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Water Lavage as an Adjunct to Cytoreductive Surgery with Hyperthermic Intraperitoneal Chemotherapy (CRS-HIPEC)

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Abstract

Background—Water lavage (WL) during gastrointestinal cancer surgery has osmotically mediated lytic effects on tumor cells. We investigated the safety and efficacy of WL with CRS-HIPEC.

Methods—This is a retrospective review, 1/2003–7/2014, of a single institution experience with CRS-HIPEC comparing patients who had WL (WL+) to those who did not (WL–).

Results—Of 157 CRS-HIPECs, 16 (10.2%) were WL+. WL+ had more PCI scores > 20 compared to WL– (56.3% vs 19.4%, respectively, $p=0.003$); however, the completeness of cytoreduction (CC) was similar. There were no differences in hospital length of stay or post-operative complications. The average POD 1 sodium (Na) level was statistically lower in the WL+ group (133.6 ± 2.5 vs 135.5 ± 3.2 mEq/L, $p=0.023$); however, the average Na at discharge for each group was 140 mEq/L. There were no differences in 3-year OS (3WL+:0.63 vs WL–:0.68, $p=0.97$) or RFS (WL+:0.32 vs WL–:0.39, $p=0.47$). A subset analysis for patients with PCI > 20 showed no difference between groups.

Conclusions—WL offers a low cost, safe and theoretically efficacious method of tumor cell lysis for peritoneal malignancy.

Introduction

Peritoneal carcinomatosis can occur in a variety of malignancies, including those of gastrointestinal (GI) origin, the genitourinary (GU) tract and mesothelioma. It is estimated to

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Author contributions:

Drs. Gabriel, Fisher, VISIONI and Skitzki contributed to the study conception and design.

Drs. Gabriel, Singla, Kim and Powers acquired and interpreted the data, and Dr. Attwood performed the statistical analysis.

Drs. Gabriel, Powers, VISIONI and Attwood drafted the manuscript.

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affect up to 13–17 % of patients with GI malignancies.[1, 2] Current treatments include systemic chemotherapy and regional therapies, such as cytoreductive surgery with hyperthermic peritoneal chemotherapy (CRS-HIPEC). This treatment modality can be associated with significant peri-operative morbidity and typically requires the expertise found in high-volume performing institutions. While the oncologic benefits of CRS-HIPEC have been reported for certain malignancies, the majority of this data has been derived from retrospective studies.[3–6] The listing of CRS-HIPEC as investigational by the National Comprehensive Cancer Network (NCCN) is reflective of these limitations.[7] As such, additional therapies for carcinomatosis are strongly needed, which may potentially be used in conjunction with existing systemic and regional options.

The use of sterile water lavage (WL) has been proposed as a simple, cost-effective means to treat peritoneal tumor cells during surgical resection of the primary tumor, particularly in the setting of tumor spillage or rupture.[8, 9] There have been several preclinical studies, suggesting that WL may reduce the burden of peritoneal tumor cells, resulting in improved survival outcomes.[10, 11] However, others have reported no benefit of WL in preclinical models,[12–14] and there is little convincing clinical data to support the routine use of WL for peritoneal disease.[8, 15] An on-going, phase III clinic trial being conducted in Japan for locally advanced gastric cancer randomizes patients to WL versus no WL, and may prospectively address the survival benefit of WL in this setting.[16] However, the effects of WL when used in conjunction with CRS-HIPEC have not been previously reported, and may offer a potential benefit for patients with carcinomatosis from a variety of tumor histologies.

The simplicity of WL and its ease of use for any practicing surgeon highlight WL as an attractive option for patients with carcinomatosis. However, the safety of WL and its effects on post-operative electrolyte balance and complications has not been reported, specifically when combined with CRS-HIPEC. Therefore, the purpose of this study was to determine the safety of the addition of WL to CRS-HIPEC and its impact on oncologic outcomes. We hypothesized that WL would be clinically safe for patients undergoing CRS-HIPEC and offer improved survival outcomes compared to patients who did not have WL.

