International Journal on Obstetrics and Gynecology

How Safe Is Urologic Surgery in Women with Locally Advanced Ovarian Cancer Concomitant to Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy?

Research Article

Volume 5 Issue 1- 2025

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Article History

Received: March 14, 2025 Accepted: March 18, 2025 Published: March 19, 2025

Abstract

Background-Aims: Urologic surgery is occasionally necessary during cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) in women with locally advanced ovarian cancer. The purpose of the study is to evaluate the impact of urologic surgery carried out concomitantly to CRS and HIPEC. Patients-Methods: Clinical variables were correlated to morbidity, in-hospital mortality, recurrence, and survival in patients with locally advanced ovarian cancer undergoing CRS and HIPEC with or without urologic surgery.

Results: From 2013 to 2024, 13 patients with locally advanced ovarian cancer underwent urologic intervention concomitant to CRS plus HIPEC. They comprised 4.26% of patients with ovarian cancer who underwent CRS and HIPEC during the same period. There were more suture lines and anastomoses in patients with urologic surgery, in addition to longer duration of surgery and ICU stay. The overall survival, the recurrence rate, the morbidity, and the in-hospital mortality were not affected by urologic surgery ($p>0.05$).

Conclusions: Patients with locally advanced ovarian cancer may safely undergo urologic surgery during CRS and HIPEC with the same morbidity and mortality as patients undergoing CRS and HIPEC without urologic intervention. The recurrence and the overall survival are not affected by the addition of urologic operation. The duration of surgery and the ICU stay is extended significantly in patients undergoing urologic surgery during CRS and HIPEC.

Keywords: Urologic Surgery; Cytoreduction; HIPEC; Morbidity; Mortality; Survival; Recurrence; Ovarian Cancer

Introduction

Complete cytoreductive surgery without macroscopically visible residual tumor has been established as the most significant prognostic factor of long-term survival in patients with locally advanced ovarian cancer [1]. The resection of all or nearly all the macroscopically visible tumor is achievable by using standard peritonectomy procedures in addition to multi-visceral resections whenever they are necessary [2,3]. Hyperthermic intraperitoneal chemotherapy (HIPEC) is used after the completion of cytoreduction with the purpose to eradicate the microscopic residual tumor. The peritoneum is the "first line of defense" and protects the retroperitoneal organs from invasion at the time of the initial peritoneal dissemination [4].

Nevertheless, high-grade cancer emboli adhered at the peritoneal surfaces may invade the sub-peritoneal space and progress as real metastases at the retroperitoneal anatomic structures [5]. Yet, the retroperitoneal structures are directly exposed to cancer emboli after iatrogenic resection of the overlying peritoneum. A few years ago, the involvement of the retroperitoneal organs in diseases with peritoneal malignancy had been considered a relative contraindication for CRS. However, the urinary anatomic structures may be involved in locally advanced ovarian cancer as a result of either a direct and spontaneous tumor invasion preoperatively or as an iatrogenic injury intraopera-

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tively during surgery. The resection of cancerous tissue infiltrating the anatomic structures of the urinary tract implies that a urological intervention is rather mandatory.

The surgical procedure in the involved urinary tract may result to complete cytoreduction and benefit the patient. Occasionally, a preoperatively uninvolved urinary tract may be iatrogenically injured during CRS requiring immediate repair. It appears that surgical operations in the urinary tract during CRS and HIPEC are sometimes absolutely required. Therefore, urinary tract involvement should not be considered an absolute contraindication for cytoreduction. Major morbidity after CRS and HIPEC for ovarian cancer has been described in the international literature but there are a few data about the urologic implications on the outcome of these patients [6].

The purpose of the present study is the evaluation of the impact of urologic surgical operations concomitant to CRS and HIPEC in patients with locally advanced ovarian cancer.

Patients-Methods

The files of the patients with locally advanced ovarian cancer that underwent at least one urologic surgical procedure during CRS and HIPEC from 2012 until 2024 were retrieved. The data were retrospectively reviewed in a prospectively maintained database and analyzed. The short and long-term results of women with ovarian cancer treated by CRS and HIPEC (C Group) were compared to the results of those women with ovarian cancer that underwent urological surgical operations (UI Group) during CRS and HIPEC.

The selection of patients for CRS and HIPEC was based on radiologic findings. Neither the PCI nor the Fagotti score were used. Patients with multiple segmental intestinal obstructions, with tumor > 5cm in its largest diameter on the Treitz ligament, with extensive seeding of the small bowel resulting to extensive segmental intestinal resection, with unresectable distant metastases, or with extensive seeding of the ureters were excluded from surgery. Laparoscopy was rarely used for those cases with inconsistent radiologic findings and only in newly diagnosed cases.

