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The impact on postoperative outcomes of intraoperative fluid management strategies during cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

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ABSTRACT

Background: The impact of intraoperative fluid management during cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) on postoperative outcomes has been poorly investigated. This study aimed to retrospectively evaluate the impact of intraoperative fluid management strategy on postoperative outcomes and survival.

Methods: 509 patients undergoing CRS and HIPEC at Uppsala University Hospital/Sweden 2004–2017 were categorized into two groups according to the intraoperative fluid management strategy: pre-goal directed therapy (pre-GDT) and goal directed therapy (GDT), where a hemodynamic monitor (CardioQ or FloTrac/Vigileo) was used to optimize fluid management. Impact on morbidity, postoperative hemorrhage, length-of-stay and survival was analyzed.

Results: The pre-GDT group received higher fluid volume compared to the GDT group (mean 19.9 vs. 16.2 ml/kg/h, $p < 0.001$). Overall postoperative morbidity Grade III-V was higher in the GDT group (30% vs. 22%, $p = 0.03$). Multivariable adjusted odds ratio (OR) for Grade III-V morbidity was 1.80 (95%CI 1.10 −3.10, $p = 0.02$) in the GDT group. Numerically, more cases of postoperative hemorrhage were found in the GDT group (9% vs. 5%, $p = 0.09$), but no correlation was observed in the multivariable analysis 1.37 (95%CI 0.64–2.95, $p = 0.40$). An oxaliplatin regimen was a significant risk factor for postoperative hemorrhage ($p = 0.03$). Mean length of stay was shorter in the GDT group (17 vs. 26 days, $p < 0.0001$). Survival did not differ between the groups.

Conclusion: While GDT increased the risk for postoperative morbidity, it was associated with shortened hospital stay. Intraoperative fluid management during CRS and HIPEC did not affect the postoperative risk for hemorrhage, while the use of an oxaliplatin regimen did.

Data availability statement

The dataset that supports the findings of this study is available from the corresponding author upon reasonable request. Data are not publicly available due to ethical restrictions.

1. Introduction

Intraoperative fluid management influences postoperative outcomes following major surgical procedures [1]. Previous experience in colorectal surgery is that intraoperative fluid restriction is associated with reduction in postoperative morbidity and length of hospital stay (LOS) as well as enhanced recovery of gastrointestinal function [2–4]. Although locoregional treatment of peritoneal surface malignancy (PM) with cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) results in promising macroscopic disease control [5,6], it has a major systemic impact with overall Clavien-Dindo Grade III-IV morbidity rates ranging from 12% to 52% [7,8]. CRS with HIPEC is a challenging procedure associated with increased capillary leak and major fluid shifts [9–11]. Replacement of these fluid losses is achieved through a combination of blood products and crystalloid/colloid solutions.

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Additionally, the duration of surgery, method of HIPEC delivery (open vs closed), and choice of drug use during HIPEC can also affect fluid management and the risk of postoperative morbidity. An example is the possible connection between oxaliplatin use in HIPEC and the risk of postoperative hemorrhage [12]. The influence of intraoperative administration of fluid and blood products during CRS and HIPEC on the postoperative morbidity rate has been poorly investigated. In 2013, goal-directed therapy (GDT) using a CardioQ device (Deltex Medical Ltd., Sussex, UK) was introduced at the Uppsala University Hospital for the management of CRS and HIPEC patients. Studies suggested that the GDT approach could minimize the risks associated with both hypovolemia (e.g. renal dysfunction) and hypervolemia (e.g. tissue edema) [10,13]. Eng et al. (2017) argued that the risk of complications was higher in patients receiving generous intraoperative fluid support compared to those receiving lesser amounts (31.5 ml/kg/h vs. 22.0 ml/kg/h, $p = 0.02$) [14]. The main aim of our study was to compare postoperative outcomes after CRS and HIPEC depending on the intraoperative fluid management strategy. The following four primary endpoints were selected: morbidity, postoperative hemorrhage, LOS and survival. In addition, the risk of postoperative hemorrhage depending on HIPEC regimen was also evaluated as a secondary endpoint.

2. Patients and methods

2.1. Study population criteria and group definition

Data were retrospectively retrieved from the HIPEC register at Uppsala University Hospital. Data were also collected from the hospital records for all fluid management variables. The main inclusion criterion was index HIPEC (first HIPEC) performed according to the Coliseum method. One patient was excluded due to early and unexpected in-hospital mortality (suicide on postoperative day four).

