

Urological Procedures in Patients with Peritoneal Carcinomatosis of Colorectal Cancer Treated with HIPEC: Morbidity and Survival Analysis

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Abstract. *Aim: To investigate whether cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS+HIPEC) is a feasible and effective option for patients with urological involvement of peritoneal carcinomatosis from colorectal cancer (CRC-PC). Patients and Methods: The characteristics of patients with CRC-PC treated with CRS+HIPEC, with or without a urological procedure, between April 2005 and June 2013 in two tertiary Centres were analyzed. Results: Thirty-eight patients (14%) out of 267 CRC-PC patients treated with CRS+HIPEC had a urological procedure during cytoreduction. The median survival was not significantly different between patients with or without a urological procedure (26.9 versus 32.1 months, $p=0.29$). Severe complications occurred more in patients with a urological procedure (47% versus 20%, $p<0.001$). In patients with a urological procedure, the most frequent complications were gastrointestinal leakage ($n=9$) and intra-abdominal abscess formation ($n=5$). Conclusion: Urological resections as a part of CRS+HIPEC in patients with peritoneal carcinomatosis of colorectal origin are feasible and effective. Severe complications are prevalent in these patients but survival is comparable to patients without involvement of the urinary system.*

Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) has a proven role in the treatment of resectable peritoneal carcinomatosis (PC) of colorectal cancer (CRC) (1, 2). One randomized controlled trial showed a

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significant survival benefit compared to systemic chemotherapy (1). Additionally, numerous studies have confirmed the benefit of CRS+HIPEC in patients with PC of CRC, with median survival rates of up to 63 months after diagnosis (3, 4).

The goal of cytoreductive surgery is removal of all macroscopic tumor nodules within the intra-abdominal cavity, and the intraperitoneal chemotherapy is aimed at neutralizing the remaining microscopic cancer cells. Depending on the extent of PC, complete cytoreductive surgery frequently consists of omentectomy and multiple peritonectomies, coupled with visceral resections of gastrointestinal or genitourinary organs.

Albeit the improved survival in selected patients with low tumor burden and good performance status, postoperative complications remain a prevalent problem after CRS+HIPEC and may be lethal in some cases (5). Postoperative complications are mostly related to the extent of peritoneal dissemination and its related quantity of cytoreduction (4). Currently, few data exist on the impact of combined urological procedures in patients treated with CRS+HIPEC for peritoneal disseminated colorectal cancer.

The goal of this study was to evaluate our experience with combined urological procedures in patients treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in terms of perioperative morbidity and mortality and long-term overall and disease-free survival. We hypothesized that CRS+HIPEC in patients with urological involvement results in a more extensive cytoreduction and an increased postoperative morbidity and decreased survival. Secondly, we hypothesized that urological anastomoses may have an impaired healing because of the chemotherapeutic perfusion.

Patients and Methods

Patients. Between April 2005 and June 2013, a total of 267 patients was treated with CRS + HIPEC for histologically-proven peritoneally-disseminated colorectal cancer in the Catharina Hospital, Eindhoven, the Netherlands and St. Antonius Hospital, Nieuwegein, The Netherlands. CRS+HIPEC was performed as

described earlier (6). Patient data consisting of baseline characteristics, operative and pathology details and follow-up were included in a prospective database. A preoperative computed tomography scan of the abdomen and thorax was performed in all patients. More advanced diagnostics, such as magnetic resonance imaging or positron emission tomography-computed tomography scan are not performed routinely. The extent of peritoneal dissemination was determined according to the seven abdominal regions system (sPCI) (7). Patients with pseudomyxoma peritonei or appendiceal cancer were excluded from this analysis as were patients without histological confirmation of peritoneal dissemination of the primary malignancy at HIPEC procedure. Postoperative complications were graded according to the Clavien-Dindo classification (8). A urological procedure was defined as an intervention of the kidney, ureter or bladder demanding subsequent closure of the respective organ. Peritonectomy of the bladder or periureteral dissection were not considered urological procedures. Bowel, bladder and ureter continuity are generally restored after HIPEC perfusion. An urologist is commonly assisting in the urological procedures.