All patients signed an informed consent and the Ethical Committee of the Hospital approved the publication of the study (EUROMEDICA Kyanous Stavros Ethical Committee decision number: 93/12.04.2024). Patients with ovarian cancer and peritoneal carcinomatosis (locally advanced ovarian cancer or FIGO stage III) were included in the study. The patients' age, the performance status (PS), the classification according to ASA stage, the tumor volume (TV), the extent of previous surgery (PSS), the extent and distribution of peritoneal carcinomatosis (PCI), the completeness of cytoreduction (CC-score), the number of peritonectomy procedures (PP), the number of suture lines (SL), the number of anastomoses (A), the treatment with neo-adjuvant chemotherapy (NACT), the estimated blood loss (BL), the blood units transfused during surgery (BU), the fresh frozen plasma units (FFP) transfused during surgery, the duration of surgery (DS), the duration of hospitalization (DH), and the duration of ICU stay were all recorded in detail.

The performance status was assessed according to Karnofsky performance scale. Implantations with maximal diameter >0.5cm were assessed as large-volume tumors and those with maximal diameter <0.5cm were assessed as small-volume tumors [7]. The blood loss was estimated in ml and the duration of surgery in minutes. The standard peritonectomy procedures included the greater omentectomy+splenectomy, the lesser omentectomy, the right and left subdiaphragmatic peritonectomy, the right and left parietal peritonectomy, the pelvic peritonectomy, and the cholecystectomy+resection of the omental bursa. Right colectomy, subtotal colectomy, segmental intestinal resection, subtotal or total gastrectomy, and distal pancreatectomy were other visceral resections than those included in standard peritonectomy procedures that were considered separately as additional procedures.

Maximal abdominal exploration was possible through a midline abdominal incision from the xiphoid process to the symphysis pubis. The PSS was estimated according to previous surgical reports. The tumor volume was evaluated after complete lysis of the adhesions and the extent of peritoneal carcinomatosis was estimated using the peritoneal cancer index (PCI). The completeness of cytoreduction was assessed using the CC-score after the completion of the surgical operation [7].

Standard peritonectomy procedures (PP) were always used for cytoreduction [2,3]. The resection of the xiphoid process facilitated the subdiaphragmatic peritonectomy procedures and was almost always used for bilateral peritonectomy procedures. The gall-bladder was routinely removed even if there were no visible implants on its surface. The surgical interventions involving the urinary system included partial resection of the ureter either with uretero-ureteral anastomosis or with ureteral implantation in the bladder, partial cyctectomy, nephrectomy, and bladder repair after iatrogenic trauma.

After tumor resection and before the reconstruction of the alimentary tract, HIPEC was performed for 90 min at 42.5-430C using the open abdominal (Coliseum) technique. The skin edges of the abdominal cavity were adequately elevated so that 2-3 liters of prime solution were instilled. A heater circulator with two roller pumps, one heat exchanger, one reservoir, an extracorporeal system of two inflow and two outflow tubes, and 4 thermal probes was used for HIPEC (Sun Chip, Gamida Tech, Paris, France). The prime solution of normal saline or Ringer's lactate was instilled rapidly, and as soon as the mean abdominal temperature reached 400C, the cytostatic drugs were administered in the abdomen.

The continuity of the gastrointestinal tract was restored after the completion of HIPEC. Proximal stoma defunctioning was always performed in those cases in which more than two gastrointestinal anastomoses needed to be protected. The reconstruction of the urinary tract was also carried out after the completion of HIPEC unless bladder trauma was evident or partial cystectomy had been performed. Immediate repair of the urinary tract was performed for bladder trauma or partial cyctectomy. After partial resection of the distal third of the ureter and before the reconstruction of the continuity of the urinary tract, the urine produced by the involved kidney was selected in a urine collector by a ureteric catheter.

The involved ureter was adequately mobilized and externalized with the catheter through a small hole at the lateral abdominal wall. In those cases that the resection was performed in the middle or the upper third of the involved ureter the uretero-ureteral anastomosis was carried out immediately after resection, and always protected by a pig-tail catheter. Cis-platin (50mg/m2) combined with doxorubicin (15mg/m2) was used for 90min in HIPEC in addition to ifosphamide (1300mg/m2), and mesna (260mg/m2), which were administered IV. All patients remained in the ICU for at least 24hours. The complications were recorded in detail and their severity was evaluated according to Clavien-Dindo classification [8]. All the resected specimens were histopathologically examined in detail and all patients were scheduled to receive adjuvant chemotherapy one month after surgery.