Patients were categorized into two groups according to intraoperative fluid management strategy. The first group included 328 patients (64%) treated with traditional intraoperative fluid administration in the pre-goal directed therapy (pre-GDT) era between November 2004 and December 2012. The second group comprised 181 patients (36%) treated with goal-directed therapy (GDT) between January 2013 and December 2017 (Table 1). Initially, GDT was monitored intraoperatively using an esophageal probe (CardioQ™, Deltex Medical Ltd., Sussex, UK) and, since early 2015, with the FloTrac/Vigileo (Edwards LifeSciences, Irvine, CA, USA). All surgical characteristics that might have an impact on the risk for postoperative bleeding were registered, such as duration of operation, volume of intraoperative blood loss, splenectomy, excision of liver capsula or liver resection, peritoneal cancer index (PCI) [15] and completeness of cytoreduction score (CCS) [15] as well as the use of different HIPEC regimens.

The study was approved by the Regional Ethics Board, in Uppsala, Sweden (reference no. 2013/203).

2.2. HIPEC regimens

Oxaliplatin (460 mg/m^2 for single use) ± irinotecan (360 mg/m^2 for both drugs) for 30 min at a mean intraabdominal temperature of 41.5 °C were used to treat primary tumors from colorectal and gastric cancers. These patients also received 5-fluorouracil intravenously at 400mg/m2 together with calcium folinate. Mitomycin C (35 mg/m^2) divided into 3 administrations for 90 min at a mean intraabdominal temperature of 41.5 °C was used to treat primary tumors from the appendix. Lastly, cisplatin ± doxorubicin (50 ± 15 mg/m^2) was used to treat patients with peritoneal mesothelioma, ovarian cancer and gastric cancer.

2.3. Intraoperative blood and fluid transfusions

Intraoperative fluids included blood, plasma, thrombocytes, colloids or crystalloids. Colloids included albumin (5% or 20%), hydroxyethyl starch (Voluven 60 mg/ml, Tetraspan 60 mg/ml). Crystalloids consisted of Ringer's acetate, sodium chloride solution (NaCl 0.9%) or glucose 5%. During the pre-GDT era of fluid management, fluid administration of 9–12 ml/kg/h was advocated to ensure a satisfactory urinary output of at least 1 ml/kg/h [4,5]. Urine output, and point-of-care blood gas measurements — lactate, base excess, and hemoglobin levels — were used to guide fluid administration. GDT treatment was monitored by intraoperative hemodynamic monitoring using the FloTrac/Vigileo device or esophageal echo-Doppler to predict the fluid responsiveness by dynamic preload parameters such as stroke volume variation (SVV) or aortic blood flow corrected flow time (FTc) [16] as a measure of intraoperative fluid replacement. Patients usually received crystalloid replacement (Ringer's acetate) 3–4 ml/kg/h. A bolus dosage of colloid (250 ml) was given if SVV >12%. Norepinephrine infusion was used to keep mean arterial pressure at ±20% from the baseline level or at least 65 mmHg. If cardiac output was deemed low by the attending anesthetist, dobutamine infusion was also started. Packed red blood cells (PRBC) were given when the transfusion limit was reached (hemoglobin value 75 g/L or lower), while plasma was given only if coagulopathy was suspected. GDT aimed to maintain intraoperative urine output of 1 ml/kg/h.

2.4. Endpoints

Postoperative morbidity was graded according to the Clavien-Dindo classification [17]. Postoperative hemorrhage was defined as a Clavien-Dindo ≥ Grade IIIa complication due to radiologically or intraoperatively proven intraabdominal hemorrhage. Length of stay was calculated from the date of surgery until discharge either to the patient's home or to a referring hospital. Discharge to referring hospital was used throughout the study period and was generally performed after 10 days uncomplicated postoperative period. Survival was defined as time between the date of surgery and date of death from any cause.

2.5. Statistics

Statistical analysis was performed using Statistica 64 software for Windows [Version 13.3, Dell Software, Round Rock, Texas, USA]. Descriptive statistics are presented as mean, percentage and range. Differences between groups were tested using the Mann-Whitney *U* test and Pearson Chi-square test. Survival analyses were done using Kaplan-Meier curves with log rank test.

