

# Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for managing peritoneal carcinomatosis from endometrial carcinoma: a single-center experience of 6 cases

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Ann Saudi Med 2014; 34(2): 159-166

DOI: 10.5144/0256-4947.2014.159

**BACKGROUND AND OBJECTIVES:** Endometrial carcinoma is the most common gynecologic malignancy worldwide. Prognosis of patients with peritoneal carcinomatosis (PC) from endometrial carcinoma is deadly, with an estimated median survival not exceeding 12 months. The objective of this study was to report our experience with cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) for managing PC from primary and recurrent endometrial carcinoma.

**DESIGN AND SETTINGS:** A retrospective analysis of 6 patients with PC arising from endometrial cancer, who were managed with CRS and HIPEC at our referral tertiary care center, from November 2010 to August 2013.

**MATERIALS AND METHODS:** Six patients underwent CRS and HIPEC. CRS was performed using standard peritonectomy procedures and visceral resections directed toward the complete elimination of tumors from abdominopelvic cavity. HIPEC was performed with cisplatin (50 mg/m<sup>2</sup>) and doxorubicin (15 mg/m<sup>2</sup>) and allowed to circulate in abdominopelvic cavity for 90 minutes at 41.0 to 42.2°C.

**RESULTS:** Two patients with primary endometrial carcinoma and 4 patients with recurrent endometrial carcinoma confined to peritoneal cavity were studied. Complete cytoreduction (CC-0) was achieved in 5 patients. The International Federation of Gynecology and Obstetrics (FIGO) stages and histopathological types were as follows: IB endometrioid adenocarcinomas (n=1), IC mesonephric carcinomas (n=1), IIIA endometrioid adenocarcinomas (n=2), IIIA papillary serous carcinomas (n=1), and IIIC clear-cell carcinomas (n=1). Anastomotic leak (grade I) was the most commonly encountered postoperative complication. Two patients developed grade IV complications due to septicemia and pulmonary embolism. No intraoperative mortality occurred. Postoperatively, all patients received chemotherapy (carboplatin and paclitaxel). In 1 patient, the clear-cell carcinoma histologic lesion relapsed within 6 months; the metastases spread to hepatic, pelvic, and mesenteric lymph nodes, and the patient died 5 months later. One patient with cytoreduction completeness of CC-2 developed hepatic metastases within 3 months and is still alive at a follow-up up 6 months. Remaining patients (n=4) are alive and disease free without evidence of recurrence of follow-ups at 35, 34, 19, and 7 months.

**CONCLUSION:** CRS and HIPEC are well-tolerated and feasibly promising management modalities in PC from primary and recurrent endometrial carcinoma. Further research is needed for in-depth analysis.

Endometrial carcinoma is the most common gynecologic malignancy and generally carries a fortunate prognosis. This is because majority of patients (75%) present with vaginal bleeding early in the course of disease, without any clinical proof of extrauterine extension (the International Federation of Gynecology and Obstetrics [FIGO] stages I and II), and undergo largely curable total hysterectomy with bilateral salpingo-oophorectomy, which have been demonstrated to yield 5-year survival rates of roughly 80% to 90%.<sup>1,2</sup> However, nearly 10% to 15% of patients with early-stage disease (stage I and II) develop recurrences.<sup>3,4</sup> Conversely, a very small group of patients is unlucky and present with advanced-stage disease with unfortunate prognoses. The 5-year survival rates for regional disease (FIGO stage III) and distant disease (FIGO stage IV) are 57% and 19%, respectively.<sup>5</sup>

The prognosis of patients presenting with recurrent and advanced metastatic disease confined to peritoneal cavity is deadly, with an estimated median survival not exceeding 12 months.<sup>6,7</sup> Patients with regional recurrence are most often managed with cytoreduction surgery—whenever technically feasible—and postoperative systemic therapy (chemotherapy or endocrine therapy).<sup>7</sup> Despite advances in surgeries and systemic anticancer drugs, overall survival (OS) from advanced and recurrent endometrial carcinomas has not positively improved over the past 3 decades.<sup>7</sup>

Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) have been utilized in a chosen series of patients with peritoneal carcinoma (PC) arising from gynecological and non-gynecological malignancies.<sup>8</sup> With respect to the gynecological cancers, the CRS and HIPEC have demonstrated fortunate results in ovarian carcinoma.<sup>9,10</sup> The objective of this study is to report our experience with CRS and HIPEC for managing PC from primary and recurrent endometrial carcinoma.