Follow-up

All patients were followed-up every 3 or 4months during the first year after surgery and every 6months later. Follow-up included physical examination, hematologic-biochemical examinations, tumor markers (CEA, CA-125), thoracic and abdominal imaging (CT-scan, or MRI, or PET-CT scan). The recurrences and the sites of recurrence were recorded in detail. The disease-free survival was estimated as the time from initial surgery until the time of recurrence. The overall survival was estimated as the time from initial diagnosis until the time of death or until the time of the last examination.

Statistical Analysis

Statistical analysis was possible using SPSS (Statistical Package for

Social Sciences, version 21). The proportion of patients with a given characteristic was compared by chi-square analysis or by Pearson's test. The survival curves were obtained using the Kaplan-Meier method and the comparison of curves was carried out using the log-rank test. Logistic regression analysis was used to identify the independent variables of recurrence, morbidity, and in-hospital mortality (30 days postoperatively). A p value < 0.05 was considered statistically significant.

Results

The files of 305 women with locally advanced ovarian cancer (FIGO stage III) who underwent CRS and HIPEC were retrieved and analyzed. There were 13/305 (4.26%) patients (UI Group) that underwent urologic surgery during CRS and HIPEC. The other 292/305 patients, consisted the Conventional Group (C Group), were treated with CRS and HIPEC without urologic surgical operation, and were compared with the UI Group.

No statistically significant difference between the C and UI Group was found in overall survival (p=0.184). The 5-year survival rate of C and UI Group women was 70% and 59% respectively (Figure 1).

The groups were similar for age, tumor volume, performance status, ASA stage, morbidity, mortality, completeness of cytoreduction, extent of previous surgery (PSS), extent of peritoneal malignancy (PCI), lymph node resection, estimated blood loss, transfused blood units, transfused FFP units, days of hospitalization, and recurrences (p>0.05). The morbidity rate for C and UI Group was 38.4% and 38.5% respectively. The hospital mortality for C and UI Group was 3.4% and 0% respectively.

The recurrence rate for C and UI Group was 49% and 31% respectively. Similarly, stoma defunctioning was performed in 4.5% for C Group and in 15.4% for UI Group. This difference showed a trend to statistical significance (p=0.055). Finally, neo-adjuvant chemotherapy was given in 26.7% of the patients of C Group and in 30.8% of patients of the UI Group. Statistically significant difference was identified in the number of suture lines, the number of anastomoses, the duration of surgery, and the ICU stay. In patients of the C Group there were more suture lines and anastomoses while the ICU stay as well as the duration of surgery was longer in UI Group patients (Table 1).

The urologic operations were as following: 1 (0.3%) uretero-ureteral anastomosis, 5 (1.6%) ureteral implantations in the bladder, 2 (0.7%) partial cystectomies, 1 (0.3%) nephrectomy, and 4 (1.3%) bladder repairs.One patient (7.7%) was complicated by cardiac failure, 1 (7.7%) by renal failure, 2 (15.4%) with wound infection, 1 (7.7%) by sepsis, and 1 (7.7%) patient by large bowel penetration. According to Clavien-Dindo there were 15 patients (4.9%) with Grade I complications, 9 (3%) with Grade II, 5(1.6%) with Grade IIIA, 40 (13.1%) with Grade IIIB, 4 (1.3%) with Grade IVA, 0 (0%) with Grade IVB, and 10 (3.3%) with Grade V complications. All patients with Grade V manifested multiple system organ failure and died.

Morbidity was found to be related to advanced age (>65 years), high ASA class, incomplete cytoreduction, multiple peritonectomy procedures, conventional lymph node resection, extended peritoneal dissemination, blood loss that required more than 3 blood units transfusions, in addition to more than 2 suture lines and gastrointestinal anastomoses (p<0.05), (Table 2). The independent variables of morbidity were the extent of peritoneal dissemination, the transfused blood units, and the ASA class (Table 2).

The performance status, the ASA class, the number of peritonectomy procedures, the extent of peritoneal dissemination, the blood loss, the transfused blood units, the transfused FFP units, the number of suture lines, and the number of anastomoses were found to be related to hospital mortality (p<0.05). The performance status and the number of the transfused FFP units were the independent variables of hospital mortality (Table 3).

