoscopic), pathological T-stage, pathological N-stage (N0/Nx or N+), pathological tumor grade, pathological lymphovascular invasion, neoadjuvant chemotherapy, and adjuvant chemotherapy. CSS, OS, and MFS were compared between TIVA and VIA groups before and after matching. Perioperative complications observed within the first 3 months after surgery were recorded and graded using the Clavien-Dindo classification (15). Prevalence in events of any grade and high-grade (3 or higher) complications were analyzed.

Surgical procedures. RNU was performed either by open procedure or retroperitoneoscopic surgery in conjunction with open distal ureter and bladder cuff removal (RRNU) based on textbook procedures (16). Whether to perform open RNU or RRNU was determined by the operating surgical team based on the patient's comorbidity, surgical history, and preference. Complete regional lymphadenectomy (LND) was considered in all cases in accordance with our previous report emphasizing the therapeutic role of complete LND for cN0 UCUT (17) but was avoided in patients with severe comorbidities. The pattern for regional LND was described previously (18).

Neoadjuvant and adjuvant chemotherapy. Neoadjuvant chemotherapy was considered when it was possible to schedule surgery only after 1 month. Adjuvant chemotherapy was considered when LN metastasis

or local invasion was confirmed in the postoperative specimen. Final decisions were made considering the patient's performance status, renal function, comorbidities, and preferences. All chemotherapy regimens were based on either cisplatin or carboplatin.

Statistical analyses. Continuous variables were analyzed using the Mann-Whitney *U*-test and categorical variables using the chi-square test or Fisher's exact test with 95% confidence intervals (CI). We used multivariable logistic regression analysis to calculate propensity scores, and matching was carried out using the nearest method with a caliper of 0.20. Both before and after matching, CSS, OS, and MFS were estimated using the Kaplan-Meier method and compared using the log-rank test. All analyses were performed using JMP software (version 14.0; SAS Institute, Cary, NC, USA), and differences were considered statistically significant at $p < 0.05$.

Results

Patient characteristics. Patient characteristics are summarized in Table I. Before matching, 90 (45.7%) and 107 (54.3%) patients were included in the TIVA and VIA groups, respectively. There were no significant differences in baseline distribution of age, sex, Eastern Cooperative Oncology Group performance status score, site of cancer, surgical approach, or regional LND performed (all $p > 0.05$). More patients in the TIVA group had a Charlson Comorbidity Index ≥ 3 (83.3 vs. 79.4%, $p = 0.484$) which did not reach significance. Pathological features including pT-stage, tumor grade, and lymphovascular invasion were comparable between the two study groups, whereas pN stage was worse in the VIA group (pN+: 5.6 vs. 15.0%, $p = 0.029$). The percentages of patients who received either neoadjuvant chemotherapy (4.4 vs. 10.3%, $p = 0.116$) or adjuvant chemotherapy (4.4 vs. 9.3%, $p = 0.174$) were both higher in the VIA group, but this did not reach statistical significance. The follow-up period was significantly longer in the TIVA group by approximately 4 months (median 30.4 vs. 25.6 months, $p = 0.022$).

After propensity score matching, the TIVA and VIA groups comprised 70 patients each. All baseline characteristics were comparable between the two groups, including the follow-up period (all $p > 0.05$).

Impact of the anesthetic technique on CSS, OS, and MFS before and after matching. The Kaplan-Meier curves of CSS, OS, and MFS based on the complete LND status before matching are shown in Figure 1. For CSS [hazard ratio (HR)=0.70, 95% CI=0.33-1.42, $p = 0.323$], OS (HR=0.75, 95% CI=0.41-1.36, $p = 0.352$), and MFS (HR=0.78, 95% CI=0.46-1.31, $p = 0.354$), no significant differences were observed between TIVA and VIA. Furthermore, all three outcome parameters were comparable in the matched cohort of patients, with HR being 1.21 (95% CI=0.45-3.39, $p = 0.702$) for CSS, 0.82 (95% CI=0.38-1.76, $p = 0.604$) for OS, and 0.84 (95% CI=0.43-1.61, $p = 0.588$) for MFS (Figure 2).

