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Use of hyperthermia versus normothermia during intraperitoneal chemoperfusion with oxaliplatin for colorectal peritoneal carcinomatosis: A propensity score matched analysis☆

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ABSTRACT

Background: Hyperthermic intraperitoneal chemotherapy (HIPEC) with oxaliplatin (OX) is increasingly used in the treatment of colorectal peritoneal carcinomatosis (PC). However, the additional benefit of hyperthermia remains clinically unproven, while it may aggravate postoperative morbidity. Here, we report the correlation of perfusion temperature with postoperative morbidity during clinical HIPEC with OX.

Patients and methods: Patients who underwent hyperthermic (41 °C, HT) or normothermic (37 °C, NT) chemoperfusion with OX for colorectal PC were identified from a prospectively kept database of HIPEC cases and matched for baseline characteristics using propensity score (PS) analysis. The groups were compared to assess the impact of perfusion temperature on morbidity. Morbidity was graded using the Clavien-Dindo (CD) classification and the Comprehensive Complication Index (CCI).

Results: Out of 612 patients, 146 patients met the inclusion criteria and from these patients, 45 HT patients were matched with 45 NT patients. Baseline variables were comparable between the PS matched groups. Overall mortality was 0.7% and major morbidity (CD $\geq$ 3) occurred in 35,6% of patients. There were no significant differences between the HT and NT cohorts in mortality, major morbidity (RR 1.33, 95% CI 0.71 to 2.49, p = 0.36), anastomotic leakage (13.8% versus 11.1%, p = 1.0), hemorrhagic complications, or systemic toxicity. A trend of increased wound infections was observed in the hyperthermia group (13.3% versus 4.4%, P = 0.27).

Conclusions: Compared to NT, the use of HT during HIPEC with OX does not aggravate postoperative mortality or morbidity in a high-volume center.

Introduction

Cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) is increasingly used in peritoneal carcinomatosis (PC) from colorectal cancer (CRC) [1]. The randomized controlled trial by Verwaal et al. reported improved overall survival after a combined treatment of 5-FU based chemotherapy and CRS + HIPEC, compared to palliative chemotherapy alone [2,3]. However, the morbidity of the procedure is high (0–62%), with most authors reporting major morbidity in around 35% of cases [4,5]. This morbidity is likely to be attributed primarily to the long and extensive surgical procedure, the safe performance of which requires extensive experience and training [6–8]. Systemic toxicity from intraperitoneal (IP) chemotherapy is usually limited, since systemic drug exposure is typically limited compared to IP exposure. Over the last decade, oxaliplatin (OX) is increasingly used for HIPEC in CRC. Oxaliplatin has a favorable pharmacokinetic profile (AUC peritoneal/plasma is approximately 15–20). In vitro, hyperthermia enhances the cytotoxic activity of OX [9]. However, hyperthermia enhances systemic release of heat shock proteins (HSP), which are implicated in treatment resistance [10]. Also, in a murine model, hyperthermia did not significantly increase tissue OX concentrations [11]. In

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animal models, HIPEC adversely affects anastomotic healing [12]. Clinically, HIPEC elicits a generalized inflammatory response, as evidenced by sharply risen levels of, among other mediators, interleukin-6 and procalcitonin; high levels of postoperative IL-6 are known to correlate with postoperative complications after major abdominal surgery [13].

These findings prompted us, in an effort to minimize postoperative morbidity, to start performing HIPEC under normothermic conditions (target intra-abdominal temperature 37 °C) in patients perceived to be at higher risk of complications. Here, we report, for the first time, a comparison of postoperative complications between patients undergoing normo-versus hyperthermic intraperitoneal chemoperfusion (IPC) using OX. Patients were matched according to clinical and treatment variables using the propensity score method.

Methods

Patients were identified from a comprehensive prospectively kept database of all IPC patients that has been maintained at our institution since January 1999. Candidates for surgery were preoperatively assessed by the surgical team and each case discussed in a multidisciplinary conference. Selection criteria were the type of cancer (CRC) and type of intraperitoneal chemotherapy (Oxaliplatin). Exclusion criteria were concomitant liver resection, IPC without CRS, multiple IPC procedures, and patients with incomplete data. The experimental protocol was approved by the institutional review board of Ghent University Hospital.