Recurrence was recorded in 156 patients (39.2%) during follow-up. In 74 patients (18.6%) recurrence was recorded at distant sites and in 83 (20.9%) patients the recurrence was loco-regional. The recurrence was recorded in 151 patients of the C Group (39.2%) and in 5 patients (38.5%) of the UI Group. Distant metastasis was found in 1 of them (7.7%) and 4 patients (30.8%) were identified with local-regional recurrence. The extent of prior surgery, the use of neo-adjuvant chemotherapy, the age, and the duration of surgery were found to be related to recurrence. Patients that had undergone extended surgery previously were at high risk to develop recurrence. The use of neo-adjuvant chemotherapy and advanced age (>65 years) appeared to protect the patients from developing recurrence. The longer the duration of surgery the more probable the recurrence was. The extent of previous surgery, the use of neo-adjuvant chemotherapy, and the duration of surgery were identified as independent variables of recurrence (Table 4).

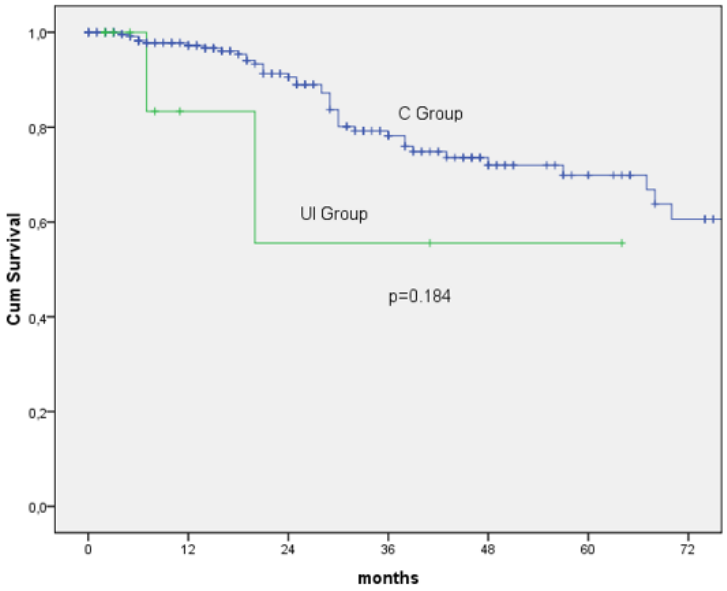

Figure 1: Overall survival for ovarian cancer patients with CRS+HIPEC (blue line) and for those with urologic surgery concomitant to CRS+HIPEC (green line).

Table 1: Comparison of Urological Intervention Group (UI) patients to Control Group (CG).

Variable	C Group	UI Group	p value
5- year survival rate	70%	59%	0.184
Age <65/>65)	174/118	08-May	0.531
PS (90-100%/70-80%/50-60%)	261/28/3	12-01-2000	0.831
ASA stage (I/II/III)	245/45/2	12-01-2000	0.518
PSS (PSS-0/PSS-1/PSS-2/PSS-3)	105/50/94/43	4/2/4/3	0.831
Tumor volume (large/small)	263/29	13/0	0.227
CC-score (CC-0/CC-1)	184/108	08-May	0.603
LNR (abdominopelvic/conventional)	114/178	04-Sep	0.944
PP (<5, 6-10, >10)	117/131/44	05-05-2003	0.726
Morbidity	112	5	0.754
Hospital mortality	10	0	0.537
Recurrence	143	4	0.626
Stoma defunctioning	13	2	0.055
DH (<8/8-15/16-30/>30 days)	28/183/76/5	3/6/3/1	0.237
NACT	78	4	0.601
PCI (0-12/13-20/21-39)	157/72/63	07-02-2004	0.697
BL (0-400/401-800/>801)	236/41/15	11-02-2000	0.624
BU (0/1-2/3-4/>4)	140/105/41/6	3/8/2/0	0.133
FFP (0/1-2/3-4/>4)	82/21/112/77	3/0/6/4	0.596
SL (<2/>2)	285/7	09-Apr	<0.001
A (<2/>2)	286/6	10-Mar	<0.001
ICU stay (<3/3-7/>7)	272/17/3	10-02-2001	0.01
DS (<300/300-480/>480)	30/254/8	0/5/8	<0.001

Explanations: PS=performance status, PSS=prior surgery score, CC-score=completeness of cytoreduction score, LNR=lymph node resection, PP=number of peritonectomy procedures, DH=days of hospitalization, NACT=neo-adjuvant chemotherapy, PCI=peritoneal cancer index, BL= blood loss, BU=transfused blood units, FFP=transfused units of FFP, SL=number of suture lines, A=number of anastomoses, DS=duration of surgery.