Statistical analysis. In case of normally distributed continuous data, results are presented as mean with a standard deviation (SD) or in case of non-normal distributed data as median and interquartile range (IQR). Comparison between groups was performed with the Mann-Whitney *U*-test. Categorical data was compared using the Chi-squared test. Odds ratios of several clinical factors for postoperative complications were calculated using logistic regression. Survival analysis was performed using the Kaplan-Meier estimator, with comparison using the log rank test. Statistical analysis was performed using Statistical Product and Service Solutions (SPSS, version 21, Chicago, IL, USA). A *p*-value <0.05 was considered as statistically significant.

Results

Patients' characteristics. Out of the 267 patients, 38 (14%) had an additional urological procedure during cytoreductive surgery followed by HIPEC. In 24 patients the resection involved the bladder and in 14 patients the resection involved the ureter. Partial cystectomy was performed in 21 patients and a complete cystectomy with urinary diversion according to Bricker in three patients. The ureteral procedures consisted of partial ureteral resection in 13 patients and nephrectomy in one patient. In two of these patients a ureteral re-implantation with psoas bladder hitch was performed to restore the urinary tract continuity.

The characteristics of patients, with a comparison between patients with and without an associated urological procedure, is depicted in Table I. Patients with a urological procedure more frequently presented with metachronous PC (66% versus 42%; *p*=0.006) had longer operating times (median, 460 versus 400 minutes; *p*<0.001), more intraoperative blood loss (median, 1275 versus 600 ml; *p*=0.004) and an increased length of hospital stay (13 versus 10 days; *p*<0.001). Patients with a resection of the ureter presented frequently with metachronous PC as compared to patients

without a ureter resection (73% versus 44%; *p*=0.03). The interval between primary surgery and HIPEC did not differ between patients with or without a combined urological procedure (synchronous PC: 2.3 versus 2.1 months; *p*=0.37 and metachronous PC: 23.9 versus 17.9 months; *p*=0.10). Patients with a urological procedure did not have a significantly higher PCI score compared to patients without a urological procedure (*p*=0.18). Although in patients with a urological procedure the location of the primary tumor was not different compared to patients without urological procedure (*p*=0.17), patients with a urological procedure showed a trend towards more sigmoid tumors (53% versus 36%; *p*=0.06). In patients with a ureter resection, 7 (50%) involved the left ureter and 7 ureters (50%) were right-sided. Tumor involvement of the urological tract was histopathologically confirmed in 21 patients (55%). The rate of urological procedures did not increase in the subsequent years of this study cohort (*p*=0.97).

Table II shows the extent of cytoreduction between groups, demonstrating that hysterectomy, rectosigmoid resection or partial small bowel resections were more frequently performed in association with a urological resection.

Post-operative morbidity and mortality. Four out of the 267 patients (1.5%) died within 30 days following CRS+HIPEC. All patients died as a result of gastrointestinal leakage. The 30-day mortality was higher in patients following a urological procedure (three patients (8%) versus one patient (0.5%); *p*<0.001).

In total, 64 patients (24%) suffered from a severe complication (grade $\geq 3a$) following CRS+HIPEC. Severe complications occurred in 18 patients (47%) in the urological-procedure group, compared to 46 patients (20%) without an associated urological resection (OR=3.58, 95% CI=1.75-7.31; *p*<0.001). Forty-nine patients (18%) required a reoperation as a result of postoperative complications. The reoperation rate was significantly higher in patients following urological resection (37% versus 15%; *p*=0.001). An overview of complications is shown in Table III. Eight patients had a severe urological complication (*i.e.*, urinoma or pyelonephritis requiring ICU admittance), out of which 7 were related to the urological procedure at cytoreduction.

Apart from specific urological complications, gastrointestinal leakage and gastrointestinal fistula were more prevalent in patients with an associated urologic procedure (24% versus 10%; *p*=0.03 and 5% versus 0%; *p*=0.01, respectively).

