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REVIEW ARTICLE

Urinary tract involvement in peritoneal metastatic disease: Is this a contraindication to cytoreductive surgery and hyperthermic intraperitoneal chemotherapy?

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Summary

Urinary tract involvement in resectable peritoneal malignancies might require extensive resections and reconstructions in the genitourinary tract during the performance of cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC), a fact which could impair the postoperative course and survival of these patients. We performed a review of the literature to assess whether urinary tract involvement in patients with peritoneal metastases undergoing CRS and HIPEC could affect the postoperative outcomes with respect to morbidity, mortality and survival rates, identifying a total of 6 retrospective studies addressing these clinical questions. Despite their heterogeneity, the existing studies demonstrate that despite a possible increase in postoperative complications when urological procedures are required as part of cytoreduction, survival outcomes do not seem to be affected. This review therefore concludes that urinary tract 6 in peritoneal metastatic disease is not a contraindication to CRS and HIPEC.

Key words: *cancer, cytoreductive surgery, HIPEC, hyperthermic intraperitoneal chemotherapy, peritoneal metastases, urinary tract*

Introduction

Up until recently peritoneal metastatic disease (PM) has been considered a terminal condition, with patients receiving palliative treatment only. CRS and HIPEC have revolutionised the management of selected cases where metastatic disease from an intra-abdominal primary tumor is confined primarily within the peritoneal cavity. Optimal cytoreduction is achieved by removing the primary tumor along with all visible intra-abdominal peritoneal deposits, by combining multi-visceral and peritoneal resections with HIPEC. This strategy has brought surgical oncology into a new era of treatment of disseminated abdominal cancer with curative intent [1]. Despite the considerable morbidity and mortality following the procedure, it seems that the quality of life of patients who undergo CRS and HIPEC is regained at 6 months postoperatively, and can even exceed the preoperative status at 12 months following the procedure [2].

However, with respect to the outcomes from this complex procedure, it is now recognised that optimal cytoreduction is based on two fundamental principles: the careful selection of patients who would benefit from CRS and HIPEC and the expertise of a trained surgical team in performing and looking after patients who have had such complex surgery [3-5]. While it is recognised that resectability of all cancer deposits is essential for optimal cytoreduction [6], a higher volume of

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peritoneal metastases, especially in the presence of previous abdominal surgery, significantly impacts the feasibility of complete cytoreduction and therefore patients' survival [7]. In addition, methods currently used to preoperatively stage the extent of peritoneal metastases are low in sensitivity, usually underestimating the true degree of disease burden and resulting in unexpected intraoperative findings [8-10]. A particularly problematic unexpected finding is the involvement of tumor in the urinary tract, especially the ureters and bladder. In such cases, questions arise such as "if the ureter is involved with tumor, should we excise the involved ureteric segment and re-implant it or consider nephro-ureterectomy?" or "if the bladder is involved is it worth doing a cystectomy?" These issues need to be addressed using the available evidence.

The aim of this review was to summarise the evidence regarding the impact of urinary tract involvement in patients with resectable peritoneal metastases undergoing CRS and HIPEC, particularly focusing on the postoperative outcomes with respect to morbidity, mortality and survival rates.

Methods

We performed a review of published studies assessing the impact of urinary tract involvement in patients with peritoneal metastatic disease that were published by May 2016 in PubMed search engine, using the following combination of key words: "intraperitoneal chemotherapy", "HIPEC", "urinary", "urological", "bladder", "ureter", "stent". The relevant references of the retrieved manuscripts were manually scanned to further identify possible relevant studies. Case reports and case series were excluded, as were studies published in other than the English language.

Table 1. Summary of characteristics and key findings of the studies assessing the impact of urinary tract involvement in patients submitted to CRS+HIPEC for peritoneal metastatic disease