Table 2: Urologic operations.

Urologic operation	No of pts	%
Uretero-ureteral anastomosis	1	0.3
Ureteral implantation in the bladder	5	1.6
Partial cyctectomy	2	0.7
Nephrectomy	1	0.7
Bladder repair	4	1.3

Table 3: Type of complications.

Complication	No of pts	%
Cardiac failure	1	7.7
Renal failure	1	7.7
Wound infection	2	15.4
Sepsis	1	7.7
Large bowel penetration	1	7.7

Table 4: Severity of morbidity (Clavien-Dindo classification) in 305 women.

Grade	No of pts	%
I	15	4.9
II	9	3
IIIA	5	1.6
IIIB	40	13.1
IBA	4	1.3
IVB	0	0
V	10	3.3

Table 5: Analysis of morbidity.

	Univariate analysis		Multivariate analysis			
	Yes	OR (95% CI)	p value	aOR	95% CI	p value
Age			0.012			
<65 years	40 (22.0)	Ref.				
≥65 years	43 (35.0)	1.91 (1.15–3.18)				
PS			<0.001			
90-100%	64 (23.4)	Ref.				
Other	19 (59.4)	4.77 (2.23–10.20)				
ASA class			<0.001			
I	58 (22.6)	Ref.				
II-III	25 (52.1)	3.73 (1.97–7.05)		3	1.46-6.14	0.003
TV			0.205			
Small	5 (17.2)	Ref.				
Large	78 (28.3)	1.89 (0.70–5.13)				
CC-score			<0.001			
CC-0	37 (19.3)	Ref.				
CC-1	38 (41.3)	2.95 (1.70-5.10)	<0.001			
CC-2 / CC-3	8 (38.1)	2.58 (1.00-6.67)	0.05			
PP			<0.001			
≤5	18 (14.8)	Ref.				
06-Oct	40 (29.4)	2.41 (1.29-4.48)	0.006			
>10	25 (53.2)	6.57 (3.07-14.05)	<0.001			
LNR			0.008			
Abdom-ino-pelvic	22 (18.6)	Ref.				
Conven-tional	61 (32.6)	2.11 (1.21-3.68)				
Stoma			0.585			
No	78 (26.9)	Ref.				
Yes	5 (33.3)	1.36 (0.45-4.10)				
NACT			0.502			

No	63 (28.3)	1.22 (0.68-2.19)				
Yes	20 (24.4)	Ref.				
PCI			<0.001			
≤13	22 (13.4)	Ref.		Ref.		
14-20	25 (33.8)	3.29 (1.70-6.36)	<0.001	2.73	1.34–5.55	0.006
>20	36 (53.7)	7.50 (3.88-14.47)	<0.001	5.34	2.61–10.95	<0.001
BL			<0.001			
≤400	56 (22.7)	Ref.				
401-800	18 (41.9)	2.46 (1.25-4.82)	0.009			
>800	9 (60.0)	5.12 (1.75-14.99)	0.003			
BU			<0.001			
0	22 (15.4)	Ref.		Ref.		
01-Feb	35 (31.0)	2.47 (1.35-4.52)	0.003	1.53	0.79-2.99	0.208
03-Apr	21 (48.8)	5.25 (2.48-11.12)	<0.001	2.76	1.19-6.39	0.018
>4	5 (83.3)	27.50 (3.06-246.84)	0.003	14.7	1.43-151.46	0.024
FFP units			<0.001			
0	16 (18.8)	Ref.				
01-Feb	3 (14.3)	0.72 (0.19-2.74)	0.629			
03-Apr	23 (19.5)	1.04 (0.51-2.12)	0.905			
>4	41 (50.6)	4.42 (2.20-8.87)	<0.001			
No SL			0.038			
1	77 (26.2)	Ref.				
2	6 (54.5)	3.38 (1.00-11.40)				
No A			0.007			
0-2	77 (26.0)	Ref.				
>2	6 (66.7)	5.69 (1.39-23.30)				
UO			0.768			
No	79 (27.1)	Ref.				
Yes	4 (30.8)	1.20 (0.36-4.00)				
DS			0.061			
<300	3 (10.0)	Ref.				
301-480	74 (28.6)	3.60 (1.06-12.23)	0.04			
>480	6 (37.5)	5.40 (1.13-25.81)	0.035			

Explanations: PS=performance status, PSS=prior surgery score, TV=tumor volume, PP=number of peritonectomy procedures, CC-score=completeness of cytoreduction score, LNR=lymph node resection, PCI=peritoneal cancer index, BL= blood loss, BU=transfused blood units, FFP=transfused units of FFP, SL=number of suture lines, A=number of anastomoses, UO=urologic operation, DS=duration of surgery.