Multivariable regression models were used to evaluate the adjusted risk differences between pre-GDT and GDT managements. For the endpoint of Clavien-Dindo morbidity Grade III-V, the following factors were used to adjust the odds ratio (OR) of the GDT group (vs pre-GDT group) in a logistical regression model: age, ASA score, primary tumor site (small intestine and gastric cancer were excluded due to few cases in both groups), neoadjuvant chemotherapy, PCI, CCS, as well as HIPEC regimen use. Likewise, the same variables were used in the multivariable Cox regression model for overall survival. The risk of postoperative hemorrhage was analyzed in uni- and multivariable logistics regression analysis, where univariate variables with a p-value <0.1 were included in the final multivariable analysis. OR or hazard ratios (HR) and corresponding 95% confidence intervals (CI) were calculated and statistical significance was defined at $p < 0.05$.

Table 1
General demographics and baseline characteristics.

Variables	The total Cohort (n = 509)	pre-GDT[a] (n = 328)	GDT (n = 181)	*p*-value
Date	Nov 2004–Dec 2017	Nov 2004–Dec 2012	Jan 2013–Dec 2017	N/A
Female:Male – n (%)	291 (57%): 218 (43%)	184 (56%): 144 (44%)	107 (59%): 74 (41%)	0.51
Age – mean (range)	56.8 (22–79)	55.4 (22–77)	59.4 (22–79)	0.0005
<40	56 (11%)	42 (13%)	14 (8%)	
40-69	373 (73%)	248 (76%)	125 (69%)	
≥70	80 (16%)	38 (11%)	42 (23%)	
BMI – mean (range)	26 (17–41)	26 (17–40)	26 (17–41)	0.46
Karnofsky performance score – n (%)				0.29
<90	31 (6%)	21 (6%)	10 (6%)	
≥90	478 (94%)	307 (94%)	171 (94%)	
Cardiovascular co-morbidity (hypertension and hyperlipidemia)	198 (39%)	110 (34%)	88 (49%)	0.06
Diabetes	41 (8%)	27 (8%)	14 (8%)	0.84
Hemorrhage predisposition (factor deficiency)	4 (0.7%)	3 (1%)	1 (0.5%)	0.65
Systemic neoadjuvant chemotherapy (within 3 months prior to surgery)	153 (30%)	91 (28%)	62 (34%)	0.001
Primary tumor site				0.71
Appendix	252 (49.5%)	178 (54%)	74 (41%)	
Colorectal	192 (37.7%)	96 (29%)	96 (53%)	
Gynecological	24 (4.7%)	21 (6%)	3 (2%)	
Mesothelioma	22 (4.3%)	18 (6%)	4 (2%)	
Small intestine	13 (2.5%)	9 (3%)	4 (2%)	
Gastric	6 (1.1%)	6 (2%)	0 (0%)	
Blood sampling upon admission – mean (range)				
Hemoglobin (g/L)[b]	130 (76–174)	131 (81–168)	129 (76–174)	0.11
Platelet count (10(9)/L)[c]	324 (104–944)	326 (104–944)	319 (106–934)	0.71
PT-INT [d]	1.01 (0.8–2.8)	1.01 (0.9–2.8)	1.00 (0.8–2.0)	0.78
Leucocyte count (10(9)/L)[e]	7.11 (3.0–41.5)	6.95 (3.0–41.5)	7.38 (3.2–24.4)	0.04

[a] Goal-directed therapy.
[b] [ref. Female 120–150, Male 130–170].
[c] [ref. 150–350].
[d] [ref. 0.9–1.2].
[e] [ref. 3.5–9.0].

3. Results

3.1. Baseline characteristics

The pre-GDT group constituted 64% of the cohort (n = 328) while the GDT group made up 36% (n = 181) (Table 1). Most of the cohort were females (57%, n = 291). The mean age was 57 (range 22–79 years), and the majority of the cohort (49%) were ≥60 years (n = 251). The percentage aged ≥70 was significantly higher in the GDT group compared to the pre-GDT group (23%, n = 42 vs. 11%, n = 38, $p = 0.0005$). The cardiovascular co-morbidity rate was higher in the GDT group compared to the pre-GDT group (49%, n = 88 vs. 34%, n = 110). but it did not reach a significant *p*-value (0.06). The main primary tumor was of appendiceal origin (49.5%, n = 252) (Table 1).

The predominant primary tumor origin in the pre-GDT group was appendix (54%, n = 178) while in the GDT group the most frequent primary tumor site was of colorectal origin (52%, n = 95). Twenty-five percent of the cohort received neoadjuvant treatment within three months prior to CRS and HIPEC (n = 127).

