10-1-2022

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Alexander P. Kenigsberg

Gianpaolo Carpinito

Samuel A. Gold

Xiaosong Meng

Alireza Ghoreifi

See next page for additional authors

Recommended Citation

Kenigsberg AP, Carpinito G, Gold SA, Meng X, Ghoreifi A, Djaladat H, Minervini A, Jamil M, Abdollah F, Farrow JM, Sundaram C, Uzzo R, Ferro M, Meagher M, Derweesh I, Wu Z, Porter J, Katims A, Mehrazin R, Mottrie A, Simone G, Reese AC, Eun DD, Bhattu AS, Gonzalgo ML, Carbonara U, Autorino R, and Margulis V. Practice trends for perioperative intravesical chemotherapy in upper tract urothelial carcinoma: Low but increasing utilization during minimally invasive nephroureterectomy. Urol Oncol 2022.

Authors

Alexander P. Kenigsberg, Gianpaolo Carpinito, Samuel A. Gold, Xiaosong Meng, Alireza Ghoreifi, Hooman Djaladat, Andrea Minervini, Marcus Jamil, Firas Abdollah, Jason M. Farrow, Chandru Sundaram, Robert Uzzo, Matteo Ferro, Margaret Meagher, Ithaar Derweesh, Zhenjie Wu, James Porter, Andrew Katims, Reza Mehrazin, Alex Mottrie, Giuseppe Simone, Adam C. Reese, Daniel D. Eun, Amit Satish Bhattu, Mark L. Gonzalgo, Umberto Carbonara, Riccardo Autorino, and Vitaly Margulis

Urologic Oncology: Seminars and Original Investigations 40 (2022) 452.e17–452.e23

UROLOGIC ONCOLOGY

Clinical-Bladder cancer

Practice trends for perioperative intravesical chemotherapy in upper tract urothelial carcinoma: Low but increasing utilization during minimally invasive nephroureterectomy

Alexander P. Kenigsberg, M.D.[a], Gianpaolo Carpinito, M.D.[a], Samuel A. Gold, M.D.[a], Xiaosong Meng, M.D., Ph.D.[a], Alireza Ghoreifi, M.D.[b], Hooman Djaladat, M.D.[b], Andrea Minervini, M.D., Ph.D.[c], Marcus Jamil, M.D.[d], Firas Abdollah, M.D.[d], Jason M. Farrow, M.D.[e], Chandru Sundaram, M.D.[e], Robert Uzzo[f], Matteo Ferro, M.D., Ph.D.[g], Margaret Meagher, M.D.[h], Ithaar Derweesh, M.D.[h], Zhenjie Wu, M.D.[i], James Porter, M.D.[j], Andrew Katims, M.D.[k], Reza Mehrazin, M.D.[k], Alex Mottrie, M.D.[l], Giuseppe Simone, M.D.[m], Adam C. Reese, M.D.[n], Daniel D. Eun, M.D.[n], Amit Satish Bhattu, M.D.[o], Mark L. Gonzalgo, M.D., Ph.D.[o], Umberto Carbonara, M.D.[p], Riccardo Autorino, M.D., Ph.D.[p], Vitaly Margulis, M.D.[a,*]

[a] *Department of Urology, University of Texas Southwestern Medical Center, Dallas, TX*
[b] *Institute of Urology & Catherine and Joseph Aresty Department of Urology, Keck School of Medicine, University of Southern California, Los Angeles, CA*
[c] *Unit of Oncologic Minimally-Invasive Urology and Andrology, Department of Experimental and Clinical Medicine, University of Florence, Careggi Hospital, Florence, Italy*
[d] *Vattikuti Urology Institute, Henry Ford Hospital, Detroit, MI*
[e] *Department of Urology, Indiana University School of Medicine, Indianapolis, IN*
[f] *Division of Urologic Oncology, Department of Surgical Oncology, Fox Chase Cancer Center, Philadelphia, PA, USA*
[g] *Division of Urology, IRCCS European Institute of Oncology, Milan, Italy*
[h] *Department of Urology, UCSD School of Medicine, La Jolla, CA*
[i] *Department of Urology, Changzheng Hospital, Second Military (Naval) Medical University, Shanghai, China*
[j] *Swedish Urology Group, Seattle, WA*
[k] *Department of Urology, Icahn School of Medicine at Mount Sinai, New York, NY*
[l] *Department of Urology, Onze Lieve Vrouw Hospital, Aalst, Belgium*
[m] *Department of Urology, IRCCS Regina Elena National Cancer Institute, Rome, Italy*
[n] *Department of Urology, Lewis Katz School of Medicine at Temple University, Philadelphia, PA*
[o] *Desai Sethi Urology Institute, University of Miami Miller School of Medicine, Miami, FL*
[p] *Division of Urology and Massey Cancer Center, VCU Health System, Richmond, VA*