In univariate analysis, the following variables were significantly correlated to postoperative complications, sPCI (OR=1.22, 95% CI=1.00-1.48, *p*=0.05), intraoperative blood loss (OR=1.36, 95% CI=1.05-1.78, *p*=0.02), operating time (OR=1.45, 95% CI=1.20-1.76, *p*<0.001) and urological procedures (OR=3.58, 95% CI=1.75-7.31, *p*<0.001). In

Table I. Baseline characteristics of patients with and without urological procedures at cytoreduction.

Baseline	Urologic procedure (%) N=38	No urologic procedures (%) N=229	p-Value
Gender			
Male	18 (42)	103 (45)	
Female	23 (58)	126 (55)	0.74
Median age (years) (IQR)	62 (52-69)	61 (54-66)	0.34
T-stage			
T1	1 (3)	1 (0)	
T2	1 (3)	10 (4)	
T3	20 (53)	93 (41)	
T4	16 (42)	114 (50)	0.30
Tx	0	11 (5)	
N-stage			
N0	16 (42)	60 (26)	
N1	9 (24)	68 (30)	
N2	11 (29)	87 (38)	0.14
Nx	2 (5)	14 (6)	
Primary location			
Right colon	14 (37)	85 (37)	
Transverse colon	0	14 (6)	
Left colon	1 (3)	19 (8)	
Sigmoid colon	20 (53)	83 (36)	
Rectum	3 (8)	27 (12)	0.17
Missing	0	1 (0)	
R-score			
R0/1	37 (97)	219 (97)	
R2	1 (3)	6 (3)	1.00
Missing	0	1 (0)	
Synchronous PC	13 (34)	133 (58)	
Metachronous PC	25 (66)	96 (42)	0.006
Median sPCI (IQR)	3 (2-4)	3 (2-4)	0.18
Median Operation duration (min) (IQR)	460 (420-480)	400 (340-450)	<0.001
Median blood loss (ml) (IQR)	1275 (475-2025)	600 (300-1200)	0.004
Median admission duration (days) (IQR)	13 (12-29)	10 (8-15)	<0.001
Histology			
Adenocarcinoma	28 (74)	146 (64)	
Mucinous adenocarcinoma	6 (16)	54 (24)	
Signet ring cell	1 (3)	11 (5)	0.42
Missing	3 (8)	18 (8)	

IQR: Interquartile range; sPCI: simplified peritoneal cancer index.

multivariate analysis, operating time (OR=1.38, 95% CI: 1.08-1.77, $p=0.01$) and a urological procedure (OR=2.66, 95% CI=1.16-6.11, $p=0.021$) were significantly correlated to severe postoperative complications.

Long-term survival. At a median follow-up of 26.7 months, 160 patients (60%) were alive. The median follow-up and percentage of surviving patients was not significantly different between patients with or without a urological procedure (34.1 months *versus* 26.7 months; $p=0.66$ and 53% *versus* 61%; respectively, $p=0.48$). Median overall survival in the entire group of patients was 32.0 months. In Figure 1, the Kaplan-Meier curve of overall survival

following CRS+HIPEC is depicted with a comparison between patients with or without an associated urological procedure, showing no significant difference between overall survival in these groups (26.9 *versus* 32.1 months; $p=0.29$).

The median disease-free survival was 14.5 months; 16.2 months in patients with an associated urological procedure and 14.5 months in patients without an associated urological procedure ($p=0.20$, see Figure 2).

Discussion

In the current study, we investigated the impact of combined urological procedures during cytoreductive surgery and

Table II. Extent of cytoreduction in patients with or without urological procedure.