The rate of ASA ≥3 was significantly higher in the GDT group compared to pre-GDT (24%, n = 44 vs. 9%, n = 31, $p < 0.0001$). However, estimated intraoperative blood loss (≥2000 ml) was much higher in the pre-GDT group (22%, n = 72) than in the GDT group (13%, n = 24, $p = 0.01$). The GDT group had a significantly higher rate of treatment with oxaliplatin ± irinotecan (71%, n = 128 vs. 43%, n = 141, $p < 0.0001$, Table 2).

3.2. Intraoperative management

Table 2 presents differences in intraoperative fluid replacement between pre-GDT and GDT groups. Total intraoperative fluid replacement was significantly decreased in the GDT group compared to the pre-GDT group (16.2 vs. 19.9 ml/kg/h). The GDT group had a relatively higher rate of liver resections (11%, n = 20) and splenectomies (33%, n = 59) compared to the pre-GDT group (3%, n = 9 and 20%, n = 66 respectively). Thirty-one percent of the pre-GDT group received early postoperative intraperitoneal chemotherapy (EPIC) treatment (n = 101) while none in the GDT group received EPIC treatment.

3.3. Postoperative outcome and survival

The overall mean stay in the ICU was 1.32 days [range 0–15]. The pre-GDT group had a mean ICU stay of 1.06 days [range 0–6]. The GDT group had a mean of 1.79 days in the ICU [range 0–15], ($p = 0.0001$). Sixteen percent of those patients needed a prolonged ICU stay ≥2 days (n = 29) (Table 3). Differences in morbidity rate between the two groups are presented in Table 3. Grade IV morbidity in the pre-GDT group was related to intraabdominal abscess (n = 1), anastomotic insufficiency (n = 1) and ileus (n = 1). In the GDT group, Grade IV morbidity was related to intra-abdominal abscess (n = 5), anastomotic insufficiency (n = 4), iatrogenic injury (n = 2), wound dehiscence (n = 2) and postoperative hemorrhage (n = 2).

The overall risk for postoperative hemorrhage was 7% (n = 35) with oxaliplatin-based HIPEC regimens having a bleeding rate of 10% (n = 27) vs. other HIPEC regimens with a rate of 3% (n = 8), *p*-value = 0.006. Most cases with hemorrhage in both groups had a late onset (≥72 h). There was a trend towards more postoperative bleeding in the GDT group (9% vs 5%, *p*-value 0.09) (Table 3). The majority of late-onset hemorrhage cases (83%) received oxaliplatin ± irinotecan as the HIPEC regimen (n = 24); 10% received cisplatin + doxorubicin (n = 3), and 7% received mitomycin C (n = 2). However, the double-drug HIPEC regimens showed no significantly increased risk for postoperative hemorrhage ($p = 0.23$).

Table 2
General anesthesia and surgical characteristics.