Authors / date	*Sample of patients / incidence of urinary tract involvement / type of primary*	*Type of urological procedure(s) and related complication(s)*	*Study key-points*
Honoré et al [11], 2012	Study sample, n=864 patients (933 CRS+HIPEC procedures) / 48/864 (8%) involvement of urinary tract with relevant urological procedures performed. Primary origin colorectal, n=27, PMP n=18, sarcoma n=2, ovarian n=2, mesothelioma n=2, NET n=1, small bowel n=1	*Urological procedures*: n=4 nephrectomies, n=12 ureteric resections with ureterouretic anastomosis, n=5 ureteric resections with ureterovesical anastomosis, n=8 bladder perforations without partial bladder resection, n=19 bladder perforations with partial bladder resection *Related complications*: 4 uroperitoneal fistulas, 2 rectovesical fistulas	Overall incidence of complications in cases of urinary tract resection: 12% (6/48). 30-day mortality 4% - 0% related to urinary fistulas; 37% & 4% Grade III & IV complications respectively; no significant differences in morbidity In multivariate analysis, malnutrition and PCI>20 the only factors associated with significantly higher occurrence of urinary fistulas (RR 7.33 and 8.33 respectively). Primary origin, HIPEC vs EPIC, prior pelvic surgery, site of urological repair, rectal/vaginal repair did not increase urological complications Urinary tract repair was associated with prolonged length of stay (34 vs 21 days of hospitalisation) Urinary tract fistulas successfully treated with nephropyelostomy and maintenance of catheter in the absence of rectal fistula; otherwise diverting ileostomy performed in addition
Leapman et al [12], 2014	Study sample, n=170 34/170 (20%) required urinary tract reconstruction Case-matched cohort of 38 patients without urinary tract involvement used to compare complication and survival rates / median follow-up 9.4 months Primary origin appendiceal (n=13 vs 11), colorectal (n=12 vs 10), gastric (n=2 vs 3), ovarian (n=2 vs 5), PMP (n=1 vs 4), other (n=4 vs 5)	*Urological procedures*: n= 23 partial bladder resection and primary repair, n=11 ureteric resection, n=8 uretero-ureterostomy, n=3 ureteroneocystotomy, n=1 partial nephrectomy, n=1 pelvic exenteration and ileal conduit, n=1 seminal vesicles/vas deferens excision *Related complications*: 2 ureteric strictures, 1 ureteric obstruction, 1 colo-ileal conduit fistula, 1 ejaculatory and erectile dysfunction	Patients with genitourinary reconstruction had more total organ involvement [mean (SD): 6.5 (2.2) vs. 4.3 (2.3)), and more commonly underwent bowel anastomoses (82.4 vs. 57.9 %] than matched controls No significant differences for 30-day major morbidity need for transfusion, operative time, ICU admission, or length of hospital stay / Persistent urologic sequelae in 5 of 34 patients (14.7 %) On univariate analysis, ureter repair, distal ureteral repair and PCI>20 were associated with development of long-term urologic complications. On binary logistic regression analysis no significant clinical or demographic characteristics predictive of urologic sequelae Median DFS was 9.4 (SE 1.4) months among those with genitourinary resection vs 9.2 (SE 2.8) months in those without genitourinary involvement

CRS: cytoreductive surgery, PMP: pseudomyxoma peritonei, NET: neuroendocrine tumour, PCI: peritoneal carcinomatosis index, HIPEC: hyperthermic intraperitoneal chemotherapy, EPIC: early postoperative intraperitoneal chemotherapy, ICU: intensive care unit, DFS: disease-free survival, OS: overall survival

Table 2. Summary of characteristics and key findings of the studies assessing the impact of urinary tract involvement in patients submitted to CRS+HIPEC for peritoneal metastatic disease