Received 20 December 2021; received in revised form 3 June 2022; accepted 12 June 2022

Abstract

Introduction: Perioperative intravesical chemotherapy (IVC) at or around the time of radical nephroureterectomy (RNU) reduces the risk of intravesical recurrence. Guidelines since 2013 have recommended its use. The objective of this study is to examine IVC utilization and determine predictors of its administration within a large international consortium.

Methods and materials: Data was collected from 17 academic centers on patients who underwent robotic/laparoscopic RNU between 2006 and 2020. Patients who underwent concomitant radical cystectomy and cases in which IVC administration details were unknown were excluded. Univariate and multivariate analyses were utilized to determine predictors of IVC administration. A Joinpoint regression was performed to evaluate utilization by year.

*Corresponding author. Tel.: 214-645-8765; fax: 214-648-8786.
E-mail address: vitaly.margulis@utsouthwestern.edu (V. Margulis).

https://doi.org/10.1016/j.urolonc.2022.06.006

Results: Six hundred and fifty-nine patients were included. A total of 512 (78%) did not receive IVC while 147 (22%) did. Non-IVC patients were older ($P < 0.001$), had higher ECOG scores ($P = 0.003$), and had more multifocal disease (23% vs. 12%, $P = 0.005$). Those in the IVC group were more likely to have higher clinical T stage disease ($P = 0.008$), undergone laparoscopic RNU (83% vs. 68%, $P < 0.001$), undergone endoscopic management of the bladder cuff (20% vs. 4%, $P = 0.008$). Multivariable regression showed that decreased age (OR 0.940, $P < 0.001$), laparoscopic approach (OR 2.403, $P = 0.008$), and endoscopic management of the bladder cuff (OR 7.619, $P < 0.001$) were significant predictors favoring IVC administration. Treatment at a European center was associated with lower IVC use (OR 0.278, $P = 0.018$). Overall utilization of IVC after the 2013 European Association of Urology (EAU) guideline was 24% vs. 0% prior to 2013 ($P < 0.001$). Limitations include limited data regarding IVC timing/agent and inclusion of minimally invasive RNU patients only.

Conclusions: While IVC use has increased since being added to the EAU UTUC guidelines, its use remains low at academic centers, particularly within Europe.

Keywords: Upper tract urothelial carcinoma; Intravesical chemotherapy; Nephroureterectomy; Practice trends

1. Introduction

Intravesical recurrence of urothelial cell carcinoma (UCC) occurs in 22% to 47% of patients with upper tract urothelial carcinoma [1]. Multiple mechanisms of pathogenesis have been proposed. Evidence of monoclonal mutations possessed by both the upper tract and metachronous bladder cancers suggest that individual cells from the primary tumor may seed additional foci [2–4]. Additional observations may further suggest that surgical manipulation directly disrupts the primary tumor, leading to lower tract seeding [5,6]. Some evidence additionally supports that certain surgical techniques may impart a higher risk of intravesical recurrence [7,8]. On the other hand, conflicting evidence of oligoclonal metachronous bladder tumors supports a pathogenesis related to long-term, whole field exposure to carcinogenic agents [9,10]. More recent evidence has suggested that both proposed mechanisms are likely at play [11].

Due to the apparently linked pathogenesis between upper tract urothelial carcinoma and intravesical recurrence, a number of studies have investigated the use of intravesical chemotherapy in the post radical-nephroureterectomy (RNU) setting. ODMIT-C, a prospective, multicenter randomized control trial demonstrated an 11% absolute risk reduction and 40% relative risk reduction with a single postoperative dose of intravesical mitomycin C following nephroureterectomy [12]. Ito et al. similarly demonstrated an effect on bladder recurrence with single-dose intravesical pirarubicin and found the absolute risk reduction to be even greater at 2 years after RNU (17% at 1 year, 25% at 2 years) [13].