Variables on which propensity score was calculated were: age, BMI, ASA score, completeness of cytoreduction score (CC) [14], previous radiotherapy, preoperative chemotherapy (<3 months), preoperative chemotherapy regimen containing bevacizumab (<3 months), major comorbidity, previous abdominal surgery, other malignancies, presence of ascites, number of affected abdominal regions, number of bowel anastomoses, enterostomy, ureteric anastomosis, and splenectomy.

Surgical procedures were performed as previously described [15]. Intraoperative chemoperfusion was performed with oxaliplatin using the open (coliseum) technique with one of two protocols: 200 mg/m^2 during 90 min or 460 mg/m^2 during 30 min. In both cases, dextrose 5% (volume 2 L/m^2) was used as a carrier fluid (perfusate).

Morbidity and mortality (up to 30 days after surgery) were recorded by type of complication and graded using the Clavien-Dindo classification and the Comprehensive Complication Index (CCI) [16]. The primary outcome was defined as major morbidity or mortality (CD $\geq$ 3). Secondary outcomes were cumulative morbidity as expressed by the comprehensive complication index score, mortality, disability and the subtype of complication.

Statistical analysis, including propensity score matching, was performed using IBM SPSS Statistics 23, R 3.1.0 & PS Matching 3.04 according to the methods described by Thoemmes et al. [17] Cases were selected by Nearest Neighbor Matching (1:1) using Logistic Regression with a caliper of 0.2. Propensity score analysis was reported in accordance with guidelines [18]. Analysis of matched groups was performed using Pearson's chi-square test, Fisher's exact test, independent samples T-test or Mann-Whitney *U* test. Figures were created and edited by IBM SPSS Statistics 23, Adobe Photoshop CS 5, Inkscape and GraphPad Prism 7. All p-values are two-tailed and statistical significance was assumed when $p \leq 0.05$. No correction for multiple testing was used. Post-hoc power analysis was performed using G*Power 3.1.9.2.

Results

Patient selection and characteristics

From a total of 612 patients treated with CRS and IPC between 1999 and 2016, 146 met the selection criteria. All included patients were treated from 2005 to 2016. Half of these patients (73) patients were treated with hyperthermic IPC (mean T 40.74 °C; SD 1.219), while the other 73 were treated with normothermic IPC (mean T 37.60 °C; SD 0.427). Baseline characteristics in both groups are presented in Table 1. Normothermic IPC patients had a higher percentage of neo-adjuvant chemotherapy and previous abdominal surgery. Additionally, fewer patients received an enterostomy. There were no significant differences in other characteristics that might impact IPC morbidity.

Propensity score matching

The propensity score was calculated for 146 patients, of which

Table 1
Population characteristics for the total population (TP), hyperthermia (H), and normothermia (N) groups. * denotes statistically significant results ($p < 0.05$). [t]: independent samples T-test. [f]: Fisher's exact test. [p]: Pearson's Chi Squared test. [m]: Mann-Whitney U test.