Authors / date	*Sample of patients / incidence of urinary tract involvement / type of primary malignancy*	*Type of urological procedure(s) and related complication(s)*	*Study key-points*
Votanopoulos et al [13], 2014	Study sample, n=864 patients n=864 patients (933 CRS+HIPEC procedures) 550/864 (64%) had preoperatively inserted ureteric stent Ureteric stent placement pre-operatively performed on case-by-case basis 7.3% incidence of urinary tract involvement requiring an additional urologic resection and reconstruction Primary origin n=404 appendiceal, n=199 colorectal, n=59 ovarian, n=56 mesothelioma, n=146 other/unknown	*Urological procedures:* n=8 nephrectomies, n=1 partial nephrectomy, n= 6 ureteric resections, n=2 ureterolysis, n=5 ureterorrhaphies, n= 12 cystorrhaphies , n=27 partial cystectomies, n=1 radical cystectomy with urinary diversion, n=2 excisions of seminal vesicle, n=1 partial prostatectomy *Related complications:* n=7 ureteric injuries, n=9 urinary fistulas, n=13 cystotomies	Preoperative ureteric stent placement was more frequent in patients with higher volume or unfavourable location of disease, low anterior resection, R2 resection, malnutrition and was positively associated with operative blood loss, length of surgery, length of hospitalization and ICU stay Preoperative cystoscopy on one occasion led to identification of metastatic spread as unresectable / not proceeded with CRS+HIPEC Comparing patients requiring urological procedures vs not, no significant difference in 30-day (27.0 vs 19.3 %) and 90-day (9.5 vs 6.0 %) grade III/IV complications, 30-day (0 vs 2.6 %) and 90-day (1.6 vs 1.9 %) mortality or completeness of optimal cytoreduction(44.4 vs 45.8 %). Survival similar between patients who had or not urologic procedures as a component of CRS/HIPEC in appendiceal primary (median OS 17.4 vs. 18.5 months for high-grade, median OS 43.6 vs 106.9 months for low-grade) and colorectal primary lesions (median OS 23.0 vs. 15.8 months)
Smeenk et al [14], 2006	Study sample, n=92 patients, all with PMP Urinary tract involvement requiring urological procedure intra-operatively in 7/92 (7.6%), Origin of PMP in patients with urinary tract involvement was appendix (n=3), ovary (n=2) and urachus (n=2) Pre-operative detection of urinary tract involvement in 2/7 patients (presenting with hydronephrosis)	*Urological procedures:* n=5 resection and re-implantation of a part of the ureter, n=2 resection and re-implantation of distal ureter due to ureteric injury, n=2 total cystectomies, n=1 partial cystectomy, n=1 formation of continence pouch *Related complications:* n=3 suture leaks of bladder, n=4 bladder fistulas (2 vesicoenteral, 2 vesicovaginal)	Surgical treatment was necessary in 3 cases of major urologic complications (re-laparotomy for suture leak of bladder, 2 re-laparotomies for 3 suture leaks of bladder and vesicoenteral fistula and relaparotomy for vesicoenteral fistula) Median hospital stay of patients with urological complications in general was 25.5 days (range 15–72), compared with 33 days (range 15–149) for patients with complications other than urologic 4/7 major urological complications occurred in patients with urinary tract involvement and 3/7 occurred in patients without urinary tract involvement – 7/7 patients with urinary tract involvement by PMP had previous history of pelvic surgery

For abbreviations see footnote of Table 1

Results

The literature search yielded 6 suitable clinical studies, all of which evaluated the significance of urological procedures performed during cytoreductive surgery and followed by HIPEC in patients with peritoneal metastatic disease [11-16]. A summary of the included studies is presented in Tables 1-3, including patient demographics, the incidence of urinary tract involvement requiring urological procedures to achieve optimal cytoreduction and associated complications. Although the 6 studies had significant differences in terms of demographics and clinical characteristics of the patients, there was detailed information regarding the extent of urinary tract involvement, type and number of urological procedures performed, associated complications and their impact on outcome.

In all studies, the authors performed retrospective data analyses from prospectively maintained institutional databases. The overall incidence of urinary tract involvement requiring urological procedures was 7-8% in 3 of the included studies [11,13,14,16], while Braam et al. and Leapman and co-workers reported a significantly higher incidence of 14-20% [12,15]. The majority of urological procedures were related to ureteric and bladder involvement. As a result, urinary tract fistulas, bladder leaks and ureteric strictures accounted for the majority of associated complications in the postoperative period. Honoré et al. and Leapman et al. [11,12] defined that a Peritoneal Cancer Index (PCI) value greater of than 20 was a prognostic factor of urological complications

Table 3. Summary of characteristics and key findings of the studies assessing the impact of urinary tract involvement in patients submitted to CRS+HIPEC for peritoneal metastatic disease