The 2013 European Association of Urology (EAU) guidelines introduced single-dose postoperative instillation of intravesical chemotherapy as a level B recommendation [14] and this recommendation remains in the present-day EAU guidelines (now as level 1 recommendation), with the highest level of evidence of any of the management guidelines. This recommendation was subsequently added to the National Comprehensive Cancer Network guidelines in 2017 [15]. Little is known about utilization patterns of perioperative single-dose intravesical chemotherapy and its utilization has been proposed as a quality metric for high-quality UTUC care [16].

Given level-1 data supporting efficacy of this treatment, we sought to better define practice patterns around its use.

2. Methods and materials

The ROBUUST collaborative is a shared database among 17 tertiary care hospitals worldwide (10 United States, 4 Europe, 2 Asia) including patients who underwent minimally invasive (robotic or laparoscopic) RNU between 2006 and 2020. Demographic, pathologic, surgical, and follow-up data are included in the dataset.

Patients with prior or concomitant cystectomy were excluded. Those with unknown information regarding perioperative IVC treatment were also excluded from analysis.

Univariate analysis was performed to detect differences between those who did not receive IVC treatment and those who did. Use of IVC was tabulated across study years. A multivariable logistic regression was conducted to evaluate for predictors of receipt of IVC. SPSS version 25 (IBM Corporation, Armonk, NY) was utilized for statistical analysis with the significance set at $P < 0.05$. A Joinpoint regression analysis using Joinpoint Trend Analysis Software Version 4.9.0.0 (National Cancer Institute, Bethesda, MD).

3. Results

Eight hundred seventy patients underwent minimally invasive RNU and were included in the dataset. A total 40 of these patients underwent prior cystectomy and an additional 89 received concomitant cystectomy. Eighty-two did not have data available regarding intravesical chemotherapy treatment. Overall, 659 patients were included in our analysis. Baseline characteristics are shown on Table 1.

Among the 659, 512 (78%) did not receive IVC, while 147 (22%) did. Patients in the non-IVC group were older, 71.6 vs. 67.9 ($P < 0.001$). Non-IVC patients were also noted to be less healthy, with 63% being ECOG 3 vs. 47% in the IVC group ($P = 0.003$). They were also more likely to have multifocal disease (23% vs. 12%, $P = 0.005$). Those

Table 1
Baseline characteristics

		$n = 659$	
	No IVC	IVC	P[a]
n	512	147	
Age	71.6	67.9	**<0.001**
Gender			
Male	330 (64.5)	94 (63.9)	0.910
Female	182 (35.5)	53 (36.1)	
Race			
Caucasian	338 (75.4)	77 (53.1)	**<0.001**
Black	28 (6.3)	5 (3.4)	
Hispanic	23 (5.1)	12 (8.3)	
Asian	48 (10.7)	49 (33.8)	
Other	11 (2.5)	2 (1.4)	
BMI	27.3	27.4	0.823
ECOG			
1	15 (3.4)	7 (4.9)	**0.003**
2	150 (33.6)	69 (48.3)	
3	282 (63.1)	67 (46.9)	
cT			
Ta/T1	279 (72.7)	77 (60.2)	**0.008**
T2-T4	105 (27.3)	51 (39.8)	
Multifocality			
No	381 (77.1)	129 (87.8)	**0.005**
Yes	113 (22.9)	18 (12.2)	
Prior ureteroscopy			
No	155 (31.3)	35 (24.8)	0.141
Yes	341 (68.8)	106 (75.2)	
Neoadjuvant chemotherapy			
No	475 (92.8)	141 (95.9)	0.174
Yes	37 (7.2)	6 (4.1)	
Bladder cuff			
Excision	468 (96.1)	111 (79.9)	**<0.001**
Endoscopic	19 (3.9)	28 (20.1)	
Surgical approach			
Robotic	424 (82.8)	98 (67.6)	**<0.001**
Laparoscopic	74 (14.5)	47 (32.4)	
Robo/Lap converted	14 (2.7)	0 (0.0)	
Region			
USA	347 (78.7)	94 (21.3)	**<0.001**
Europe	133 (91.1)	13 (8.9)	
Asia	32 (44.4)	40 (55.6)	
Median length of stay (IQR)	4 (2-6)	4 (3-6)	0.722
30-d readmit			
No	482 (94.9)	140 (95.9)	0.619
Yes	26 (5.1)	6 (4.1)	

[a] Bold values denote statistical significance at the p < 0.05 level.