Characteristics	**TP** (n = 146)	Before Matching			After PS Matching		
		H (n = 73)	**N** (n = 73)	p	**H** (n = 45)	**N** (n = 45)	p
Temperature		**40.74 °C (1.22)**	**37.6 °C (0.43)**		**40.66 °C (1.31)**	**37.6 °C (0.41)**	
Age	61.03 (11.11)	60.07 (10.68)	62 (11.51)	0.295[t]	61.02 (10.78)	60.71 (11.90)	0.897[t]
ASA	2 (0.55)	3 (0.58)	2 (0.52)	0.275[m]	2 (0.58)	2 (0.28)	0.630[m]
Sex (male)	71 (48.6%)	33 (45.2%)	38 (52.1%)	0.408[p]	24 (53.3%)	23 (51.1%)	0.833[p]
BMI	25.46 (4.14)	25.23 (3.64)	25.68 (4.60)	0.511[t]	25 .47 (3.56)	25.76 (4.39)	0.733[t]
Radiotherapy	12 (8.2%)	6 (8.2%)	6 (8.2%)	1[p]	4 (8.9%)	5 (11.1%)	1[f]
Chemotherapy (<3 m)	79 (54%)	33 (45.2%)	46 (63.0%)	**0.031***[p]	24 (53.3%)	23 (51.1%)	**0.833**[p]
Major comorbidity	53 (36.3%)	23 (31.5%)	30 (41.1%)	0.228[p]	14 (31.1%)	16 (35.6%)	0.655[p]
Other malignancy	16 (11%)	7 (9.6%)	9 (12.3%)	0.596[p]	5 (11.1%)	3 (6.7%)	0.714[p]
Bevacizumab (<3 m)	33 (22.6%)	15 (20.5%)	18 (24.7%)	0.553[p]	11 (24.4%)	10 (22.2%)	0.803[p]
Previous Abdominal surgery	64 (43.8%)	24 (32.9%)	40 (54.8%)	**0.008***,[p]	18 (40.0%)	19 (42.2%)	**0.830**[p]
Ascites	17 (11.6%)	9 (12.3%)	8 (11.0%)	0.796[p]	4 (8.9%)	3 (6.7%)	1[f]
Affected abdominal regions	4 (2.15)	4 (1.87)	4 (2.40)	0.454[m]	4 (2.01)	4 (1.84)	0.803[m]
Number of intestinal anastomosis	1 (0.91)	1 (0.95)	1 (0.88)	0.474[m]	1 (0.74)	1 (0.83)	0.762[m]
Ureteric anastomosis	14 (9.6%)	7 (9.6%)	7 (9.6%)	1[p]	4 (8.9%)	5 (11.1%)	1[f]
Splenectomy	8 (5.5%)	5 (6.8%)	3 (4.1%)	0.719[f]	3 (6.7%)	3 (6.7%)	1[f]
Enterostomy	45 (30.8%)	28 (38.4%)	17 (23.3%)	**0.049***,[p]	13 (28.9%)	13 (28.9%)	**1**[p]
CCR	0 (0.46)	0 (0.44)	0 (0.49)	0.288[m]	0 (0.42)	0 (0.52)	0.547[m]

90 could be 1:1 matched (i.e. 61.6% of the total population). Pre- and post matching histograms showed a significant decrease in the standardized differences of matched patient characteristics (Fig. 1). Table 1 shows the population characteristics of matched groups. No clinically or statistically significant differences remained. Post-hoc power analysis showed a power >0.95 for detecting a statistically medium effect size (Cohen's w = 0.3) in the unmatched population, and a power > 0.8 in the matched group.

Primary outcome

Of the entire population, 35.6% of patients suffered a complication severe enough to warrant an invasive intervention or ICU admission (CD ≥ 3; Table 2). In the unmatched as well as in the propensity score matched group analysis, the hyperthermia group had a slightly higher incidence of major morbidity (CD ≥ 3), but this difference was not significant (respectively: RR 1.17, 95% CI 0.75 to 1.81, p = 0.49; and RR 1.33, 95% CI 0.71 to 2.49, p = 0.36).

Secondary outcomes

A summary of secondary outcomes is provided in Table 2. There was no significant difference in cumulative morbidity as expressed by the CCI score. Also, there were no differences in mortality or disability. In the unmatched analysis, there was a significant increase in hemorrhagic, thrombotic and other hematologic complications in the normothermia group (RR 2.75, 95% CI 1.31 to 5.77, p = 0,004). However, after matching, there remained zero difference between both groups (RR 1.0, 95% CI 0.38 to 2.62, p = 1). Interestingly, while the median number of days in intensive care was the same (2 days) for both groups, non-parametric analysis before matching still withheld a significant difference in distribution with more patients having a shorter stay in the normothermia group (p = 0.012). This difference disappeared after matching (p = 0.2).

A trend suggesting a higher incidence of wound infections was observed in the hyperthermia group, but this did not reach statistical significance (unmatched RR 2.0, 95% CI 0.86 to 4.67, p = 0.099; and matched RR 3.0, 95% CI 0.64 to 14.08, p = 0.27).