Variables	The total Cohort (n = 509)	pre-GDT (n = 328)	GDT (n = 181)	*p*-value
ASA score − n (%)				<0.0001
1-2	434 (85%)	297 (91%)	137 (76%)	
≥3	75 (15%)	31 (9%)	44 (24%)	
Estimated blood loss in ml − mean (range)	1122 (25−15325)	1256 (25−15325)	874 (40−5500)	0.004
<2000 ml	412 (81%)	255 (78%)	157 (87%)	
≥2000 ml	96 (19%)	72 (22%)	24 (13%)	
Intraoperative erythrocytes transfusion (ml/h) − mean (range)	60 (0−545)	67 (0−545)	49 (0−471)	0.0003
0 packs	227 (44.5%)	122 (37%)	105 (58%)	
1-4	213 (42%)	149 (46%)	64 (35%)	
>4	69 (13.5%)	57 (17%)	12 (7%)	
Intraoperative plasma transfusion (ml/h) − mean (range)	58 (0−764)	79 (0−764)	19 (0−375)	<0.0001
0 packs	321 (63%)	168 (51%)	153 (85%)	
1-4	101 (20%)	81 (25%)	20 (11%)	
>4	87 (17%)	79 (24%)	8 (4%)	
Intraoperative thrombocytes transfusion (ml/h)− mean (range)	1.15 (0−90)	1 (0−90)	1 (0−43)	0.92
0 pack	494 (97%)	319 (97%)	175 (97%)	
≥1 pack	15 (3%)	9 (3%)	6 (3%)	
Intraoperative crystalloid[a] fluids replacement (ml/h) − mean (range)	946 (222−2313)	998 (222−2313)	852 (333−1729)	<0.0001
<7500 ml	257 (50.5%)	112 (34%)	145 (80%)	
≥7500 ml	252 (49.5%)	216 (66%)	36 (20%)	
Intraoperative colloid[b] fluids replacement (ml/h) − mean (range)	294 (0−1018)	311 (7−900)	264 (0−1018)	<0.0001
<2000 ml	172 (34%)	56 (17%)	116 (64%)	
≥2000 ml	337 (66%)	272 (83%)	65 (36%)	
Total fluid replacement (ml/kg/h) − mean (range)	18.6 (4−46)	20 (6−45)	16 (4−46)	<0.0001
Duration of surgery in minutes − mean (range)	523 (180−1080)	581 (240−1080)	417 (180−840)	<0.0001
Liver resection	37 (7%)	17 (5%)	20 (11%)	0.01
Extirpation of liver capsule	71 (14%)	65 (20%)	6 (3%)	<0.0001
Splenectomy	195 (38%)	136 (41%)	59 (33%)	0.04
PCI: 1-20	304 (60%)	177 (54%)	127 (70%)	0.01
21-39	194 (38%)	140 (43%)	54 (30%)	
Unidentified	11 (2%)	11 (3%)	0 (0%)	
CCS: 0-1	463 (91%)	284 (87%)	179 (99%)	<0.0001
2-3	46 (9%)	44 (13%)	2 (1%)	
HIPEC regimen:				<0.0001
Oxaliplatin ± Irinotecan	269 (53%)	141 (43%)	128 (71%)	
Mitomycin C	153 (30%)	107 (33%)	46 (25%)	
Cisplatin ± Doxorubicin	80 (16%)	79 (24%)	1 (1%)	
Miscellaneous	7 (1%)	1 (0.3%)	6 (3%)	
HIPEC regimen:				<0.0001
Single drug	347 (68%)	168 (51%)	179 (99%)	
Double drug	162 (32%)	160 (49%)	2 (1%)	
CRS/HIPEC + EPIC	101 (19.8%)	101 (31%)	0 (0%)	<0.0001

[a] Crystalloid fluid included Ringer's acetate, glucose, NaCl.
[b] Colloid fluids included albumin and HES.

Table 3
Postoperative outcomes for pre-GDT compared to GDT.

Clinical variables	pre-GDT (n = 328)	GDT (n = 181)	*p*-value
Clavien-Dindo III-V − n (%)	71 (22%)	54 (30%)	0.03
IIIa	43 (61%)	29 (53.7%)	
IIIb	25 (35%)	9 (16.6%)	
IV	3 (4%)	15 (27.7%)	
V	0 (0%)	1 (2%)	
Total reoperation rate	29 (9%)	20 (11%)	0.41
Clinically significant postoperative hemorrhage	18 (5%)	17 (9%)	0.09
Hemorrhage onset − n (%)			0.27
Early postoperative hemorrhage (<72 h)	5 (1.5%)	1 (0.5%)	
Late postoperative hemorrhage (≥72 h)	13 (3.9%)	16 (8.8%)	
Reoperation due to hemorrhage	13 (4%)	6 (3%)	0.71
Time to reoperation due to hemorrhage (h) − mean (range)	160 (3−384)	281 (8−600)	0.15
Days in ICU − mean (range)	1.06 (0−6)	1.79 (0−15)	0.0001
0−1 d, n (%)	313 (95%)	152 (84%)	
≥2 d, n (%)	15 (5%)	29 (16%)	
Total fluid replacement in patients with ≥2d in the ICU − mean (range)	26.6 16−44)	14.3 (6−30)	<0.0001
Length of hospital stay (days) − mean (range)	26 (10−124)	17 (6−50)	<0.0001
Postoperative erythrocytes transfusion − mean (range)	473 (0−4800)	414 (0−3300)	0.27
0 packs	135 (41%)	85 (47%)	
1-4	169 (52%)	86 (47.5%)	
>4	24 (7%)	10 (5.5%)	

In-hospital mortality was 0.2% (n = 1) and 2% mortality was observed within 90 days (n = 9). There was no difference in 90-day mortality between the groups. No patient died from postoperative hemorrhage. Survival analyses are presented in Fig. 1. Median overall survival in Fig. 1 was 83 months for the pre-GDT group and 72 months for the GDT group ($p = 0.50$).