Authors / date	*Sample of patients / incidence of urinary tract involvement / type of primary malignancy*	*Type of urological procedure(s) and related complication(s)*	*Study key-points*
Braam et al [15], 2015	Study sample, n=92 patients, all with CRC primary Urinary tract involvement requiring urological procedure intra-operatively in 38/267 (14%)	*Urological procedures:* n=21 partial cystectomies, n=3 complete cystectomies, n=13 partial ureteral resection, n=1 nephrectomy *Related complications:* n=3 urinary tract infections, n=4 urine leakage/ urinomas	Patients with urologic procedures presented more frequently with metachronous peritoneal metastases (66% vs 42%, p=0.006), had significantly greater operating time (median 460 vs 400 min, p<0.001) greater blood loss (median 1275 vs 600 mls, p=0.004) and greater LOS (13 vs 10 days, p<0.001) n.s. differences regarding completeness of cytoreduction, PCI and location of primary cancer however urological procedures more frequent in pts with sigmoid primary Overall 30-day mortality 1.5% - cause was gastrointestinal leakage in 100% of cases / 8% vs 0.5% in cases with vs without urological procedure (p<0.001) Severe complications (Grade 3a or greater) & reoperation rates more frequent in cases of urological procedure (47% vs 20%, p<0.001 and 37% vs 15, p=0.001 respectively)/ in multivariate analysis urological procedure & operating time correlated to severe post-operative complications n.s. differences in OS & DFS with respect to the performance or not of urological procedure – 26.9 vs 32.1 months, p=0.29 & 16.2 vs 14.5 months respectively, p=0.20)
Lyon et al [16], 2016	Study sample, n=889 patients (938 cytoreductive procedures, 86% with HIPEC) Preoperative ureteral stenting in 2.3% of patients Urinary tract involvement requiring urological procedure intra-operatively in 71/938 (7.6%) Primary tumour origin: appendiceal 43.8%, colorectal 25.9%, mesothelioma 9.8%, other 20.5%	*Urological procedures:* n=32cystorrhaphies, n=5 partial cystectomies, n=21 ureteral repairs, n=5 ureteral re-implantations, n=5 nephrectomies, n=1 partial nephrectomy, n=2 nephroureterectomy, n=2 seminal vesicle resections, n=2 cystectomies *Related complications* (urologic procedures group): urine leak/fistula in 2/71 (2.8%), ureteral stent placement for obstruction in 2/71 (2.8%), and vesicovaginal fistula and ureteroenteric anastomotic stricture in 1/71 (1.4%) each	Patients requiring urologic procedures had a longer length of stay [15 (11–23) vs 12 (9–18) days in urological procedures group vs non-urological procedures group, p=0.003] n.s. difference between groups for length of ICU stay rate of ICU readmission or need for reoperation during initial postoperative hospitalization no difference in overall perioperative complications between groups; however, cases with a urologic procedure had more major complications (31% vs 20%, p=0.028) n.s. difference in perioperative mortality between groups (2.8% in urological procedures vs 1.6% in non-urological procedures group) n.s. differences in OS with respect to the performance or not of urological procedure for patients with PSM of colorectal and appendiceal origin

For abbreviations see footnote of Table 1

in patients who underwent a genitourinary resection/reconstruction during the cytoreduction. Of note, Braam and co-workers in their cohort of patients did not find a statistically significant difference of the PCI score in cases of urinary tract involvement [15]. Of note, Votanopoulos et al. [13] who used prophylactic ureteric stent insertion prior to CRS/HIPEC on an *ad hoc* basis, recommend routine ureteric stenting for patients with an estimated PCI>18. In their cohort, 64% of the patients had been stented prior to CRS/ HIPEC in order to prevent ureteric injury. This highlights an important issue, as prophylactic ureteric stenting has been proposed as a feasible strategy in order to prevent urinary tract complications in CRS, particularly in the absence of stent-related complications [17-19].

With respect to the impact of urological procedures on the length of hospitalisation, the results appear to be conflicting. While Honoré et al., Braam et al. and Lyon et al. reported an approximately 25-50% prolongation of length of stay in

patients undergoing urinary tract reconstruction [11,15,16], Leapman et al. [12] and Votanopoulos et al. [13] did not find any significant differences in the duration of hospitalisation. In addition, Smeenk et al. [14] identified that non-urological complications were responsible for a longer length of stay in pseudomyxoma peritonei patients. Interestingly, Braam et al. demonstrated that the presence of gastrointestinal leaks accounted for the 100% of their 30-day mortality. However, in their series, the occurrence of a gastrointestinal leak was more frequent in the group of patients with urological procedures [15].

Importantly, in 5 out of the 6 studies [11-14,16], genitourinary resection and reconstruction did not impact negatively on overall postoperative morbidity and mortality rates, despite the fact that urinary tract involvement was more frequent in patients with greater peritoneal dissemination requiring multiple visceral resections to achieve optimal cytoreduction. On the contrary, Braam and co-workers found that the need for urological procedures as part of cytoreduction was significantly associated with greater re-operation rates and greater postoperative morbidity [15]. It should be noted that the studies assessing the impact of urological procedures on survival rates [12,13,15,16] failed to demonstrate any significant differences in disease-free and overall survival. Both Braam et al. and Votanoploulos et al. demonstrated that performing urological procedures did not affect the completeness of cytoreduction [13,15], which could explain why survival rates were not affected.

Conflict of interests

The authors declare no confict of interests.

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