Discussion

Surgery and HIPEC are increasingly regarded as a rational option for patients with colorectal PC. Nevertheless, the efficacy of HIPEC compared to modern systemic therapy alone remains to be demonstrated. Also, although expert centers report major morbidity rates in the range of 30–35%, debulking and HIPEC is a formidable undertaking with potentially serious functional and quality of life consequences [19]. Anastomotic leakage is one of the most dreaded postoperative complications, and occurs in 7–20% of patients with at least one bowel anastomosis [20,21]. Intraperitoneal hyperthermia is based on the premise that hyperthermia increases the effect and/or uptake of cytotoxic drugs. However, hyperthermia may impair anastomotic healing by causing edema of the bowel wall [22]. Pelz et al. found a reduced wound strength of colonic anastomosis after HIPEC in a rat model [23]. Also, hyperthermia adversely affects the tight junctions that form the intestinal epithelial barrier function, potentially leading to permeation of luminal antigens, endotoxins, and bacteria into the blood [24]. When used with OX, hyperthermia may exacerbate the risk of immediate postoperative bleeding, which is considerable and has led to discontinuation of a French multicenter trial after it was observed that 30% of patients required urgent laparotomy for hemoperitoneum [25]. On the other hand, thermal enhancement of OX anticancer efficacy has been demonstrated in cell lines only, but not in vivo or clinically. Animal studies have

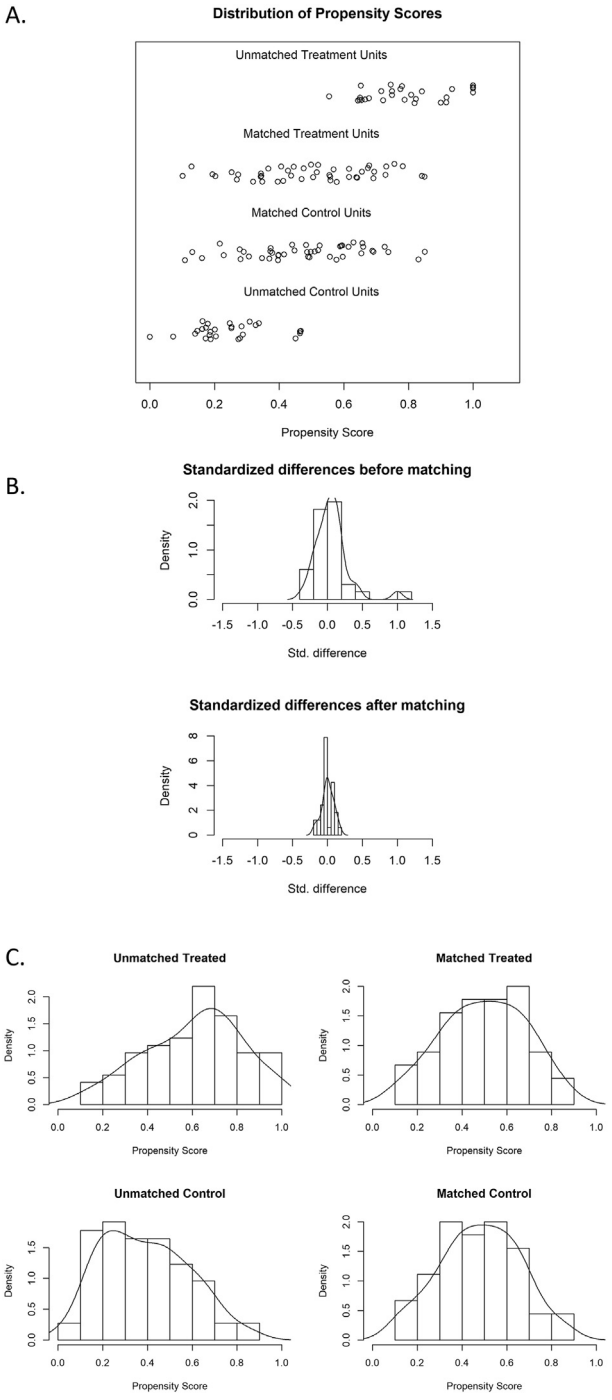

Fig. 1. A. Jitter plot of patients according to propensity score. B. Histogram of standardized differences before and after matching. C. Histogram of propensity scores before and after matching.