Table 6: Analysis of hospital mortality.

	Univariate analysis			Multivariate analysis		
	Yes	OR (95% CI)	P Value	aOR	95% CI	p value
Age			0.197			
<65 years	4 (2.2)	Ref.				
≥65 years	6 (4.9)	2.28 (0.63–8.26)				
PS			<0.001			
90-100%	5 (1.8)	Ref.				
Other	5 (15.6)	9.93 (2.70–36.47)		4.27	1.05-17.4	0.043
ASA			0.032			
I	6 (2.3)	Ref.				
II-III	4 (8.3)	3.80 (1.03–14.03)				
TV			0.297			
Small	0 (0.0)	-				
Large	10 (3.6)	-				
CC-score			0.151			
CC-0	4 (2.1)	Ref.				
CC-1	4 (4.3)	2.14 (0.52-8.74)	0.291			
CC-2 / CC-3	2 (9.5)	4.95 (0.85-28.81)	0.075			
PP			0.008			
≤5	2 (1.6)	Ref.				
06-Oct	3 (2.2)	1.35 (0.22-8.24)	0.743			
>10	5 (10.6)	7.14 (1.34-38.21)	0.022			
LNR			0.566			
Abdom-ino-pelvic	3 (2.5)	Ref.				
Conven-tional	7 (3.7)	1.49 (0.38-5.88)				
Stoma			0.465			
No	10 (3.4)	-				
Yes	0 (0.0)	-				
NACT			0.221			
No	9 (4.0)	3.41 (0.43-27.32)				
Yes	1 (1.2)	Ref.				
PCI			0.049			
≤13	2 (1.2)	Ref.				
14-20	3 (4.1)	3.42 (0.56-20.93)	0.183			
>20	5 (7.5)	6.53 (1.24-34.55)	0.027			
BL			0.002			
≤400	4 (1.6)	Ref.				
401-800	5 (11.6)	7.99 (2.06-31.10)	0.003			

>800	1 (6.7)	4.34 (0.45-41.44)	0.202			
BU			<0.001			
0	0 (0.0)	Ref.				
01-Feb	5 (4.4)					
03-Apr	3 (7.0)	3.77 (0.87-16.37)	0.077			
>4	2 (33.3)	25.10 (3.70-170.24)	0.001			
FFP			0.001			
0	0 (0.0)					
01-Feb	0 (0.0)	Ref.				
03-Apr	2 (1.7)					
>4	8 (9.9)	12.16 (2.53-58.58)	0.002	7.55	1.41-40.48	0.018
No SL			0.005			
1	8 (2.7)	Ref.				
2	2 (18.2)	7.94 (1.47-42.87)				
No A			0.001			
0-2	8 (2.7)	Ref.				
>2	2 (22.2)	10.29 (1.84-57.52)				
UO			0.497			
No	10 (3.4)	-				
Yes	0 (0.0)	-				
DS			0.474			
<300	0 (0.0)	Ref.				
301-480	9 (3.5)					
>480	1 (6.3)	2.07 (0.25-17.46)				

Explanations: PS=performance status, PSS=prior surgery score, TV=tumor volume, PP=number of peritonectomy procedures, CC-score=completeness of cytoreduction score, LNR=lymph node resection, PCI=peritoneal cancer index, BL= blood loss, BU=transfused blood units, FFP=transfused units of FFP, SL=number of suture lines, A=number of anastomoses, UO=urologic operation, DS=duration of surgery.

Table 7: Analysis of recurrence.