3.4. Multivariable adjusted analysis

The multivariable adjusted OR for Clavien-Dindo Grades III-V morbidity according to the prespecified covariables in the methods section was 1.80 (95%CI 1.10–3.10, $p = 0.02$) for the GDT group compared to the pre-GDT group. The full univariate and multivariable logistics analyses for postoperative hemorrhage are presented in Table 4. The multivariable adjusted HR for overall survival according to the prespecified covariables in the methods section was 0.97 (95%CI 0.71–1.31, $p = 0.85$) for the GDT group compared to the pre-GDT group. Subgroup analysis with PMP and colorectal cancer separately did not show that GDT use was associated to overall survival (data not shown).

4. Discussion

With over 500 patients, our study is one of the largest to date evaluating goal-directed fluid therapy management in CRS and HIPEC treatment. Unexpectedly, patients in the GDT group had increased Clavien-Dindo morbidity. Despite these findings, patients were discharged home or to the referring hospitals earlier in the GDT group.

To our knowledge, there is only one small, randomized trial investigating GDT in HIPEC patients performed by Colantonio et al. (2015) with 38 patients in the GDT arm and 42 with standard fluid therapy [13].

The same study concluded that the use of GDT minimized the incidence of major postoperative abdominal morbidity (10.5% in GDT group, n = 4 vs. 38%, n = 16, $p = 0.005$) and shortened LOS (19 days in the GDT group vs. 29 days, $p < 0.0001$) [13]. Likewise, among the few observational studies published, cohort sizes are relatively small and have demonstrated conflicting results [12,14,18]. Castellanos et al. (2021) demonstrated that the use of overly restrictive intraoperative fluid margins may actually increase the risk of major postoperative complications [18], while most studies have shown a benefit in LOS and morbidity [12,14]. However, Castellanos et al. (2021) used very restrictive fluid management at <9 ml/kg/h in the GDT group, which is significantly lower than our study's GDT group (16 ml/kg/h in total fluid replacement).

The increased morbidity in the GDT group is probably partially explained by widened indications for treatment. Because our center has developed long-standing expertise, it is clear that older and more frail patients have been included for treatment. Both age and ASA score were significantly increased in the GDT period (Table 1). Despite this increase in age and ASA, the length of stay has decreased, demonstrating that successful treatment in higher age and comorbid groups appears feasible.

Concerning the specific complication of postoperative hemorrhage, Charrier et al. (2016) conducted a registry study that demonstrated a risk of around 10% for postoperative hemorrhage after CRS and HIPEC, which is slightly higher than in our study (7%) [12]. The same study demonstrated a significant increase in the risk for postoperative hemorrhage with oxaliplatin-based HIPEC in comparison to other HIPEC regimens [12]. This result was confirmed in our cohort as oxaliplatin was an independent prognostic factor for postoperative hemorrhage with three times the risk of non-oxaliplatin HIPEC regimens. Nevertheless, there was no increased risk of postoperative mortality related to postoperative hemorrhage. Therefore, being vigilant would appear to be sufficient to prevent mortality related to postoperative hemorrhage. While there was a trend towards increased risk of bleeding in the GDT group, the difference disappeared in the multivariable analysis, in part due to more oxaliplatin-based HIPEC treatments in the GDT period.

The LOS was significantly shorter in the GDT group compared to the pre-GDT group (17 vs. 26 days, $p < 0.001$, Table 3) despite the fact that postoperative care in the ICU was longer. The mean

