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Evaluation of perioperative outcomes of hyperthermic intraperitoneal chemotherapy treatment in ovarian cancer patients undergoing interval cytoreduction: a retrospective analysis

Interval sitoredüksiyon uygulanan over kanseri hastalarında hipertermik intraperitoneal kemoterapi tedavisinin perioperatif sonuçlarının retrospektif değerlendirilmesi

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ABSTRACT

Aims: To evaluate the intraoperative and postoperative outcomes of the patients underwent interval cytoreduction and hypertermic intraperitoneal chemotherapy

Materials and Methods: This retrospective study included 23 patients who underwent cytoreductive surgery with HIPEC for high-grade serous ovarian cancer between December 2021 and September 2023 at our gynecologic oncology unit. HIPEC was performed using cisplatin at a dose of 100 mg/m², with continuous perfusion at 42°C for 90 minutes. Clinical characteristics, including age, comorbidities, preoperative CA-125 levels, and surgical details, were collected. Intraoperative parameters such as the extent of resection, anesthesia duration, transfusions, and urine output were analyzed. Postoperative complications, including acute renal insufficiency (ARI), were evaluated using daily creatinine measurements. Statistical analyses were conducted using SPSS 25, with continuous variables presented as mean ± standard deviation or median (range).

Results: The mean age of patients was 61 ± 10 years, and 78.6% were postmenopausal. The median gravida and parity were 3 (range: 2–7). 69.6% had ascites, with a median volume of 1000 mL (0–3000 mL). The median peritoneal carcinomatosis index (PCI) score was 14 (6–28). Neoadjuvant chemotherapy was administered to 91.3% of patients, with a median interval of 31.6 ± 4.6 days between NACT and surgery. The most common procedures performed included omentectomy (100%), colonic resection (13%), small bowel resection (8.7%), and splenectomy (21.7%). The median operation time was 316 minutes, and the median intraoperative bleeding was 400 mL (300–1000 mL). The median hospital stay was 10 days (5–19). Acute renal insufficiency (ARI) occurred in 21% of patients, while other complications included ileus (13%), wound infection (17%), and atelectasis (21%). Median creatinine levels were 0.8 mg/dL on Postoperative Day 1, 1.1 mg/dL on Postoperative Day 2, and 0.9 mg/dL on Postoperative Day 3, indicating a transient postoperative rise in renal dysfunction. All patients who required renal replacement therapy had received cisplatin-based HIPEC at a dose of 100 mg/m². The median urine output during HIPEC was 400 mL, suggesting the need for close renal monitoring.

Conclusion: Cytoreductive surgery with HIPEC in ovarian cancer is a feasible option for advanced ovarian cancer with acceptable renal and surgical morbidity

Keywords: Ovarian cancer, interval cytoreduction, hyperthermic intraperitoneal chemotherapy

ÖZ

Amaç: Intetval sitoredüksiyon ve hipertermik intraperitoneal kemoterapi (HIPEC) uygulanan hastaların intraoperatif ve postoperatif sonuçlarını değerlendirmek.

Gereç ve Yöntemler: Bu retrospektif çalışmaya, Aralık 2021 ile Eylül 2023 tarihleri arasında jinekolojik onkoloji birimimizde yüksek dereceli seröz over kanseri nedeniyle sitoredüktif cerrahi ve HIPEC uygulanan 23 hasta dahil edildi. HIPEC, 100 mg/m² dozunda sisplatin ile 42°C'de 90 dakika boyunca sürekli perfüzyon şeklinde uygulandı. Hastaların klinik özellikleri (yaş, ek hastalıklar, preoperatif CA-125 seviyeleri ve cerrahi detaylar) kaydedildi. Yapılan cerrahi işlemler, anestezi süresi, kan transfüzyonu gereksinimi ve idrar çıkışı bilgilerine ulaşıldı. . Postoperatif komplikasyonlar, özellikle akut böbrek yetmezliği (ABY), günlük kreatinin ölçümleri ile değerlendirildi. İstatistiksel analizler SPSS 21 kullanılarak yapıldı; sürekli değişkenler ortalama ± standart sapma veya medyan (min–maks) olarak sunuldu.