Cytoreduction	Urologic procedure (%) N=38	No urologic procedures (%) N=229	p-Value
Appendectomy	3 (8)	28 (12)	0.44
Cholecystectomy	3 (8)	13 (6)	0.59
Hysterectomy*	14 (64)	41 (34)	0.008
Ovariectomy*	17 (77)	86 (70)	0.48
Ileocaecal resection	10 (26)	47 (21)	0.42
Partial small bowel resection	24 (63)	87 (38)	0.004
(Partial) pancreatectomy	0	6 (3)	0.31
(Partial) gastrectomy	1 (3)	2 (1)	0.34
Rectosigmoid resection	24 (63)	93 (41)	0.011
Splenectomy	0	12 (5)	0.15
Subphrenic peritonectomy left	2 (5)	11 (5)	0.90
Subphrenic peritonectomy right	6 (16)	40 (18)	0.80

*Only in female patients.

Table III. Postoperative complications (grade $\geq 3a$).

Complication	Urologic procedure (%) N=38	No urologic procedures (%) N=229	p-Value
Bleeding	0	3 (1)	0.48
Ileus	1 (3)	4 (2)	0.71
Gastrointestinal leakage	9 (24)	22 (10)	0.03
Abscess	5 (13)	14 (6)	0.22
Fistula	2 (5)	0	0.01
Pneumonia	0	2 (1)	0.56
Urinary tract infection	3 (8)	0	<0.001
Urine leakage/urinoma	4 (11)	1 (0.4)	<0.001

hyperthermic intraperitoneal chemotherapy in patients with peritoneally-metastasized colorectal cancer. Although patients with a urological procedure showed a significantly increased rate of postoperative morbidity and mortality, long-term and disease-free survival was not different between patients with or without urological procedures. The increased morbidity rate was probably mostly related to the extent of visceral resections, rather than the urological procedure by itself. As shown, postoperative morbidity predominantly consisted of gastrointestinal complications, *i.e.*, gastrointestinal leakage, intra-abdominal abscess and fistula formation. Additionally, although the extent of peritoneal dissemination, measured by sPCI, was comparable between the groups, patients with urological procedures presented with more extensive locoregional recurrent disease requiring more visceral resections. Patients with a urological procedure had an increased rate of rectosigmoid resections, hysterectomies and partial small bowel resections most likely arising from their close anatomical relation.

Urological procedures were significantly more performed in patients with metachronous PC compared to patients with

synchronous PC. An explanation for this phenomenon may be that retroperitoneal involvement of peritoneal metastasis may develop more frequently after prior surgical trauma, giving free floating tumor cells the possibility to reach the retroperitoneal plane (9).

Direct metastasis of colorectal cancer to the urogenital tract is rare and has only been described in case-reports or small case series (10). In contrast, primary tumor in-growth or locoregional or peritoneal metastases is more frequent. Accurate incidence data are currently not available. In our study, involvement of the urological tract was confirmed histopathologically in 21 patients (55%). This shows that it is difficult to preoperatively distinguish inflammatory adhesions between anatomical structures from malignant invasion. This is also demonstrated in other studies investigating *en bloc* resections of urological organs without HIPEC (11). In doubtful intraoperative situations, one often decides in favour of extended *en bloc* resections. This may result in a higher number of complete cytoreductions and better survival at the cost of more

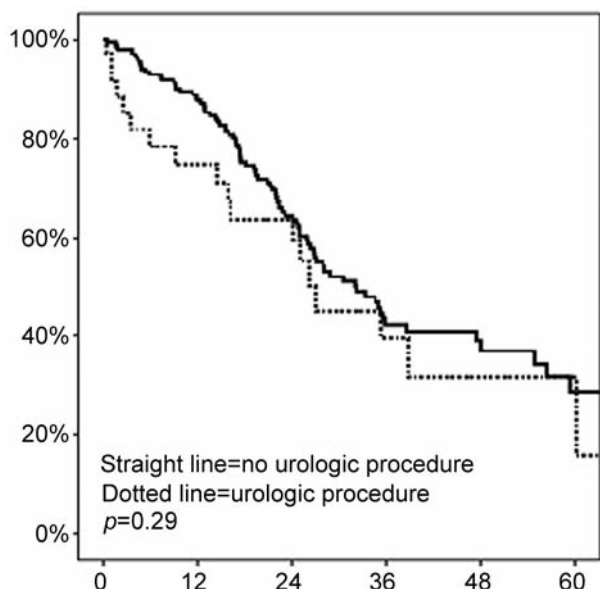


Figure 1. Kaplan-Meier survival curve following HIPEC in months, median OS: 32.1 versus 26.9 months.