	Univariate analysis	**Multivariate analysis**			
Variable	p value	HR	p value	95% CI	
PS	0.273				
ASA	0.366				
PSS	0.003	14.04	<0.001	0.58-0.843	
TV	0.43				
CC-score	0.574				
LNR	0.455				
Stoma	0.602				
NACT	0.012	5.536	0.019	1.1-2.838	
PCI	0.864				
BL	0.882				
BU	0.05				
FFP	0.652				

Morbidity	0.096				
SL	0.666				
A	0.716				
UO	0.956				
Age	0.02				
DS	0.03	6.915	0.009	0.276-0.829	

Explanations: PS=performance status, PSS-prior surgery score, TV=tumor volume, CC- score=completeness of cytoreduction score, LNR=lymph node resection, NACT=neo-adjuvant chemotherapy, PCI=peritoneal cancer index, BL=blood loss (in ml), BU=transfused blood units, FFP=transfused FFP units, SL=number of suture lines, A=number of anastomoses, UO=urologic operation, DH=days of hospitalization, ICU=days of ICU stay, DS=duration of surgery (in min).

Discussion

A few years ago the identification of peritoneal metastases at the urinary tract was considered an almost absolute contraindication for radical treatment of peritoneal malignancy using CRS and HIPEC. Nevertheless, urologic surgery was carried out during CRS and HIPEC following iatrogenic injury of the bladder or the ureters although it was believed that morbidity and mortality could possibly be adversely influenced. Suturing of the bladder, uretero-ureteral anastomosis, re-implantation of the ureter in the bladder was frequently required particularly in patients with recurrent peritoneal carcinomatosis. Since the last decade the experience with urologic surgical manipulations following iatrogenic trauma of the urinary tract has changed the concept that urinary tract involvement is a contraindication for CRS and HIPEC. Over the last 15 years, urologic surgery during CRS and HIPEC has been performed in many tertiary centers for oncological reasons with the same mortality and morbidity as cytoreductions without urologic intervention [9-14].

It has been estimated that urologic intervention during CRS and HIPEC is required in 7-21% [12-14]. In our study the incidence of urologic surgery in women with locally advanced ovarian cancer did not exceed 4.26%. In one case the upper surface of the right kidney was totally involved with implantantions and in two more cases the bladder was partially invaded by tumor. In the first case right nephrectomy was mandatory and in the other two cases partial resection of the bladder was absolutely necessary. All the other 10 cases (77%) were iatrogenic trauma. It is obvious that the urologic surgical intervention might have been probably avoided in 10 cases. Moreover, 11 of the UI Group patients had undergone in the past extensive cytoreductive surgery and they were vulnerable to iatrogenic trauma of the urinary tract. No patient had preoperatively undergone ureteral stenting.

The preoperative ureteral stenting does not mean that ureteral trauma may be definitely avoided but it is a method of protection of the ureteral anatomic integrity. Duzgun et al. reported that urologic intervention during CRS and HIPEC was required in 21% of the patients undergoing CRS and HIPEC despite routine preoperative ureteral stenting [15]. Yet, Coccolini et al. strongly advocate pre-operative stenting in patients undergoing CRS and HIPEC, although they conclude that a prospective randomized trial would be more helpful in identifying if ureteral stenting is mandatory [16].

Ji Hyun Kim et al. have reported an incidence of urologic surgery concomitant to CRS for ovarian cancer 1.7%. The vast majority of those patients underwent urologic surgery for tumor invasion and a small minority for iatrogenic trauma [17]. Votanopoulos et al. showed that morbidity was not increased in patients undergoing urologic surgery during CRS and HIPEC, and concluded that urinary tract involvement should never be considered a contraindication for CRS in patients with resectable peritoneal malignancy [11]. In a meta-analysis Seretis et al. showed that genitourinary surgery during CRS and HIPEC had no negative impact on morbidity and mortality [18].

Braam et al. showed that gastrointestinal anastomotic failures and fistulas as well as intra-abdominal abscesses developed more frequently in patients undergoing urologic intervention. In addition, urologic surgery was more frequently performed in patients that had undergone previously extended surgery. Restaino et al. in a very recent paper have described how to protect gastrointestinal anastomoses in ovarian cancer cytoreductive surgery [19]. The duration of surgery, the estimated blood loss, and the hospital stay was increased but the overall survival was not affected. However, in a small percentage of patients with urologic surgery urologic leakage was present [13]. Honore et al. have identified that urinary fistulas are related to high PCI [9]. In our study we identified a significant increase in blood loss while the duration of surgery remained the same. The duration of surgery and the blood loss are likely to depend on the extent of the peritoneal dissemination.

In fact, the duration of surgery in many patients with extensive peritoneal malignancy and especially in those with recurrent disease that do not undergo urologic surgery is quite long. A small number of the UI Group was identified with extensive peritoneal disease. Leapman et al. showed that patients undergoing urologic surgery had more organ involvement and more commonly underwent intestinal anastomoses. A difference in regard to major morbidity, transfusion, and hospitalization was not observed [10]. On the contrary, urologic surgery was required in 9.8% of the patients in the study of Tan et al. who showed that the hospital stay was significantly increased [20].