Bulgular: Hastaların yaş ortalaması 61 ± 10 yıl olup, %78,6'sı postmenopozaldı. Medyan gravida ve parite sırasıyla 3 (2–7) idi. Hastaların %69,6'sında asit mevcuttu ve medyan hacmi 1000 mL (0–3000 mL) olarak ölçüldü. Medyan peritoneal karsinomatoz indeksi (PCI) 14 (6–28) idi. Neoadjuvan kemoterapi hastaların %91,3'üne uygulanmış olup, cerrahi ile neoadjuvan kemoterapi arasındaki medyan süre 31,6 ± 4,6 gündü. En sık uygulanan cerrahi işlemler omentektomi (%100), kolonik rezeksiyon (%13), ince bağırsak rezeksiyonu (%8,7) ve splenektomi (%21,7) idi. Medyan operasyon süresi 316 dakika, medyan intraoperatif kanama miktarı ise 400 mL (300–1000 mL) olarak kaydedildi. Postoperatif olarak, medyan hastanede kalış süresi 10 gündü (5–19). Akut böbrek yetmezliği (ABY) %21 oranında görülürken, diğer komplikasyonlar arasında ileus (%13), yara enfeksiyonu (%17) ve atelektazi (%21) yer aldı. Medyan kreatinin seviyeleri postoperatif 1. günde 0,8 mg/dL, 2. günde 1,1 mg/dL ve 3. günde 0,9 mg/dL olarak ölçüldü ve postoperatif dönemde geçici bir böbrek fonksiyon bozukluğunu gösterdi. Renal replasman tedavisi gerektiren tüm hastalar 100 mg/m² dozunda sisplatin bazlı HIPEC almıştı. Medyan intraoperatif idrar çıkışı 400 mL olup, bu durum böbrek fonksiyonlarının yakından izlenmesi gerekliliğini göstermektedir.

Sonuç: Over kanseri tedavisinde interval sitoredüktif cerrahi ve eş zamanlı sıcak intraperitoneal kemoterapi kabul edilebilir renal ve cerrahi morbidite ile ilişkili bir tedavi yöntemidir.

Anahtar Kelimeler: Over kanseri, sıcak intraperitoneal kemoterapi, interval sitoredüksiyon

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INTRODUCTION

Ovarian cancer is one of the gynecological malignancies that is typically diagnosed at an advanced stage (1). The main reasons for the lack of early diagnosis are the absence of an effective screening method and the asymptomatic nature of the disease in its early stages (2). As with all cancer types, treatment becomes more complicated as the disease progresses. Given that the majority of ovarian cancer cases are diagnosed at an advanced stage, a multimodal treatment approach is often required rather than a single treatment modality (3).

For many years, the cornerstone of ovarian cancer treatment has been surgery aimed at achieving optimal cytoreduction, which remains the most effective therapeutic intervention (4). The maximum benefit of surgical treatment can only be achieved when optimal cytoreduction is accomplished. In cases where optimal surgery cannot be performed, the use of neoadjuvant chemotherapy followed by interval cytoreduction has been shown to provide benefit if a good response is achieved with chemotherapy (4, 5).

Hyperthermic intraperitoneal chemotherapy (HIPEC) is utilized in ovarian cancer to enhance the efficacy of chemotherapy by targeting tumor cells on the peritoneal surfaces with higher drug concentrations (6). Although the benefit of HIPEC has been demonstrated in some studies, particularly in interval cytoreduction following neoadjuvant chemotherapy, many studies have failed to show a significant advantage (7). Complications associated with HIPEC, such as nephrotoxicity and the risk of intestinal anastomotic leakage, are significant concerns that need to be addressed.Current literature on HIPEC provides no definitive recommendations, emphasizing the need for further research to establish its role in ovarian cancer treatment (8).

In light of this information, the aim of our study was to evaluate the intraoperative and postoperative outcomes associated with HIPEC in patients who underwent interval cytoreduction for ovarian cancer.

MATERIAL AND METHOD

This retrospective study was conducted after obtaining institutional review board approval. Data from patients treated for ovarian cancer between 2021 and 2023 were reviewed. Patients with histopathologically confirmed high-grade serous ovarian cancer were included, while those with mucinous carcinoma, pseudomyxoma peritonei, or non-gynecologic peritoneal carcinomatosis were excluded from the analysis. Patient records were retrieved from the hospital database. All samples were evaluated by experienced gynecopathologists to confirm the diagnosis.