generated conflicting results regarding the anticancer benefit of intraperitoneal hyperthermia, with some authors reporting improved and others a similar or even a decreased tumor control or animal survival. In a recent experimental study using patient derived CRC organoids, hyperthermic administration did not enhance the cytotoxicity of OX [26]. Finally, when compared to normothemia, clinical hyperthermic chemoperfusion increases systemic OX levels. In a phase I clinical study, we compared the area under the curve (AUC) of OX blood concentrations over 7 days and maximal plasma concentrations after HIPEC using 460 mg/m^2 during 30 min at either

Table 2
Primary and secondary endpoints for the total population (TP), hyperthermia (H), and normothermia (N) groups.* denotes statistically significant results ($p < 0.05$).[t]: independent samples T-test.[f]: Fisher's exact test.[p]: Pearson's Chi Squared test.[m]: Mann-Whitney *U* test.[n]: patients without intestinal anastomosis were omitted from this analysis.

Outcomes	**TP** (n = 146)	Before Matching			After PS Matching		
		H (n = 73)	**N** (n = 73)	p	**H** (n = 45)	**N** (n = 45)	p
Primary							
Major morbidity (CD ≥ III)	**52 (35.6%)**	**28 (38.4%)**	**24 (32.9%)**	**0.489**[p]	**16 (35.6%)**	**12 (26.7%)**	**0.362**[p]
Secondary							
CCI (mean, SD)	27.78 (20.24)	28.82 (21.51)	26.73 (18.97)	0.536[t]	26.95 (22.63)	23.29 (18.09)	0.399[t]
Mortality	1 (0.7%)	1 (1.4%)	0 (0%)	1[f]	1 (2,2%)	0 (0%)	1[f]
Disability	23 (15.8%)	10 (13.7%)	13 (17.8%)	0.496[p]	6 (13.3%)	8 (17.8%)	0.561[p]
Gastrointestinal	67 (45.9%)	29 (39.7%)	38 (52.1%)	0.135[p]	19 (42.2%)	22 (48.9%)	0.525[p]
Anastomotic leak	11 (12.0%)[n]	5 (10.6%)[n]	6 (13.3%)[n]	0.690[p]	4 (13.8%)[n]	3 (11.1%)[n]	1[f]
Pulmonary	27 (18.5%)	12 (16.4%)	15 (20.5%)	0.522[p]	6 (13.3%)	7 (15.6%)	0.764[p]
Cardiovascular	22 (15.1%)	10 (13.7%)	12 (16.4%)	0.818[p]	8 (17.8%)	5 (11.1%)	0.368[p]
Urogenital/nefrologic	43 (29.5%)	22 (30.1%)	21 (28.8%)	1[p]	10 (22.2%)	10 (22.2%)	1[p]
Hemorrhagic, thrombotic or hematologic	30 (20.5%)	8 (11.0%)	22 (30.1%)	**0.004***[,p]	7 (15.6%)	7 (15.6%)	**1**[p]
Thrombotic	2 (1.4%)	0 (0%)	2 (2.7%)	0.497[f]	0 (0%)	0 (0%)	/
Hemorrhagic	9 (6.2%)	3 (4.1%)	6 (8.2%)	0.494[f]	2 (4.4%)	0 (0%)	0.494[f]
Hematologic	25 (17%)	5 (6.8%)	20 (27.4%)	**0.002**[f]	5 (11.1%)	7 (15.6%)	0.535[p]
Neurologic	15 (10.3%)	6 (8.2%)	9 (12.3%)	0.414[p]	5 (11.1%)	3 (6.7%)	0.714[f]
IV catheter	3 (2.1%)	2 (2.7%)	1 (1.4%)	1[f]	1 (2.2%)	1 (2.2%)	1[f]
Infections	53 (36.3%)	31 (42.5%)	22 (30.1%)	0.121[p]	18 (40.0%)	11 (24.4%)	0.114[p]
Wound infections	21 (14.4%)	14 (19.2%)	7 (9.6%)	0.099[p]	6 (13.3%)	2 (4.4%)	0.266[f]
Intensive care stay	2	2	2	**0.012***[,m]	2	2	0.196[m]
(days, median, mean, SD)	3.48 (6.76)	3.89 (9.41)	3.07 (1.81)		3.00 (3.36)	2.71 (1.31)	
Hospital stay	16	16	16	0.282[m]	16	15	0.286[m]
(days, median, mean, SD)	21.05 (15.87)	23.64 (20.16)	18.47 (9.34)		21.71 (16.24)	17.62 (9.54)	