Methods

Patients

A retrospective review was performed of a prospectively maintained database containing all patients who had undergone CRS-HIPEC at Roswell Park Cancer Institute (RPCI) from January 2003 to June 2014. The study was reviewed and approved by the RPCI Institutional Review Board. Patients were divided into two cohorts, those who underwent water lavage (WL+) and those who did not (WL–). Variables analyzed included patient demographics, tumor characteristics, peri-operative outcomes, complications, other treatments such as systemic chemotherapy and survival outcomes, including recurrence-free survival (RFS) and overall survival (OS). Assessment of peritoneal disease burden was measured using the established peritoneal carcinomatosis index (PCI) score.[17] Similarly, assessment of resection was measured using the established completeness of cytoreduction (CC) score.[18]

To be considered for CRS-HIPEC at our institution, patients must have disease localized to the peritoneal cavity, no solid organ metastases and a baseline functional status of Eastern Cooperative Oncology Group (ECOG) 2. Procedures were performed by 3 faculty surgeons at RPCI during this time period. One of these surgeons began performing WL in 2009 and then routinely performed WL beginning in January of 2012.

The technique of CRS-HIPEC performed at our institution has been previously described. [19] In brief, prior to committing to CRS-HIPEC, inspection of the abdomen was performed through a mini-laparotomy to determine the feasibility of obtaining a CC of 0. Standard CRS for appropriate patients included both greater and lesser omentectomies, resection of the falciform ligament and ligamentum teres, resection of previous abdominal scars, and bilateral salpingo-oophorectomy (BSO) in female patients. Additional sites of gross disease were cytoreduced, including visceral resections and peritonectomies, or fulgurated with argon beam coagulation as indicated at the time of surgery. Following CRS, closed HIPEC was initiated.

For patients who underwent WL, 5–6 L of sterile, warm water was lavaged into the abdomen. This was performed by the assistant (resident or fellow) just prior to the saline lavage used to prime the circuit. As WL was performed while the HIPEC infusion circuit was being established and verified by the attending and the perfusionist, no additional time for WL was added to the procedure. Total time of WL was routinely and consistently between 15–20 minutes. The basis for this time period was formed from our preclinical mouse model of 15 minutes of WL.[10]

Following WL, 3 liters of a balanced saline solution were instilled into the peritoneum via the HIPEC circuit, and flow and warming commenced. When the inflow and outflow temperatures reached approximately 41°C, HIPEC was performed for 60–120 min. Within the last 5 years, the institutional trend for HIPEC duration has been 90 minutes. All patients received 30 mg of Mitomycin C (MMC). Gentle peritoneal shaking was performed to minimize apposition of internal contents (such as small bowel mesentery) on the inflow and outflow catheters and maximize distribution of chemotherapy. At the end of this period, for all patients (both those who underwent WL and those who did not) a lavage with 1 liter of normal saline was performed to remove the circulating mitomycin C. Reconstruction of any bowel anastomoses was then completed. All patients were transferred to either the intensive care unit (ICU) or intermediate care unit (IMCU) postoperatively.

Intraoperative and immediate post-operative serum laboratory tests are not routinely checked unless the patient has concerning signs or symptoms, such as hypotension or altered mental status. Post-operative day (POD) 1 labs included a basic metabolic panel (BMP) and complete blood count (CBC). A CBC is also routinely obtained on POD number 7 to assess for neutropenia.

Statistical Analysis

Patient demographics, tumor characteristics, peri-operative findings, and treatments were reported by cohort (WL+ and WL–) using the mean and standard deviations for continuous variables; frequencies and relative frequencies were used for categorical variables.

Comparisons were made using the Mann-Whitney U and Fisher's exact tests for continuous and categorical variables, respectively. Patient complications were reported by cohort using frequencies and relative frequencies, with complication rates compared using Fisher's exact test. The overall (OS) and recurrence-free (RFS) survival outcomes were summarized by cohort using standard Kaplan-Meier methods, where median survival and 1- and 3-year survival rates estimated with 95% confidence intervals. Comparisons of RFS and OS were made using the log-rank test. All analyses were conducted in SAS v9.4 (Cary, NC) at a significance level of 0.05.

Results

A total of 157 patients underwent CRS-HIPEC during the study period, 16 (10.2%) of whom had WL. Table 1 shows patient demographic and tumor factors by cohort. The groups were otherwise well matched with regard to age, comorbidities, tumor histologies, tumor grade, and pre-operative obstruction and perforation rates. The only difference found was a higher rate of hypertension in the WL+ group. Adenocarcinoma of appendiceal or colonic origin was the most common histology. The time from diagnosis of carcinomatosis to CRS-HIPEC was also similar.