Patients who underwent primary cytoreduction were excluded from the study. For patients deemed unsuitable for primary cytoreduction three cycles of platinum-based neoadjuvant chemotherapy were administered. Chemotherapy response was assessed using imaging modalities and CA-125 tumor marker levels. Patients who showed no response to chemotherapy were considered inoperable and continued with systemic chemotherapy and excluded from the study. Conversely, patients with a favorable chemotherapy response underwent interval cytoreduction surgery within 20 to 30 days after completing the three chemotherapy cycles included to the study.

All interval cytoreduction procedures began with an exploratory laparotomy via a midline xiphoid-to-pubic incision. Surgical exploration was performed to assess the extent of disease, and any patient with tumor involvement of the small intestine root, pancreatic head, or residual tumor at the celiac trunk level following chemotherapy was not subjected to further surgical resection. For all other patients, the procedure commenced with a parietal peritonectomy. The parietal peritoneum was separated extraperitoneally from the fascia transversalis. The liver and spleen were mobilized to allow diaphragmatic peritonectomy. Parietal peritonectomy was extended caudally, and in cases with tumor involvement of the pelvic peritoneum, uterus, adnexa, or rectosigmoid colon, en bloc resection was performed, including the affected segment of the colon. In cases where tumor implants were detected on the small intestine mesentery, visceral peritonectomy was performed. When intestinal resections were performed, intestinal anastomoses were routinely carried out, even when HIPEC was planned.

Four chemotherapy infusion catheters and a temperature probe were inserted into the abdominal cavity. HIPEC was administered after the closure of all abdominal layers to ensure a contained perfusion environment. Cisplatin was used at a dose of 100 mg/m², diluted in 3000-4000 mL of isotonic saline solution. The procedure was performed using the Belmont Hyperthermic Intraperitoneal Perfusion System (Belmont Instrument Corporation, Billerica, MA, USA), which maintained the inflow temperature of the perfusate at 42°C through afferent ports. The HIPEC procedure was performed for 90 minutes, with urine output closely monitored throughout the process to assess renal function and fluid balance.

Comprehensive data were collected from the hospital records and demographic characteristics including age, gravida, parity, menopausal status, and body mass index, comorbidities, pre-HIPEC

CA-125 levels, the interval between neoadjuvant chemotherapy and interval cytoreduction, ECOG performance score, ASA score, presence and volume of ascites, details of surgical procedures including colon or small bowel resections, number of anastomoses, omentectomy, splenectomy, and lymphadenectomy), intraoperative parameters including duration of surgery and anesthesia, estimated blood loss, and transfusion requirements), and postoperative outcomes including hospital stay, daily creatinine monitoring, and complications.

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA). Continuous variables were summarized as mean ± standard deviation (SD) or median (range), depending on the data distribution, which was assessed using the Shapiro-Wilk test. Categorical variables were presented as frequency (percentage).

RESULTS

The study included a total of 23 patients with a mean age of 61±10 years. The median gravida and parity values were 3 (2-7). Among the participants, 78.6% were postmenopausal, with a median menopausal age of 51 years. The median height and weight of the patients were 160 cm (153-170) and 79 kg (42-114), respectively, with a median BMI of 30 (17-45) Table 1 showed patients characteristics of the patients that underwent cytoresuctive surgery and HIPEC.

At least one of the comorbidities including diabetes (30.4%) and hypertension (26%) was present. One patient (2.7%) had a history of nephrolithiasis, and one patient (2.7%) had a history of breast cancer. The median preoperative CA-125 level was 824 (26-10,000). Neoadjuvant chemotherapy was administered to 91.3% of the patients, with a median interval of 31.6±4.6 days between NACT and surgery. The majority of patients (91.3%) showed a partial response, while 8.7% had a complete response. Preoperative diagnosis was established by tru-cut biopsy (30.4%), laparoscopic biopsy (21.7%), or other methods (21.6%) (Table 1).

Ascites was present in 69.6% (n:16) of patients, with a median volume of 1000 mL (0-3000 mL). The median peritoneal carcinomatosis index (PCI) score was 14 (6-28). Colonic resection was performed in 13%, small bowel resection in 8.7%, and anastomosis in 13% of the patients. Appendectomy was required in 47.9%, while omentectomy was performed in all patients (100%). Splenectomy was required in 21.7% of the patients. The median anesthesia duration was 406 minutes (275-646), and the median operation time was 316 minutes (185-556). The median intraoperative blood loss was 400 mL (300-1000), and the median transfusion of red blood cells (RBC) and fresh frozen plasma (FFP) was 2 units (0-4) each. Table 2 showed intraoperative characteristics of the patients.