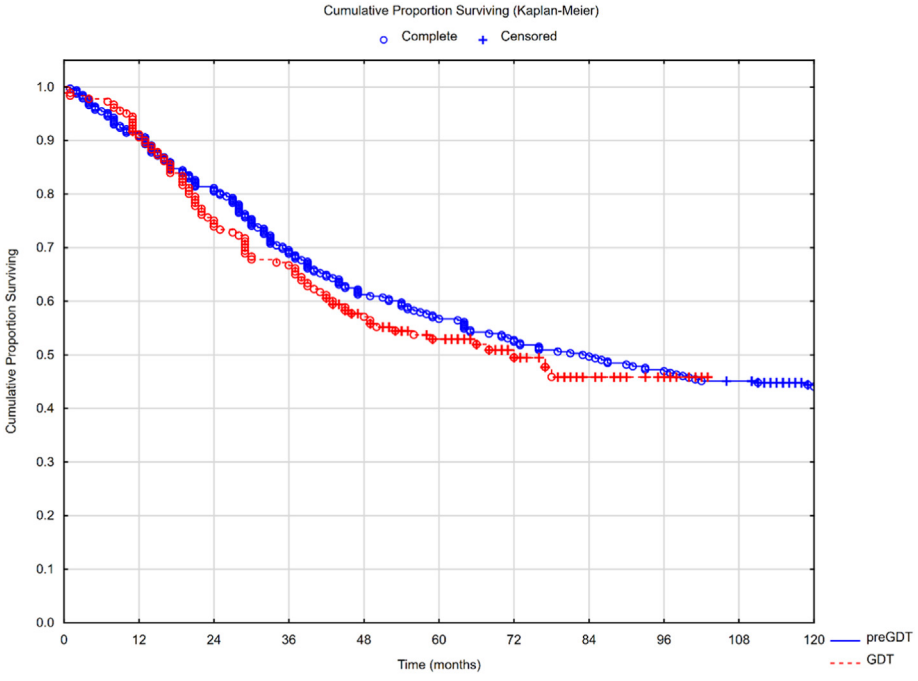

Fig. 1. Overall survival for the pre-GDT group compared to the GDT group.

Table 4
Univariate analysis and multivariate logistic regression with postoperative hemorrhage as endpoint.

	Univariate analysis OR (CI)	*p*-value	Multivariate analysis OR (CI)	*p*-value
Age at treatment	1.00 (0.97–1.03)	0.83		
≥70	1.96 (0.88–4.36)	0.09	1.77 (0.77–4.06)	0.17
Gender				
Female	Reference			
Male	0.88 (0.44–1.75)	0.72		
BMI (kg/m^2)	1.07 (0.97–1.17)	0.14		
Cardiovascular comorbidity	1.09 (0.53–2.25)	0.80		
ASA score:				
1-2	Reference			
≥3	1.49 (0.62–3.55)	0.36		
Previous abdominal surgery for primary tumor	2.88 (0.86–9.62)	0.08	2.23 (0.65–7.63)	0.19
Preoperative intravenous chemotherapy, within 3 months	0.99 (0.45–2.19)	0.99		
Fluid management:				
Group 1 (pre-GDT[a])	Reference			
Group 2 (GDT)	1.78 (0.89–3.55)	0.09	1.37 (0.64–2.95)	0.40
HIPEC regimen:				
Mitomycin C	Reference			
Oxaliplatin ± Irinotecan	3.07 (1.36–6.90)	0.006	3.32 (1.11–9.94)	0.03
Cisplatin ± Doxorubicin	0.28 (0.09–0.81)	0.01	2.20 (0.52–9.30)	0.28
HIPEC regimen:				
Single drug	Reference			
Double drug	0.61 (0.27–1.38)	0.24		
PCI:				
1-20	Reference			
21-39	0.92 (0.45–1.87)	0.81		
CCS:				
0-1	Reference			
2-3	0.28 (0.03–2.09)	0.21		
Splenectomy	1.57 (0.78–3.12)	0.19		
Liver resection	1.21 (0.35–4.16)	0.75		
Extirpation of liver capsule	0.78 (0.26–2.29)	0.65		
HIPEC + EPIC	0.50 (0.17–1.45)	0.20		
Surgery duration (min)	1.00 (0.99–1.00)	0.35		
Estimated blood loss (ml):				
<2000 ml	Reference			
≥2000 ml	0.70 (0.26–1.85)	0.47		
Intraoperative erythrocytes infusion (ml)				
0 PRBC	Reference			
1–4 PRBC	1.04 (0.52–2.09)	0.90		
>4 PRBC	1.06 (0.39–2.85)	0.89		
Intraoperative plasma infusion (ml)				
0 FFP	Reference			
1–4 FFP	1.21 (0.53–2.75)	0.64		
>4 FFP	0.60 (0.20–1.76)	0.36		
Intraoperative thrombocytes	1.03 (0.13–8.10)	0.97		
Intraoperative crystalloid fluids replacement				
<7500 ml	Reference			
≥7500 ml	0.66 (0.32–1.33)	0.24		
Intraoperative colloid fluids replacement				
<2000 ml	Reference			
≥2000 ml	0.58 (0.29–1.16)	0.12		
Total fluid replacement (ml/kg/h)	1.00 (0.95–1.05)	0.85		

[a] Goal-directed therapy.

intraoperative fluid replacement in the GDT group with extended ICU (more than 2 days) was 14.3 ml/kg/h [range 8–36] which was lower than the GDT group as a whole.