Table 2 shows intra-operative and peri-operative outcomes. There were no intra-operative mortalities or mortalities within 30 days. There was a difference in the HIPEC duration with a higher percentage of patients in the WL+ group having 90 minutes of HIPEC, consistent with the trend toward 90 minute treatment during the latter part of the study period. There was no difference in overall OR time. There was a significant difference between the two cohorts with regard to the PCI score, with more significant burden of disease for WL+ (PCI > 20 was 9/16 or 56.3%) compared to WL- (PCI > 20 was 27/139 or 19.4%). The only other statistically significant finding was a difference in the mean post-operative day (POD) 1 serum sodium (Na) level, whereby the WL+ group had a lower average POD 1 Na (135.5 mEq/L vs 133.6 mEq/L in the WL- group). However, this difference was not considered clinically significant. There was no difference in requiring additional CRS-HIPEC.

Figure 1 shows the RFS (A) and OS (B) for each cohort. The overall median follow-up was 41.4 months (mo). The median follow-up periods for the WL+ group and the WL- group were 30.0 mo (range, 3.6–69.2) and 50.1 mo (range, 0.7–114.6), respectively. There were no statistically significant differences in either RFS or OS at 1 and 3 years. The 1-year RFS for WL+ was 0.56 (95% CI 0.29–0.76) and 0.61 (95% CI 0.52–0.69) for WL-. The 3-year RFS for WL+ was 0.32 (95% CI 0.11–0.56) and 0.39 (95% CI 0.31–0.48) for WL-. Regarding OS, the 1-year OS for WL+ was 0.86 (95% CI 0.54–0.96) and 0.87 (95% CI 0.80–0.92) for WL-, whereas the 3-year OS for WL+ was 0.63 (95% CI 0.26–0.85) and 0.68 (95% CI 0.58–0.76) for WL-.

Table 3 compares the rate of complications between the two cohorts. No significant differences were found with respect to overall complications, including infection, pulmonary, cardiac, renal or GI complications. There were also no differences with respect to requiring re-operation.

A subgroup analysis of WL+ versus WL– was performed among patients with PCI > 20. In the WL+ group, 9 patients had a PCI score > 20, while in the WL– group, 27 patients had a score > 20. There were no statistically significant differences in baseline characteristics (Supplemental Table 1). Similarly, there were no significant differences in RFS or OS (as shown in Figure 2).

Discussion

The concept of WL for osmotically-mediated lysis of tumor cells has been studied in a variety of models. However, the preclinical data for WL among different tumor histologies has been conflicting.[10, 12] There is limited clinical data supporting WL, with an absence of any evidence for its use in conjunction with CRS-HIPEC. The effect of WL on survival is a question that may be answered by the Japanese trial CCOG 1102,[16] although this would specifically apply in the setting of advanced gastric cancer in the absence of HIPEC. Thus, this study was the first to our knowledge to investigate the effects of WL on adverse events and oncologic outcomes for patients undergoing CRS-HIPEC for peritoneal disease from a wide array of tumor histologies. We performed this study to determine if WL provided benefit to survival outcomes for patients undergoing CRS-HIPEC and could be performed without added risk of adverse complications.

The relevance of effective therapies for carcinomatosis cannot be understated. The presence of tumor cells during lavage of GI cancers has been shown to portend a poor prognosis.[20–23] Thus, there exists a need for improved treatments that may be added to existing regional and systemic therapies. It is important to emphasize that this study did not show an added benefit of WL to RFS or OS. However, there was an important inherent bias within the WL+ group. These patients had a more severe disease burden as noted by their overall higher PCI score (Table 2). As such, the oncologic outcomes for the WL+ group would be expected to be poorer as compared to the WL– group. One may hypothesize that if the two groups were more balanced with respect to PCI score, then perhaps the WL+ group would have shown an improved survival outcome compared to the WL– group. However, we recognize that this current study is limited in the ability to draw this conclusion.

Numerous studies have characterized the variety of complications for which patients undergoing CRS-HIPEC are at risk.[24–26] These complications, in turn, have been shown to have significant impact on peri-operative mortality.[27] In addition to the burden of peritoneal disease, complications that arise from the treatment of carcinomatosis can also have significant impacts on oncologic outcomes. For example, a recent study by Simkens et al showed that having serious adverse reactions (SAEs) following CRS-HIPEC, such as anastomotic leak requiring intervention, was associated with a reduced RFS compared to patients who did not sustain SAEs (22.1 vs 31.0 months, respectively, $p=0.02$).[28] Similar evidence to suggest poorer outcomes has also been derived from colorectal cancer studies whereby patient readmission and hospital length of stay are associated with worse outcomes.[29, 30] The safety of WL on peri-operative outcomes, specifically when combined with CRS-HIPEC, has not been previously reported. Our findings provide the first evidence that the addition of copious WL with 5 or more liters of water did not result in an increased

complication rate compared to patients who did not undergo WL, showing that WL is a safe adjunct to CRS-HIPEC.