Table 1. Clinical and Demographic Characteriscs of Patient that undervent Cytoreduction and HIPEC

Variable	Data
Age	61±10
Gravida	3 (2-7)
Parity	3 (2-7)
Menapause	
Premenaposal	3 (22,4%)
Postmenaposal	11 (78,6%)
Manaposal age	51 (4-61)
Height	160 (153-170)
Weight	79 (42-114)
BMI	30 (17-45)
Comorbidity	
None	9 (24.3%)
Yes	14 (37.8%)
Comorbidities	
Nefrolithiasis	1 (2.7%)
Diabetes	7 (30.4%)
Hypertension	6 (26%)
Breast Cancer	1 (2.7%)
Ca 125	824 (26-10000)
Diagnostic Laparoscopy	
No	14 (60.9%)
Yes	9 (24.3%)
Preoperative Diagnosis	
Tru-cut biopsy	7 (30,4%)
Laparoscopic biopsy	5 (21,7%)
Other	8 (21.6%)
Neoadjuvant Chemotherapy	
No	2 (8.7%)
Yes	21 (91.3%)
Time between NACT and Surgery	31.6±4.6
Response to NACT	
Partial response	21 (91,3%)
Total response	2 (8.7%)
ECOG Perfomance Score	
1	15 (65.2%)
2	8 (34.8%)
ASA Score	
1	3 (13%)
2	18 (91.3%)
3	3 (8.7%)

Postoperative pathological analysis revealed that 78.6% of the patients underwent lymphadenectomy due to palpable lymph nodes. The majority of tumors were grade 3 (91.3%), and the median number of resected pelvic and paraaortic lymph nodes was 16 (0-40) and 19 (0-37), respectively. Metastasis was detected in 0-7 pelvic lymph nodes and 0-10 paraaortic lymph nodes. The median hospital stay was 10 days (5-19) (Table 3).

Table 2. Intraoperative findings

Variable	Data
Ascites	
None	7 (30.4%)
Yes	16 (69.6%)
The amount of ascites	1000 (0-3000)
PCI Score	14 (6-28)
Colonic resection	
None	20 (87%)
Yes	3 (13%)
Small Bowel Resection	
None	21 (91.3%)
Yes	2 (8.7%)
Anastomosis	
None	20 (87%)
Yes	3 (13%)
Number of Anastomosis	
1	2 (66%)
2	1 (33%)
Appendicectomy	
None	12 (52.1%)
Yes	11 (47.9%)
Diaphragma stripping	14 (100%)
Torocal tube placement	-
Omentectomy	23 (100%)
Splenectomy	
None	18 (78.3)
Yes	5 (21.7%)
Anesthesia Time	406 (275-646)
Operation Time	316 (185-556)
Transfusion of RBC	2 (0-4)
Transfusion of TDP	2 (0-4)
Urine output during HIPEC	400 (300-1100)
Bleeding	400 (300-1000)

Postoperative complications were observed in several patients. The most common complications included acute renal insufficiency (21%), atelectasis (21%), and wound infection (17%). Ileus occurred in 13% of patients, while intestinal perforation, deep venous thrombosis, acute respiratory distress syndrome (ARDS), and myocardial infarction were each observed in 4.3% of cases (Table 3).

Figure 1 showed the trends in creatinine levels over time, depicting median, minimum, and maximum values at different time points.

DISCUSSION

Our study investigated intraoperative and postoperative characteristics of the ovarian cancer patients that underwent cytoreductive surgery and HIPEC. The fact that morbidities associated with HIPEC do not have long-term adverse effects and

Table 3. Postoperative pathological data of patients that underwent Cytoraduction and HIPEC aa

Variable	Data
Lympadenectomy	
None	5 (21,4%)
Palpable	19 (78,6%)
Grade	
2	2 (8.7%)
3	21(91.3%)
Pelvic Lymph node	16 (0-40)
Paraaortic Lymph node	19 (0-37)
Pelvic lymph nod metastasis	0 (0-7)
Paraaortic Lymph node metastasis	0 (0-10)
Hospital Stay	10 (5-19)
Complications	
Intestinal perforation	1 (4.3%)
Ileus	3 (13%)
Wound Infection	4 (17%)
Deep venous thrombosis	1 (4.3%)
Acute renal Insufficiency	5 (21%)
Atelektasis	5 (21%)
ARDS	1 (4.3%)
Myocardial Infarctus	1 (4.3)