In Table 3, we see 29 patients needing more than 2 days in ICU, but only 15 patients who had Clavien-Dindo Grade IV morbidity (requiring ICU care). It is possible that overly restrictive fluid replacement could be behind these other cases and that fluid balance issues have led to prolonged intermediate care needs. Further follow-up analysis could be warranted to interpret the differences that have been demonstrated in our morbidity analysis. Nonetheless, the LOS was shortened, and, while we do not possess data on return of bowel function, we hypothesize that GDT may support this effort leading to a shortened overall LOS.

The study results in both the Kaplan-Meier analysis and the multivariable analysis demonstrated no survival benefits for patients treated with GDT compared to those receiving liberal intraoperative management (Fig. 1). The slight difference in trend (Fig. 1) is explained by a larger proportion of pseudomyxoma patients in the pre-GDT period and, conversely, a larger proportion of colorectal patients in the GDT period.

4.1. Strengths and limitations of the study

A strength of our study is the cohort size, which increases the power to detect differences between the groups concerning the impact on outcomes following CRS and HIPEC. Moreover, our single center routines, with excellent documentation of fluid management, mean that there are no missing data. The main limitation of this study is the time aspect. Learning and patient selection improves over time. With this comes increased confidence in when to discharge patients to referring hospitals for rehabilitation. It is inevitable that intraoperative GDT management is not solely

responsible for decreased LOS. The discharge policy has changed dynamically during the time of the study mainly due to treatment aspects such as the significant improvement in learning curve, non-use of EPIC and shorter operation time. The shortage in hospital beds, the increased workloads and staff shortages are other thinkable aspects that might impact hospital transfers and LOS.

GDT treatment has evolved over time, with different monitoring techniques. Even though it is difficult to completely separate time-dependent learning improvement from GDT use, we believe this study corroborates the fact that LOS has indeed decreased and that GDT use is probably associated with this improvement. Finally, even though the study is based on a prospective HIPEC register, some of the variables were retrospectively retrieved and as such there is always a certain risk of biases in evaluation.

5. Conclusion

GDT is associated with significantly improved LOS despite an increase in morbidity in some patients. Intraoperative GDT management during CRS and HIPEC does not affect the postoperative risk for hemorrhage, although the choice of oxaliplatin HIPEC does. Personalized GDT based on patients' characteristics and surgery should be utilized during the management of CRS and HIPEC patients.

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CRediT authorship contribution statement

P. Dranichnikov: Data curation, Formal analysis, Writing – original draft, identified the cases. identified the cases. collected the data, performed the initial analysis, and wrote the manuscript. helped revise the manuscript. **E. Semenas:** Data curation, Formal analysis, Writing – review & editing, helped with improving the design of the study. helped improved the data analysis and reviewed the manuscript. helped revise the manuscript. **W. Graf:** Data curation, Formal analysis, Writing – review & editing, helped improved the data analysis and reviewed the manuscript. helped revise the manuscript. **P.H. Cashin:** Data curation, Formal analysis, Writing – review & editing, designed the study. identified the cases. helped improved the data analysis and reviewed the manuscript. helped revise the manuscript.

Declaration of competing interest

There is no conflict of interest in this study or in the article submitted. None of the authors has personal or financial interests in, or has received financial support from, any industrial source.

List of abbreviations

5-FU	5-Fluorouracil®
CCS	Complete Cytoreduction Score
CI	Confidence Interval
CRS	Cytoreductive Surgery
EPIC	Early Postoperative Intraperitoneal Chemotherapy
FFP	Fresh Frozen Plasmas
GDT	Goal-Directed Therapy
HIPEC	Hyperthermic Intraperitoneal Chemotherapy
ICU	Intensive Care Unit
OR	Odds Ratio
OS	Overall Survival
PCI	Peritoneal Cancer Index
PM	Peritoneal Surface Malignancy
PMP	Pseudomyxoma peritonei
POD	Postoperative Day
PRBC	Packed Red Blood Cells
SVV	Stroke Volume Variation

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