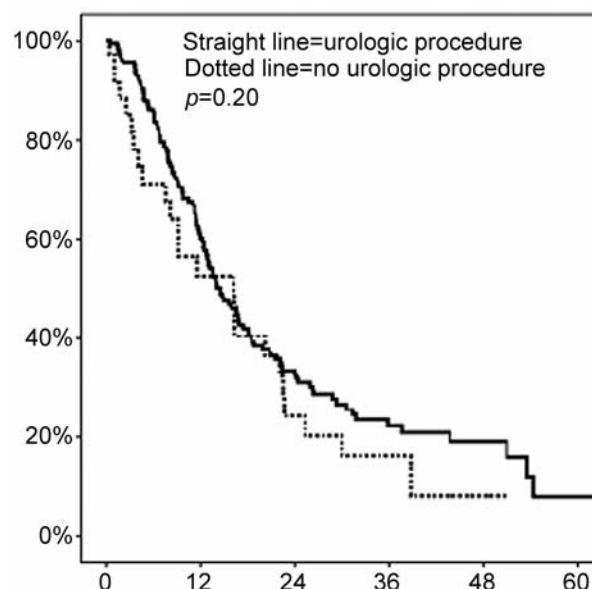


Figure 2. Kaplan-Meier disease-free survival curve following HIPEC in months, median DFS: 14.5 versus 16.2 months.

extensive resections with non-malignant definite pathology findings. Frozen section procedures are more often than not a helpful tool in this situation; in the future, intraoperative tumour-specific fluorescence imaging may possibly aid in a more accurate diagnosis of malignant and non-malignant adhesions and degree of peritoneal dissemination (12).

The current study may be limited by its retrospective design, which precludes definite conclusions especially with regard to the post-operative mortality. To our knowledge, we reported on the largest cohort of urological procedures in exclusive colorectal cancer patients treated with CRS+HIPEC for peritoneal carcinomatosis. Four other studies have investigated the influence of an associated urological procedure during cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (13-16). All these studies incorporated procedures for various primary malignancies. Between 7 and 20% of patients needed a urological procedure. Contrary to our study, all these reports concluded that urinary tract procedures at CRS+HIPEC do not increase postoperative morbidity and can be performed safely. Similar to our study, no adverse effect on the survival of patients treated with CRS+HIPEC was reported.

The rationale of hyperthermic intra-peritoneal chemotherapy is to eradicate residual tumor cells by cytotoxic chemotherapy. Inevitably the chemotherapeutic drugs also affect healthy tissues and impaired wound healing may occur. For instance, decreased strength of colonic

anastomoses has been described in experimental models following hyperthermic intraperitoneal chemoperfusion with mitomycin or cisplatin (17, 18). The effect of hyperthermic intraperitoneal chemotherapy on the healing of urological anastomoses is currently unknown. In our study the number of urological leakages is limited (11%) and comparable to similar urological procedures without hyperthermic intraperitoneal chemotherapy (11).

In conclusion, cytoreductive surgery in combination with HIPEC in patients requiring urological resection, as part of the cytoreduction, is associated with significant postoperative morbidity and mortality, probably due to an overall more extensive cytoreduction. Urological procedures as a part of CRS+HIPEC can be performed safely, with limited urological-associated complications. Long-term survival was shown to be similar in patients with a urological procedure during CRS+HIPEC, compared to patients without additional surgery of the urinary system. Patients with peritoneal carcinomatosis with urologic involvement should be evaluated in an experienced peritoneal surface malignancy centre and treatment should be based on individual patient characteristics. Urological involvement of colorectal peritoneal metastases should not be regarded as an exclusion criterion in these patients.

Conflicts of Interest

The Authors report no conflicts of interest in this work.

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