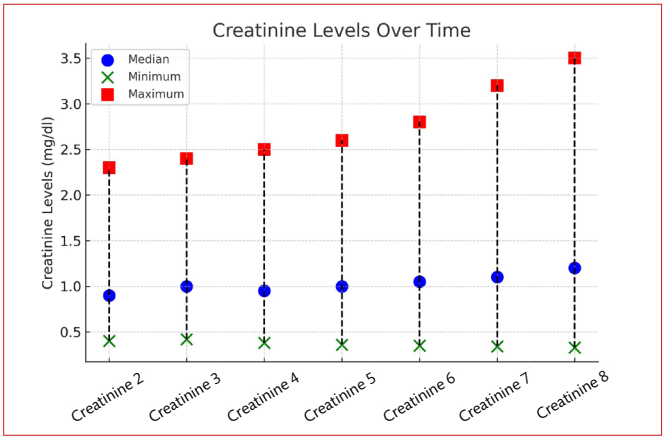

Figure 1. Trends in creatinine levels over time

that most of them are reversible in a short time may influence the decision-making process in favor of offering this treatment to the patients underwent inteval cytoreduction.

Several studies have evaluated the efficacy and safety of HIPEC in ovarian cance and reported mixed results. The OVHIPEC-1 trial demonstrated an improvement in both progression-free and overall survival when HIPEC was added to interval cytoreduction and and complete resection was achieved (9). On the other hand, following randomized studies, including the work by Lim et al., did not confirm a survival benefit when HIPEC was used either in the primary or interval setting (10). Furthermore, a phase II study by Zivanovic et

al. evaluating HIPEC with carboplatin in recurrent ovarian cancer failed to demonstrate an improvement in overall survival compared to surgery alone (11). The ongoing OVHIPEC-2 trial may help clarify the role of HIPEC in the upfront setting. As our study included only the patients underwent interval cytoreduction followed by neoadjuvant chemotherapy the application of the procedure is correlated with the usage of HIPEC reported in the literature.

A systematic review by Chiva et al. reported grade 3–4 complications in 19% of primary cases and 25% of recurrent cases, with mortality rates ranging from 0% to 7% (12). Similarly, a meta-analysis by Huo et al. found that mortality after HIPEC was 1.8%, comparable to our findings(13). Although we did not report any mortality this may be related with limited number of patients eligible for the study. Another meta-analysis by Bouchard-Fortier et al. showed that primary surgery plus HIPEC resulted in grade 3–4 complications in 34% of cases and an 8% rate of reoperation (14). These findings align with existing literature that reports common complications such as acute renal insufficiency, atelectasis, and wound infections, with similar incidence rates.

The variation in results across these studies can be attributed to differences in patient selection, chemotherapy regimens, and surgical expertise. Some centers have reported better outcomes with strict patient selection criteria, particularly excluding patients with extensive disease that cannot be optimally debulked. Additionally, the choice of chemotherapeutic agents, HIPEC duration, and temperature settings have varied significantly among studies, contributing to inconsistent findings (15). In our study we applied a standart HIPEC regimen whic was never the time below 90 minutes indicatig more acccurate results associated with treatment. On the other hand there is a tendency among the surgeons to cease the HIPEC before the standart time to avoid the complications. The studies reporting lesser complications may have used lower dose and decreased time of application of the HIPEC treatment.

HIPEC is associated with significant perioperative morbidity due to the extent of surgical resection required to achieve optimal cytoreduction and the cytotoxic effects of intraperitoneal chemotherapy. Previous studies have reported median PCI scores ranging from 10 to 20, reflecting extensive peritoneal disease (16, 17). The presence of ascites in up to 70% of patients and the frequent need for additional procedures such as colonic resection (10–25%), small bowel resection (5–15%), and splenectomy (15–30%) have been highlighted in various studies, demonstrating the aggressive nature of surgery required in HIPEC cases(17).