Lyon et al. have also found that the duration of hospitalization was longer in patients with urologic operations [14], and Morkavuk et al. found that the urologic interventions extended significantly the duration of hospitalization, although the morbidity and mortality was not affected [6].Although the groups of our study were similar in regard to PSS, the majority of the UI Group had already undergone extensive surgery previously. This is consistent with the report of Bij et al. [21]. Direct metastasis from any origin to the urinary tract is a very rare phenomenon that has been referred to as a case report only [22]. The UI Group was different from the C Group in the longer ICU-stay. From [Table 4] it becomes obvious that the majority of the recorded complications were not related to urinary tract. Pinar et al. showed that the re-implantation of the ureter with uretero-neocystostomy seems safer than end-to-end uretero-ureteral-anastomosis [23]. Our study does not confirm such an observation. The anastomotic failures were identified in the gastrointestinal tract and all the other complications were common in patients undergoing major surgery. No leakage from urologic anastomoses was identified in our study. The statistical analysis showed that the ASA class and the extent of peritoneal spread were the independent variables of morbidity although many other variables were found to be related.

The performance status and the number of the transfused FFP units were identified as the independent variables of hospital mortality. A severe delayed complication is the development of anastomotic stricture that has been estimated up to 4% of the uretero-ureteral anastomoses. Most of them are successfully treated with balloon dilatation but in 10% relaparotomy is required for reconstruction [24]. The overall 5-year survival rate was 54% and 62% in the UI Group and C Group respectively. No statistical difference in survival was found. This is in agreement with the results of other studies [11,20].

The completeness of cytoreduction, the extent of the peritoneal dissemination, the transfusion of FFP, and the performance status were found to be related to survival. The independent variables of survival were found to be the performance status and the transfusion of FFP. The urologic surgical implication does not affect adversely the oncologic result. Patients that underwent CRS and HIPEC with concomitant urologic surgery had the same overall survival and the same recurrences as did patients that underwent CRS and HIPEC without urologic surgery. This implies that the underlying disease in patients undergoing CRS and HIPEC with concomitant urologic surgery is not more aggressive [11].

The strength of the study is the large sample derived in 11 years period and treated by the same surgical and anesthesiological team. Although the patients were prospectively enrolled the end-points were identified retrospectively which includes selection biases. Other important variables like nutritional status, and the BMI were not taken into account, in addition to histological data. Another possible limitation of the study is the small number of the UI Group patients. No patient was followed-up with the intention of recording the late genito-urinary complications.

During follow-up, the physical examination and the findings from the imaging techniques have provided all the data about the postoperative genito-urinary status. As a consequence definitive conclusions cannot be conducted. So far, it has not been clear if the anastomoses of the urinary tract are adversely affected by HIPEC in contrast to the anastomoses of the gastrointestinal tract. We may only assume that the urological anastomoses do not seem to be affected by CRS and HIPEC during the healing process [13].

Conclusions

Patients with peritoneal carcinomatosis from locally advanced ovarian cancer may safely undergo urologic surgery during CRS and HIPEC with the same morbidity and mortality as patients undergoing CRS and HIPEC without urologic operations. Urologic surgery during CRS and HIPEC is associated by more suture lines and anastomoses, and longer duration of surgery. There is no adverse oncologic impact because the recurrence and the overall survival are not affected.

Author Contribution

Dimitrios Massaras: Writing-Review and Editing Grigorios Tripsiannis: Statistical analysis

Dimitrios Kyziridis: Writing-Original Draft Preparation Apostolos Kalakonas: Writing-Review and Editing Antonios-Apostolos Tentes: Conceptualization-Supervision

Funding

This research received no external funding. INSTITUTIONAL REVIEW BOARD STATEMENT.

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved for publication by the Ethical Committee of EUROMEDICA Kyanous Stavros Decision No: 93/12.04.2024.

Written Informed Consent

Informed consent was obtained from all patients involved in the study. All patients signed an informed consent for publication of the manuscript to a medical journal.

Data Availiability Statement

The data presented in this study are available on request from the corresponding author due to ethical reasons.

Acknowledgements

The authors need to thank Pr Vasilios Papaziogas President of the Ethical Committee of EUROMEDICA Kyanous Stavros for approving the publication of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

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