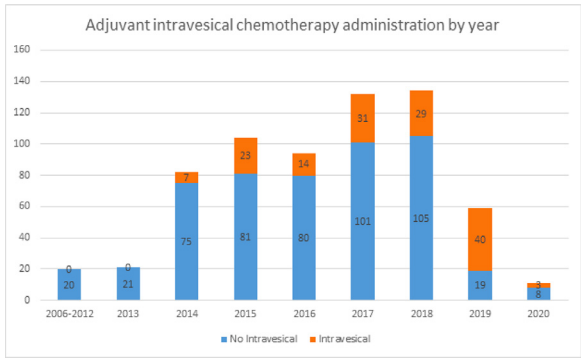

Fig. 1. Utilization of perioperative IVC over time.

who did not receive IVC were more likely to have undergone a robotic, rather than laparoscopic RNU (83% vs. 68%, $P < 0.001$). Patients in the IVC group were disproportionately likely to be Asian (34% vs. 11%, $P < 0.001$). Among those treated at US centers, 21% received IVC, as compared with 9% at European sites and 56% at Asian institutions ($P < 0.001$). Those who received IVC had higher clinical stage disease (40% cT2-4 vs. 27%, $P = 0.008$). Patients in the IVC group were more likely to have undergone endoscopic management of the bladder cuff than those in the non-IVC group (20% vs. 4%, $P < 0.001$). There were no significant differences between prior use of ureteroscopy or neoadjuvant chemotherapy between the IVC and non-IVC groups. There were also no differences between median length of stay or 30-day readmission rates between the groups.

The utilization of IVC is noted in Fig. 1. No patients received IVC prior to 2014. In 2014, 7/82 (9%) of patients received IVC. This increased to 23/104 (22%) in 2015, but again declined in 2016 to 15%. In 2017 31/132 (23%) received IVC and a roughly similar number 29/134 (22%) underwent this therapy in 2018. Incompletely collected data from 2019 indicates a possible uptick in utilization, 40/59 (68%). Joinpoint regression indicated a trend in annual growth of 8% between 2013 and 2019 ($P = 0.02$). There was noted to be variability in institutional usage of IVC, with a range of 0% utilization (7 centers) to 93% utilization at one center (mean 19.9%, standard deviation 31.8%). Only 3 centers reported usage with >50% of cases.

On multivariable analysis (Table 2), older age was associated with a lower utilization of IVC (OR 0.940, $P < 0.001$). The geographic location of the center was independently associated with IVC use, as those treated in European centers were less likely to receive IVC (OR 0.278, $P = 0.018$). The years 2014 to 2017 were associated with lower utilization of IVC relative to 2018 to 2020 (OR 0.547, $P = 0.025$). Laparoscopic approach was associated with receipt of IVC (OR 2.403, $P = 0.008$), as did endoscopic management of the bladder cuff (OR 7.619, $P < 0.001$). While not explicitly noted in Table 1, patients who underwent a laparoscopic RNU were far more likely to undergo endoscopic management of the bladder cuff than those who underwent robotic RNU (45% vs. 17%, $P < 0.001$). There was a trend toward decreased utilization of IVC among those who had received neoadjuvant chemotherapy (OR 0.320, $P = 0.072$).

4. Discussion

This study demonstrated low rates of utilization of perioperative intravesical chemotherapy at the time of RNU.

Table 2
Multivariable regression: predictors of IVC administration

	OR	95% CI	*P*
Age	0.940	0.913–0.967	**<0.001**
ECOG			
1	–	–	–
2	0.774	0.206–2.912	0.705
3	0.522	0.134–2.036	0.349
Race			
Caucasian	–	–	–
Black	0.499	0.121–2.054	0.335
Hispanic	1.251	0.434–3.610	0.678
Asian	1.722	0.532–5.577	0.365
Other	0.459	0.054–3.929	0.477
Surgery Year			
2018–2020	–	–	–
2014–2017	0.458	0.264–0.793	**0.005**
2006–2013	0.000	0.000	0.998
cT			
cTa/Tis/T1	–	–	–
cT2-4	0.729	0.365–1.455	0.370
Multifocal			
No	–	–	–
Yes	0.734	0.364–1.480	0.387
NAC			
No	–	–	–
Yes	0.320	0.092–1.107	0.072
Prior URS			
No	–	–	–
Yes	1.242	0.622–2.477	0.539
Region			
USA	–	–	–
Europe	0.278	0.096–0.804	**0.018**
Asia	1.522	0.393–5.893	0.543
Surgical approach			
Robotic	–	–	–
Laparoscopic	2.403	1.260–4.584	**0.008**
Robotic/Lap converted	0.000	0.000	0.999
Bladder cuff			
Excision	–	–	–
Endoscopic	7.619	3.530–16.445	**<0.001**

This is one of very few studies to examine utilization patterns of IVC from clinical data.