WL would be expected to have effects on electrolyte balance due to its osmotic effect across the peritoneal surfaces, theoretically drawing Na into the peritoneal cavity and potentially lowering the serum Na concentration. Indeed, this was observed in our study. However, the magnitude of this difference was not clinically relevant, as reflected by the similar proportion of neurologic complications (altered mental status, delirium) between the two groups. Furthermore, the Na level at discharge was equivalent for the two groups, showing that the Na typically returns to homeostatic values and that there were no long-term effects to serum Na levels from the addition of WL. It may be important to recognize this difference, however, for certain patient populations, such as those with renal disease who may be more sensitive to fluid and electrolyte shifts following CRS-HIPEC with WL.

We acknowledge that there are important limitations to this study. It is a single institution, retrospective review with a small number of patients within the WL+ cohort. Selection bias may have significant effect on our survival results. As previously discussed, the higher PCI score among the WL+ cohort limits the interpretation of the effect on RFS and OS. Furthermore, quantification of PCI may vary across the operating surgeons at our institution as this is a subjective measure. As the WL+ cases were performed by a single surgeon in the latter half of the study period, a learning curve with CRS-HIPEC may also have influenced outcomes. Approximately 40–50% of patients in either cohort had systemic chemotherapy prior to HIPEC, which may have impacted the PCI score gauged intra-operatively in relation to the initial PCI score at diagnosis. Thus, it is difficult to determine if PCI scoring at the time of surgery adequately incorporated the effect of systemic therapy and led to another selection bias favoring responders to systemic therapy who underwent CRS-HIPEC. Differences in the follow-up periods between the two groups also differed, with a shorter follow-up for patients in the WL+ group compared to the WL– group that could have confounded the survival analysis.

In spite of these limitations, this study offers the first evidence demonstrating the safety of WL when used in conjunction with CRS-HIPEC. WL is potentially a simple and cost-effective adjunct to CRS-HIPEC. Given our technique of performing WL for about 15–20 minutes while the HIPEC perfusion circuit is being established and verified, there is virtually no additional OR time due to WL. It is a straightforward option that could be employed by any surgeon. WL is safe and results in a clinically insignificant drop in serum Na. Indeed, our early results did not show a survival benefit, making this a negative study with regard to oncologic outcomes. However, continued prospective analysis of patients with better matched PCI scores may determine if WL improves long-term outcomes. Therefore, further prospective randomized study is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Dr. Emmanuel Gabriel and Dr. Joseph Skitzki had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Figure 1. Recurrence-free survival (RFS) and overall survival (OS) for patients by cohort. A shows the RFS for WL+ and WL-, and B shows the OS for WL+ and WL-. No statistically significant differences were observed.

Figure 2. RFS and OS for patients with PCI score > 20. A shows the RFS for WL+ and WL-, and B shows the OS for WL+ and WL-. No statistically significant differences were observed.

Patient and tumor characteristics by cohort, water lavage (WL+) versus no water lavage (WL-).

Table 1

	N	WL-	WL+	Overall	P-value
Overall		141 (89.8)	16 (10.2)	157 (100%)	
Age	Mean/Std ¹	52.03/12.88	55.06/9.32	52.34/12.58	0.50
Gender	Male	58 (41.1%)	9 (56.3%)	67 (42.7%)	0.29
ECOG ²	0	82 (58.2%)	10 (62.5%)	92 (58.6%)	0.56
	1	45 (31.9%)	6 (37.5%)	51 (32.5%)	
	2	14 (9.9%)	0 (0.0%)	14 (8.9%)	
ASA ³	I	39 (27.7%)	2 (12.5%)	41 (26.1%)	0.43
	II	83 (58.9%)	12 (75.0%)	95 (60.5%)	
	III	19 (13.5%)	2 (12.5%)	21 (13.4%)	
BMI ⁴	Mean/Std	28.29/6.26	27.26/7.25	28.17/6.36	0.93
Previous Surgery	No	9 (6.4%)	1 (6.3%)	10 (6.4%)	1.00
	Yes	132 (93.6%)	15 (93.8%)	147 (93.6%)	
Diabetes	No	125 (88.7%)	12 (75.0%)	137 (87.3%)	0.13
	Yes	16 (11.3%)	4 (25.0%)	20 (12.7%)	
COPD ⁵	No	131 (92.9%)	15 (93.8%)	146 (93.0%)	1.00
	Yes	10 (7.1%)	1 (6.3%)	11 (7.0%)	
CHF ⁶	No	140 (99.3%)	16 (100.0%)	156 (99.4%)	1.00
	Yes	1 (0.7%)	0 (0.0%)	1 (0.6%)	
CAD ⁷	No	132 (93.6%)	16 (100.0%)	148 (94.3%)	0.60
	Yes	9 (6.4%)	0 (0.0%)	9 (5.7%)	
Hypertension	No	91 (64.5%)	5 (31.3%)	96 (61.1%)	0.014
	Yes	50 (35.5%)	11 (68.8%)	61 (38.9%)	
Stroke	No	137 (97.2%)	16 (100.0%)	153 (97.5%)	1.00
	Yes	4 (2.8%)	0 (0.0%)	4 (2.5%)	
Liver Disease	No	139 (98.6%)	16 (100.0%)	155 (98.7%)	1.00