Table I. Patient characteristics before and after propensity score matching.

Variable		Before matching			After matching		
		TIVA (n=90)	VIA (n=107)	p-Value	TIVA (n=70)	VIA (n=70)	p-Value
Age at surgery, years	Median (IQR)	75.9 (66.7-80.6)	76.0 (69.0-82.2)	0.319	76.1 (68.2-81.2)	74.2 (68.7-81.5)	0.650
Gender, n (%)	Male	56 (62.2)	73 (68.2)	0.378	46 (65.7)	45 (64.3)	0.859
ECOG-PS score, n (%)	≤1	88 (97.8)	105 (98.1)	0.861	68 (97.1)	69 (98.6)	>0.999
Charlson Comorbidity	≥3	75 (83.3)	85 (79.4)	0.484	59 (84.3)	58 (82.9)	>0.999
Index score, n (%)							
Site of cancer, n (%)	Pelvis	54 (60.0)	63 (58.9)	0.873	43 (61.4)	40 (57.1)	0.606
Tumor size on preoperative imaging, n (%)	<1 cm	3 (3.3)	6 (5.6)	0.208	3 (4.3)	4 (5.7)	0.774
	1-3 cm	33 (36.7)	50 (46.7)		27 (38.6)	30 (42.9)	
	>3 cm	54 (60.0)	51 (47.7)		40 (57.1)	36 (51.4)	
Preoperative T stage, n (%)	≤T1	16 (17.8)	15 (14.0)	0.234	11 (15.7)	12 (17.1)	0.872
	T2	47 (52.2)	64 (59.8)		43 (61.4)	39 (55.7)	
	T3	26 (28.9)	23 (21.5)		15 (21.4)	17 (24.3)	
	T4	1 (1.1)	5 (4.7)		1 (1.4)	2 (2.9)	
Type of surgery, n (%)	Open	68 (75.6)	77 (72.0)	0.568	52 (74.3)	51 (72.9)	0.848
LND, n (%)	Yes	45 (50.0)	58 (54.2)	0.556	34 (48.6)	40 (57.1)	0.309
Pathological T stage, n (%)	≤T1	28 (31.1)	43 (40.2)	0.511	28 (40.0)	26 (37.1)	0.510
	T2	19 (21.1)	23 (21.5)		17 (24.3)	19 (27.1)	
	T3	37 (41.1)	34 (31.8)		24 (34.3)	21 (30.0)	
	T4	6 (6.7)	7 (6.5)		1 (1.4)	4 (5.7)	
Pathological N stage, n (%)	pN0/Nx	85 (94.4)	91 (85.0)	0.029	66 (94.3)	66 (94.3)	>0.999
	pN+	5 (5.6)	16 (15.0)		5 (7.1)	5 (7.1)	
Pathological tumor grade, n (%)	High	71 (78.9)	80 (74.8)	0.495	54 (77.1)	55 (78.6)	0.839
Pathological lymphovascular invasion, n (%)	Positive	38 (42.2)	36 (33.6)	0.216	23 (32.9)	25 (35.7)	0.722
Neoadjuvant chemotherapy, n (%)	Yes	4 (4.4)	11 (10.3)	0.116	2 (2.9)	6 (8.6)	0.275
Adjuvant chemotherapy, n (%)	Yes	4 (4.4)	10 (9.3)	0.174	3 (4.3)	8 (11.4)	0.208
Distant recurrence or metastasis, n (%)	Yes	26 (28.9)	34 (31.8)	0.661	18 (25.7)	19 (27.1)	0.848
Died from cancer, n (%)	Yes	13 (14.4)	18 (16.8)	0.647	9 (12.9)	7 (10.0)	0.791
Died from any cause, n (%)	Yes	20 (22.2)	25 (23.4)	0.849	13 (18.6)	14 (20.0)	0.830
Follow-up period, months	Median (IQR)	30.4 (17.8-66.7)	25.6 (14.4-41.0)	0.022	32.3 (18.5-71.3)	31.8 (15.8-47.3)	0.235

ECOG-PS: Eastern Cooperative Oncology Group performance status; IQR: interquartile range; LND: lymphadenectomy; TIVA: total intravenous anesthesia; VIA: volatile inhalation anesthesia.