37 °C or 41 °C. We found that both were significantly higher after 41 °C versus 37 °C (158.0 ± 70.9 versus 129.6 ± 15.6 μg*h/g and 5.1 ± 2.4 versus 3.8 ± 0.9 μg/g, L De Smet and W Ceelen, unpublished data).

These findings prompted us to use a lower perfusion temperature in patients undergoing HIPEC with OX. Here, we report the first clinical study on the association of the temperature used during intraperitoneal perfusion using OX with perioperative morbidity and mortality. We employed a prospective database of 612 IPC patients, 146 of whom with PC from colorectal cancer were selected, treated with either normothermic (37.6 °C; mean T) or hyperthermic (40.7 °C; mean T) perfusion with oxaliplatin. This selection was then further specified by propensity score matching of possible confounders. This validated technique is a tool for equating baseline variables of nonrandomized groups to mimic the balance that is achieved by randomization. It is important to include all known variables and confounders that may impact treatment allocation. Post-matching analysis demonstrated a much more balanced population.

We found major morbidity in 35.6% of patients undergoing cytoreductive surgery and intraperitoneal chemotherapy, which is consistent with published experience. There was no statistically significant difference between the hyperthermia and normothermia groups. On the other hand, analysis before matching did show a significantly longer intensive care unit stay for the hyperthermia group. Mortality was low at 0.7% of the population. However, disability, defined as morbidity persisting at discharge requiring further follow-up, was present in 15.8% of the population. This parameter of the CD classification is not frequently reported used in the surgical literature, and reflects long term quality of life. Others have noted the adverse effect of IPC on quality of life, with an impairment often lasting up to 6 months [27]. Notably, a significant difference in hemorrhagic, thrombotic and other hematological complications was present in the unmatched normothermia group, but disappeared entirely after matching. It is likely that one of the matching variables affected the risk of these complications. Specifically, the use of preoperative chemotherapy may act as a confounder, as this variable also differed significantly in the unmatched dataset. In our population, 21 of 79 patients with preoperative chemotherapy had a thrombotic, hemorrhagic or hematological complication (RR 1.98, 95% CI 0.97 to 4.02, $p = 0.05$; Pearson's Chi Squared test), which was not included in the results because it was not a per-protocol analysis. Cumulative bone marrow suppression may explain some of these differences. Interestingly, Delhorme et al. explored the association of hemorrhagic events and preoperative systemic chemotherapy in a recent report of 47 IPC patients [28]. The authors hypothesized that preoperative systemic chemotherapy (5FU based) may protect against hemorrhagic events by inducing a procoagulant state. Conversely, Charrier et al. explored this association in a large multicenter analysis, but in the IPC with oxaliplatin group, preoperative chemotherapy did not impact on hemorrhagic events [29].

Several limitations apply to the interpretation of our findings. First, although we have used propensity score matching to ensure that both groups were comparable, this technique cannot correct for unmeasured or unknown potentially confounding covariates, which can only be achieved with prospective random assignment. Second, the small size of the matched samples did not allow to perform a meaningful comparison of any differences in disease free or overall survival, given the heterogeneity in tumor characteristics (primary site and stage, use of chemotherapy or radiotherapy, molecular and genetic tumor profile).

In conclusion, hyperthermia does not increase the risk of major postoperative morbidity (Clavien-Dindo ≥3) after CRS + IPC using OX in a high-volume center. A trend suggesting increased infections, especially wound infections, was observed but the size of this effect did not reach statistical significance. Further, adequately powered studies in homogeneous cancer types are needed to assess the impact of hyperthermia on disease recurrence and overall survival.

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