Overall	N	WL-	WL+	Overall	P-value
Overall	141 (89.8)	16 (10.2)	157 (100%)		
Renal Failure	Yes	2 (1.4%)	0 (0.0%)	2 (1.3%)	
	No	139 (98.6%)	15 (93.8%)	154 (98.1%)	0.28
Ascites	Yes	2 (1.4%)	1 (6.3%)	3 (1.9%)	
	No	109 (77.3%)	10 (62.5%)	119 (75.8%)	0.22
	Yes	32 (22.7%)	6 (37.5%)	38 (24.2%)	
Obstruction	No	120 (85.1%)	14 (87.5%)	134 (85.4%)	1.000
	Yes	21 (14.9%)	2 (12.5%)	23 (14.6%)	
Perforation	No	123 (87.2%)	16 (100.0%)	139 (88.5%)	0.219
	Yes	18 (12.8%)	0 (0.0%)	18 (11.5%)	
Tumor Histology	Adenocarcinoma *	79 (56.0%)	11 (68.8%)	90 (57.3%)	0.54
	DPAM [§]	30 (21.3%)	3 (18.8%)	33 (21.0%)	
	Mesothelioma	17 (12.1%)	0 (0.0%)	17 (10.8%)	
	Other [‡]	15 (10.6%)	2 (12.5%)	17 (10.8%)	
Differentiation	Well	33 (27.3%)	3 (18.8%)	36 (26.3%)	0.84
	Moderate	57 (47.1%)	8 (50.0%)	65 (47.4%)	
	Poorly	31 (25.6%)	5 (31.3%)	36 (26.3%)	
Neoadjuvant Chemo	No	72 (51.1%)	9 (56.3%)	81 (51.6%)	0.80
	Yes	69 (48.9%)	7 (43.8%)	76 (48.4%)	
Adjuvant Chemo	No	105 (74.5%)	11 (68.8%)	116 (73.9%)	0.76
	Yes	36 (25.5%)	5 (31.3%)	41 (26.1%)	

¹ Std = standard deviation

² ECOG = Eastern Cooperative Oncology Group

³ ASA = American Society of Anesthesiologists

⁴ BMI = Body mass index

⁵ COPD = chronic obstructive pulmonary disease

⁶ CHF = congestive heart failure

⁷ Other histologies include ovarian, Fallopian tube and gastric adenocarcinoma

^{*} Adenocarcinoma of appendiceal or colonic origin

⁸ DPAM = Disseminated Peritoneal Adenomucinosis

⁷ CAD = coronary artery disease

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Table 2

Intra-operative and peri-operative characteristics of each cohort, WL- versus WL+.