Figure 1. Impact of anesthetic technique on cancer-specific survival (CSS), overall survival (OS), and metastasis-free survival (MFS) before propensity score matching. HR: Hazard ratio; TIVA: total intravenous anesthesia; VIA: volatile inhalation anesthesia.

Figure 2. Impact of anesthetic technique on cancer-specific survival (CSS), overall survival (OS), and metastasis-free survival (MFS) after propensity score matching. HR: Hazard ratio; TIVA: total intravenous anesthesia; VIA: volatile inhalation anesthesia.

Table II. Perioperative outcomes before and after propensity score matching.

		Before matching			After matching		
		TIVA (n=90)	VIA (n=107)	p-Value	TIVA (n=70)	VIA (n=70)	p-Value
Surgical time, min	Median (range)	236.0 (205.8-288.5)	260.0 (215.0-305.0)	0.103	236.0 (205.8-303.0)	259.0 (212.0-298.3)	0.366
EBL, ml	Median (range)	150.0 (50.0-295.5)	160.0 (65.0-380.0)	0.158	150.0 (50.0-302.5)	186.5 (77.3-352.5)	0.166
Perioperative complications, n (%)	Any grade	16 (17.8)	14 (13.1)	0.362	14 (19.7)	9 (12.9)	0.362
	CDC grade ≥ 3	2 (2.2)	3 (2.8)	>0.999	1 (1.4)	2 (2.9)	>0.999
Hospital stay, days	Median (range)	7.0 (6.0-9.0)	8.0 (7.0-10.0)	0.115	8.0 (6.0-9.0)	8.0 (6.8-9.3)	0.703

CDC: Clavien-Dindo classification; EBL: estimated blood loss; TIVA: total intravenous anesthesia; VIA: volatile inhalation anesthesia.

Other perioperative outcomes according to the anesthetic technique. Both surgical time [median (range) of 236.0 (205.8-288.5) vs. 260.0 (215.0-305.0) min, $p=0.103$] and estimated blood loss during surgery [median (range) of 150.0 (50.3-295.5) vs. 160.0 (65.0-380.0) ml, $p=0.158$] tended to be higher for patients of the VIA group but without significant difference before matching. After matching, the results were again comparable between the study groups for both surgical time [median (range) of 236.0 (205.8-303.0) vs. 259.0 (212.0-298.3) min] and estimated blood loss [median (range) of 150.0 (50.0-302.5) vs. 186.5 (77.3-352.5) ml] without reaching significance (both $p>0.05$). The incidences of perioperative complications were not significantly different between TIVA and VIA groups both before (17.8 vs. 13.1%, $p=0.362$) and after (19.7 vs. 12.9%, $p=0.362$) matching. The occurrence of high-grade complications also did not significantly differ between the two groups before (2.2 vs. 2.8%, $p>0.999$) and after (1.4 vs. 2.9%, $p>0.999$) matching. The numbers of days of hospital stay were comparable between the two groups both before [median (range) of 7.0 (6.0-9.0) vs. 8.0 (7.0-10.0)] and after [median (range) of 8.0 (6.0-9.0) vs. 8.0 (6.8-9.3)] matching (both $p>0.05$; Table II).

Discussion

In the present study, CSS, OS, and MFS after RNU did not significantly differ according to the type of anesthetic technique. The differences were further reduced in the propensity score-matched cohort.

Locoregional or distant recurrence after RNU is not rare and has a high mortality rate once occurred, with limited systemic therapy options available (14). Factors contributing to recurrence are complex and multifocal but include tissue damage, subsequent tumor cell release into the systemic circulation, inflammation, and immune response (19, 20). The association between anesthetics and oncological outcomes such as recurrence after surgery, which has been gaining attention, is considered to be linked to such mechanisms. Propofol, a mainstay drug in TIVA, is thought to have anti-inflammatory or antitumor properties through multiple pathways such as preserving natural killer cell function (11), up-regulating interferon-gamma, or inhibiting HIF1 α activation or nuclear factor-kB (21). On the other hand, volatile agents have been suggested to disrupt or modulate cells of the immune system, such as neutrophils, lymphocytes,

and natural killer cells (4), and to help promote tumor cell proliferation by up-regulating HIF1 α and phosphoinositide 3-kinase–AKT serine/threonine kinase 1 pathway (3).