Across the centers that contribute to our aggregate data, the recorded administration rate of IVC after 2013 (when the EAU guidelines were updated) was 24%. This is markedly lower than the estimate of 51% acquired from self-report survey data from Lu et al. [17], although somewhat favorable relative to a survey of Japanese urologists, which estimated usage at 10.5% [18]. Utilization of IVC is surprisingly low considering the extent of its benefit. While its usage appears to be increasing given the annual trends, no completely reported year exceeded 25% utilization across the 17 sites. Further compounding this low utilization is the fact that these 17 sites are academic centers in which the evidence for IVC is theoretically better known than in the community setting. Further studies will be necessary to evaluate utilization of IVC outside of high-volume academic centers.

It is interesting to note that utilization of IVC is lower in European centers, relative to United States and Asian institutions. The reasons for this are somewhat unclear, given the EAU recommendations appear to be the catalyst for initiation of IVC use. ODMIT-C [12] was conducted across 46 centers in Great Britain and no British institutions, which may have had experience in the trial phase, are included in this multi-center analysis, potentially skewing the European numbers. It is difficult to assess whether there are healthcare system-specific factors hindering European centers from widespread adoption of IVC. Further investigations are needed to further evaluate the role of systemic barriers to IVC administration. It should be noted, however, that our understanding of regional disparities in IVC utilization is limited by institutional variability in usage. For example, one Asian center reported 93% utilization of IVC while another noted 0%. Therefore, some of the found regional differences may in fact be driven by institutional practices of participating centers rather than by geographic factors.

Among the entire cohort, the reason utilization rates lag may in large part pertain to concerns over extravasation of chemotherapeutic agents. Such leakage associated with the bladder cuff cystotomy is one of the more often discussed reasons why the treatment may be avoided [17]. While no increased length of stay or 30-day readmission rate was observed in our study with administration of IVC, there are reports in the bladder cancer literature that extravasation of chemotherapeutic agents may cause severe effects – including necrosis, inflammation, and ulceration of the bladder and surrounding tissue [19]. Also, given the relatively high ECOG scores of the patient population (no ECOG 0 patients included), perceived frailty in the context of perceived harms may have contributed to lower utilization of IVC.

That said, multiple studies in the non-muscle invasive bladder cancer literature for both gemcitabine and mitomycin C administration have demonstrated comparable rates of adverse events among those who receive perioperative intravesical chemotherapy and placebo [20,21]. Its use has also been demonstrated safe in the minimally invasive RNU setting [22]. Despite this favorable safety profile, utilization of postoperative IVC in the non-muscle invasive bladder cancer setting is also low [23,24].

Survey data in the UTUC setting indicated that some urologists avoided treatment on account of a theoretical risk of leak after RNU and extravasation of chemotherapy and 12% indicated that they did not use IVC for fear of overtreatment [17]. A perforation is notably a steadfast contraindication to IVC following transurethral resection of bladder tumor [25]. It is possible the risk of extravasation explains decreased utilization of IVC among older patients in our study, as they may be presumed less likely to heal a new cystotomy. The evidence, however, suggests that even in the setting of a RNU this concern is overstated. Moriarty et al. evaluated a cohort of 51 patients who received intraoperative IVC with mitomcyin C ($n = 48$) and adriamycin

($n = 3$), the majority of whom had an extravesical bladder cuff taken, and found that none of these patients had complications attributable to intravesical chemotherapy administration [26]. The ODMIT-C trial similarly reported no adverse events related to postoperative IVC administration and the majority of these patients had a formal bladder cuff excision [12].