Postoperative complications such as ileus and intestinal perforation are of particular concern, as prior research has indicated a higher risk of anastomotic leaks when HIPEC is performed following bowel resection . The CHIPOVAC trial, which used oxaliplatin for HIPEC, had to be closed prematurely due to excessive rates of hemoperitoneum (18). Additionally, renal toxicity is a well-recognized adverse effect of HIPEC, particularly when cisplatin is used. Despite the absence of sodium thiosulfate use in our study, nephrotoxicity rates remained low, consistent with findings from studies that suggest optimized perioperative hydration protocols may help mitigate this risk (19). Other studies have reported nephrotoxicity rates as high as 48% in some cohorts, yet our findings align with research indicating that renal function can be preserved with adequate intraoperative management.

Furthermore, ICU admission rates have varied across studies, ranging from 20% to 89%, depending on the perioperative management strategies used (17, 20). This variability suggests that optimization of perioperative care, including fluid management and early mobilization, may help reduce ICU stays and postoperative morbidity.

Given the high rates of complications and the lack of consistent survival benefit in randomized trials, HIPEC should be considered cautiously and offered within clinical trials or high-volume centers with expertise in ovarian cancer surgery. The Enhanced Recovery After Surgery (ERAS) guidelines for cytoreductive surgery recommend meticulous perioperative management to mitigate morbidity, emphasizing fluid management, early mobilization, and nutritional support (21). The potential benefits of HIPEC must be weighed against its risks, particularly in patients with pre-existing comorbidities such as renal dysfunction (22).

Our findings align with the retrospective analysis by Liesenfeld et al., which identified cisplatin-based HIPEC regimens as a significant contributor to HIPEC-associated nephrotoxicity. Their study reported an ARI incidence of 31.8%, a rate comparable to our findings (23). Notably, our results also indicate a marked increase in creatinine levels post-HIPEC, with the most substantial rise observed on postoperative day 2, consistent with previous reports (24). The preclinical mouse model presented by Liesenfeld et al. demonstrated that cisplatin, rather than hyperthermia, was the primary driver of ARI, supporting the hypothesis that nephrotoxicity in HIPEC is largely chemotherapy-induced rather than a direct consequence of hyperthermic perfusion (23)

Importantly, all patients who required renal replacement therapy had received cisplatin-based HIPEC, further emphasizing its nephrotoxic potential (23). The high incidence of acute renal insufficiency may be explained with the dose that we administered to the patients was standart of 100 mg/m². Patient selection is

crucial when considering HIPEC, and its use should be restricted to those likely to achieve complete cytoreduction. Some studies have suggested that HIPEC may be more beneficial in patients with a low tumor burden and optimal resection, whereas those with extensive peritoneal involvement may not derive significant survival advantages (25). In addition, although recent trials have suggested that genetic and molecular profiling of ovarian cancer may provide insights into which patients are most likely to benefit from HIPEC, our study did not include genetic testing, preventing any conclusions regarding the interaction between HIPEC efficacy and molecular tumor characteristics (24).

The retrospective nature of our study introduces potential selection bias. Additionally, our sample size is relatively small, limiting the generalizability of our findings. Another limitation is the heterogeneity in chemotherapy regimens and patient characteristics, which may affect outcomes. Future prospective studies with standardized HIPEC protocols and robust quality-of-life assessments are needed to determine whether the benefits of HIPEC outweigh the risks in select patient populations.

Despite these limitations, our study contributes to the growing body of literature on HIPEC in ovarian cancer by highlighting its intraoperative and postoperative challenges. Moving forward, ongoing randomized trials such as OVHIPEC-2 and CHIPPI-1808 will be crucial in refining the role of HIPEC in ovarian cancer management (26). Furthermore, long-term follow-up studies will help assess the impact of HIPEC on disease recurrence and patient quality of life, ultimately guiding future treatment protocols.

CONCLUSION

HIPEC treatment, although leading to temporary renal morbidity in patients undergoing interval cytoreduction, is a feasible treatment option that can be performed without causing life-threatening complications.

Author Contributions

Study concept and design: S.E., C.A. Data collection: S.Ö., A.B.Ö., S.İ., U.A. Statistical analysis and interpretation: İ.Ç., S.E. Manuscript drafting: H.A.A., T.B.B. Manuscript review and editing: S.E., C.A. All authors have read and approved the final version of the manuscript.

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Conflict of Interest Statement

The authors declare no conflicts of interest related to the authorship and publication of this article.

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