Based on theories which were derived from experimental studies, the assumption that TIVA is superior to VIA regarding cancer control has been made, and clinical studies have been conducted to clarify this question. The results, however, remain conflicting. A meta-analysis of studies that looked into surgery for breast, lung, and esophageal cancer showed that TIVA is associated with better RFS (22). A large propensity score-matched study based on a Danish database that focused on colorectal cancer surgery showed minimal RFS as well as no OS benefit in TIVA (23). A large-scale Japanese database study on digestive tract cancer failed to demonstrate a benefit from either anesthetic technique for both recurrence and survival (10). Two retrospective studies report the superiority of TIVA to VIA in terms of distant recurrence in UC but not in OS for robotic radical cystectomy (*i.e.*, bladder cancer) (13, 24). The results of the present study, which focused solely on UCUT, are not in line with these findings, as we failed to show the superiority of TIVA over VIA, not only for CSS and OS but also for RFS. There are several explanations for this inconsistent observation. Firstly, UCUT is more challenging than UC of the bladder in terms of accurate staging, adjuvant chemotherapy, and lymphadenectomy (25). Variability in these clinical parameters may have had an impact on recurrence. Additionally, the surgical time required for RNU is generally shorter than radical cystectomy, partly because urinary diversion can be omitted. The longer a surgical procedure lasts, the higher the total anesthetic dose administered to the patient. Thus, it can be argued that UCUT and UC of the bladder are alike but disparate, and the impact of the anesthetic technique may, therefore, differ between them.

One strength of our study is its design to match every possible patient and tumor characteristic, substantially minimizing selection bias. Detailed pathological data (lymphovascular invasion, margin status, tumor grade, *etc.*) are often limited in or missing from large-scale population analyses. Although Pfail *et al.* utilized multivariate analysis to demonstrate the independence of the anesthetic type as a predictor of RFS, not all factors were considered as variables (13). Moreover, considering the highly lethal and incurable potential of metastatic UC, results showing benefit in RFS while comparable OS raise the question of adequate follow-up (26, 27). As in our study detailed follow-up information including cause of death was available, we were able to provide CSS data, which were not included in previous reports, in addition to OS. In any case, based on both our current results and prior conflicting data, we propose that there is no clear rationale for choosing TIVA over VIA in anticipation of better cancer control. Each anesthetic

modality has specific benefits, such as accessibility, prevention of postoperative nausea/vomiting, or costs, and decisions should be made on such a basis (28, 29).

The limitations of our study are primarily attributed to its retrospective nature. Secondly, the limited number of patients may raise questions about the statistical power of the study. Thirdly, the reasons why anesthesiologists chose TIVA or VIA for a specific patient were not elucidated by the medical chart review; this may have introduced potential selection bias even though propensity score matching was applied. Future prospective studies with larger patient cohorts are needed to address these issues, as well as to confirm our results.

Conclusion

No apparent advantage in survival for TIVA was observed after RNU for localized UCUT compared to VIA when patients were matched for background characteristics. Further prospective trials are warranted to clarify if anesthetics have an impact on outcomes of UC management.

Conflicts of Interest

The Authors have no conflicts of interest to declare.

Authors' Contributions

Yudai Ishiyama: Study concept and design; acquisition, analysis, and interpretation of data; manuscript preparation. Tsunenori Kondo: Study concept and design; analysis and interpretation of data; article editing. Hidekazu Tachibana: Article review. Hiroki Ishihara: Article review. Haruka Ito Nishioki: acquisition of data and article review. Kazuhiko Yoshida: Article review. Kazunari Tanabe: Article review. Junpei Iizuka: Article review. Toshio Takagi: Article editing and review.

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