	N	WL-	WL+	Overall	P-value
Overall		141 (89.8)	16 (10.2)	157 (100%)	
Nodes Examined	Mean/Std	12.98/14.00	14.50/12.33	13.10/13.84	0.54
Nodes Positive	Mean/Std	1.87/4.06	1.50/2.24	1.84/3.94	0.77
Organs Resected	0	27 (19.1%)	2 (12.5%)	29 (18.5%)	0.44
	1	47 (33.3%)	4 (25.0%)	51 (32.5%)	
	2	40 (28.4%)	4 (25.0%)	44 (28.0%)	
	3	27 (19.1%)	6 (37.5%)	33 (21.0%)	
GI Anastomoses	0	61 (43.3%)	5 (31.3%)	66 (42.0%)	0.65
	1	52 (36.9%)	7 (43.8%)	59 (37.6%)	
	2	23 (16.3%)	4 (25.0%)	27 (17.2%)	
	3	5 (3.5%)	0 (0.0%)	5 (3.2%)	
Ostomy	No	128 (90.8%)	15 (93.8%)	143 (91.1%)	1.00
	Yes	13 (9.2%)	1 (6.3%)	14 (8.9%)	
Complete Cytorreduction (CC)	No	43 (30.5%)	2 (12.5%)	45 (28.7%)	0.16
	Yes	98 (69.5%)	14 (87.5%)	112 (71.3%)	
PCI Score ¹	< 20	112 (80.6%)	7 (43.8%)	119 (76.8%)	0.003
	> 20	27 (19.4%)	9 (56.3%)	36 (23.2%)	
Time (months) Diagnosis to Surgery	Mean/Std	17.27/22.08	16.69/19.65	17.21/21.79	0.921
OR time (min)	Mean/Std	639.29/141.39	581.38/101.66	631.30/137.69	0.07
HIPEC Time	120 min	83 (58.9%)	3 (18.8%)	86 (54.8%)	0.003
	90 min	58 (41.1%)	13 (81.3%)	71 (45.2%)	
EBL ²	Mean/Std	311.74/315.78	340.63/249.14	314.68/309.09	0.16
ICU Stay ³	Mean/Std	1.89/2.30	3.19/4.55	2.02/2.63	0.18
Total Hospital LOS ⁴	Mean/Std	13.84/11.27	13.88/6.09	13.85/10.84	0.54
POD ⁵ 1 Sodium (Na)	Mean/Std	135.52/3.19	133.63/2.55	135.30/3.18	0.023

	WL−	WL+	Overall	P-value
Overall	141 (89.8)	16 (10.2)	157 (100%)	
Na at Discharge	Mean/Std	140.06/2.59	140.35/2.75	0.63
Reoperation	No	15 (93.8%)	140 (89.2%)	1.00
	Yes	1 (6.3%)	17 (10.8%)	
Another Cytoreduction	No	126 (90.6%)	142 (91.6%)	0.36
	Yes	13 (9.4%)	13 (8.4%)	

¹ pCI = Peritoneal Carcinomatosis Index

² EBL = estimated blood loss

³ ICU = intensive care unit

⁴ LOS = length of stay

⁵ POD = post-operative day

Table 3

Comparison of post-operative complications by cohort, WL– versus WL+.

		WL–	WL+	Overall	P-value
Overall	N	141 (89.8)	16 (10.2)	157 (100%)	
Surgical Site Infection	No	117 (83.0%)	13 (81.3%)	130 (82.8%)	0.74
	Yes	24 (17.0%)	3 (18.8%)	27 (17.2%)	
Pulmonary	No	133 (94.3%)	15 (93.8%)	148 (94.3%)	1.00
	Yes	8 (5.7%)	1 (6.3%)	9 (5.7%)	
Cardiac	No	137 (97.2%)	16 (100.0%)	153 (97.5%)	1.00
	Yes	4 (2.8%)	0 (0.0%)	4 (2.5%)	
Renal	No	137 (97.2%)	16 (100.0%)	153 (97.5%)	1.00
	Yes	4 (2.8%)	0 (0.0%)	4 (2.5%)	
Urinary Tract Infection	No	135 (95.7%)	15 (93.8%)	150 (95.5%)	0.54
	Yes	6 (4.3%)	1 (6.3%)	7 (4.5%)	
Venous Thromboembolism	No	134 (95.7%)	16 (100.0%)	150 (96.2%)	1.00
	Yes	6 (4.3%)	0 (0.0%)	6 (3.8%)	
GI	No	123 (87.2%)	15 (93.8%)	138 (87.9%)	0.70
	Yes	18 (12.8%)	1 (6.3%)	19 (12.1%)	
Hematologic	No	140 (99.3%)	16 (100.0%)	156 (99.4%)	1.00
	Yes	1 (0.7%)	0 (0.0%)	1 (0.6%)	
Neutropenia	No	127 (90.1%)	16 (100.0%)	143 (91.1%)	0.36
	Yes	14 (9.9%)	0 (0.0%)	14 (8.9%)	
Neurologic	No	136 (96.5%)	15 (93.8%)	151 (96.2%)	0.48
	Yes	5 (3.5%)	1 (6.3%)	6 (3.8%)	
Any Complication	No	77 (54.6%)	10 (62.5%)	87 (55.4%)	0.61
	Yes	64 (45.4%)	6 (37.5%)	70 (44.6%)	