Various administration approaches have been studied to see if alternate modes of administration with timing, toxicity, or cost-benefits could provide a path to more widespread use of the practice. Freifeld et al. examined intraoperative vs. postoperative administration of mitomycin C and gemcitabine and demonstrated the efficacy of intraoperative IVC, as well as the safety and efficacy of gemcitabine in this setting [27]. A currently-enrolling prospective trial is examining the use of intraoperative intravesical gemcitabine as well [28]. Studies from the non-muscle invasive bladder cancer literature have demonstrated a high level of efficacy and favorable safety profile for gemcitabine in preventing bladder recurrence of urothelial carcinoma, as well as a favorable cost relative to mitomycin C [20,29]. Other studies have questioned the need for chemotherapeutic agents at all. Yamamoto et al. investigated the use of intravesical sterile water continuous bladder irrigation at the time of nephroureterectomy and demonstrated a significant reduction in intravesical recurrence, consistent with previously reported improvements with postoperative IVC. It is possible that use of gemcitabine or sterile water, given reduced toxicity and cost relative to mitomycin C and pirarubicin, and intraoperative timing of IVC could increase utilization of IVC in the future. Due to limitations of multi-institutional data reporting, our study was unable to analyze the timing of IVC administration.

IVC use was noted to be increased among those who underwent laparoscopic, rather than robotic RNU. The clinical significance of this finding is unclear. Perhaps centers which preferentially perform laparoscopic RNU tend to also favor IVC use. It is possible that the increased receipt of IVC among those who underwent laparoscopic approach is related to the fact that significantly more patients who underwent the laparoscopic approach had endoscopic management of the bladder cuff, which was strongly associated with use of IVC. This is a logical association, as it makes sense that fears of IVC toxicity might be lowered without a fresh open cystotomy and given the logistical ease of instilling chemotherapy while already accessing the bladder in a retrograde fashion. Given recent analysis demonstrating increased intravesical recurrence with endoscopic management of the bladder cuff [30], it is clear that this approach to the bladder cuff is not the preferred management. Our findings merely indicate an association between the practice and IVC use.

One particular data trend in the multivariable analysis lends itself to interesting hypothesis generation. There was a trend toward decreased use of IVC in those who underwent neoadjuvant chemotherapy. ECOG 8141 demonstrated a 14% pathological complete response rate to neoadjuvant chemotherapy in UTUC, as well as significant downstaging of invasive disease [31]. It is possible that some practitioners believe the utility of IVC is decreased in the setting of systemic chemotherapeutic agent administration, particularly in light of level-1 evidence for administration of adjuvant systemic chemotherapy [32].

Our cohort includes only patients who underwent minimally invasive (laparoscopic or robotic) nephroureterectomy. Over the past decade, minimally invasive nephroureterectomy has become a more popular surgical approach to the treatment of UTUC [33,34]. Multiple studies have demonstrated oncologic comparability between open and minimally invasive techniques, although there is some debate about the optimal surgical approach in cases of higher stage disease [8,35,36]. Our study is unable to address the effect of a minimally invasive RNU relative to open RNU on IVC administration, due to its limited inclusion criteria.

This study does not attempt to evaluate rates of intravesical recurrence, as stratified by IVC usage. Multiple randomized-control trials have demonstrated the benefit of IVC use [12,13]. Given poorly matched IVC and non-IVC cohorts and the presence of numerous confounders, we felt that attempts to draw conclusions about the efficacy of IVC administration from these data would not yield clinically meaningful conclusions.

There are a number of other limitations to our study. Given the multi-institutional nature of the database, it is possible that non-reporting of IVC administration could bias the overall percentage of IVC administered, as some centers regularly utilize this practice, while others less so. Regardless, even if exclusions were not carried out and all excluded cases assumed to have used IVC, IVC use would remain lower than previously estimated values. Also, our study does not have the granularity to determine postoperative vs. intraoperative intravesical chemotherapy, so our findings represent a combination of those 2 interventions as "perioperative" IVC. While preliminary literature shows there may be some equivalence between these practices, high-level data demonstrating that is still pending. There is also no data on the choice of chemotherapeutic agent. Another limitation of our study is that certain study sties' practice patterns may skew our results. For example, certain sites in Asia had extremely high rates of IVC use. Therefore, it is possible that the observation that utilization was much higher in Asia than other regions may be a reflection of individual sites' practice patterns rather than true geographic differences.

5. Conclusions

Despite guideline recommendations and level 1 evidence, use of perioperative IVC at time of RNU remains lower than previously estimated. Use within European

centers is particularly low. Older patients are less likely to receive the intervention, despite limited demonstrated toxicity. Further studies are necessary to determine if alterations in timing of IVC or chemotherapeutic agent will provide equivalent oncologic efficacy and increased utilization of perioperative IVC.

Conflict of interest

The authors have no conflict of interest.

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