## MATERIALS AND METHODS

From November 2010 to August 2013, all patients who presented to our institution (King Faisal Specialist Hospital and Research Center [KFSHRC]) with PC from primary and recurrent endometrial carcinoma were included in the study and considered for CRS and perioperative HIPEC. The approval of Research Advisory Council was obtained to publish this study.

Preoperatively, all patients were fully worked up. Workup included the following: physical examination, laboratory tests (hematological, hepatic, coagulation, renal, bone, and electrolyte profiles), serum tumor markers (cancer antigen [CA]-125, CA 19-9, and carcinoem-

bryonic antigen), electrocardiogram, echocardiography, spirometry, abdominopelvic ultrasonography, whole-body contrast-enhanced computed tomography (CT) scan, and whole-body positron emission tomography/computed tomography (PET/CT) scan. Furthermore, Karnofsky performance scale was used to assess physical/performance status of the patients.

Inclusion criteria for considering aggressive CRS and HIPEC included the following: (1) satisfactory physical status (Karnofsky performance status > 50%), (2) satisfactory hematological profile, (3) satisfactory hepatic and coagulation profiles, (4) satisfactory renal and electrolyte profiles, (5) proof of PC from primary or recurrent endometrial carcinoma, (6) no proof of distant endometrial carcinoma metastatic foci to brain, lungs, liver or bones, (7) no proof of other concurrent malignancies elsewhere, and (8) signed written informed consent by the patients.

All surgical procedures were carried out by surgeons from the departments of surgical oncology and gynecologic oncology at KFSHRC. Under general anesthesia, a midline incision extending from xiphoid process to pubic tubercle was performed to completely explore the abdominopelvic cavity for PC. The extent of PC was evaluated intraoperatively utilizing peritoneal cancer index (PCI).<sup>11</sup>

As previously outlined by Sugarbaker,<sup>8</sup> CRS included a compilation of standard peritonectomy procedures and visceral resections directed toward the complete (optimal) elimination of tumors from abdominopelvic cavity. Standard peritonectomy procedures used in our study included the following: total peritonectomy, subtotal peritonectomy, right subdiaphragmatic peritonectomy, left subdiaphragmatic peritonectomy, greater omentectomy, lesser omentectomy, pelvic peritonectomy, mesenteric peritonectomy, Glisson capsule peritonectomy, and antrectomy. Furthermore, total abdominal hysterectomy (TAH) with bilateral salpingo-oophorectomy (BSO) was performed in all patients with primary endometrial carcinoma.

After completing CRS, residual tumors were assessed intraoperatively using completeness of cytoreduction (CC) scores as follows: CC-0, no gross residual tumor remained in abdominopelvic cavity; CC-1, less than 2.5 mm residual tumor remained in abdominopelvic cavity; CC-2, 2.5 mm to 2.5 cm residual tumor remained in abdominopelvic cavity; and CC-3, more than 2.5 cm residual tumor or confluence of unresectable residual tumor remained in abdominopelvic cavity.<sup>11</sup> Only CC-0 scores were regarded as CC.

HIPEC was performed at the end of CRS. Abdominopelvic cavity was lavaged 15 times with 1 L of normal saline prior to HIPEC. Two inflow drains were

positioned below hemidiaphragms, whereas 2 outflow drains were positioned in the pouch of Douglas. All drains were connected to an extracorporeal closed sterile circuit in which 2 L perfusate was circulated by means of 2 peristaltic rollup pumps (one inflow and the other outflow) at a flow rate of 2 L/min. Cisplatin (50 mg/m<sup>2</sup> or) and doxorubicin (15 mg/m<sup>2</sup>) were supplemented to the perfusate and allowed to circulate in the abdominopelvic cavity for 90 min at 41.0 to 42.2°C. The heated perfusate and chemotherapy (41.0–42.2°C) were achieved by means of a heat exchanger connected to the sterile circuit. Intraperitoneal temperature was continuously checked by thermometers (thermal probes) situated in the abdominopelvic cavity to ensure the maintenance of temperature at 41.0 to 42.2°C. During the HIPEC procedure, hemodynamic and cardiopulmonary parameters were continuously and carefully monitored. At the end of HIPEC procedure, abdominopelvic cavity was again lavaged 15 times with 1 L of normal saline. Moreover, the left hemidiaphragmatic drain was kept for a couple of days to facilitate draining of residual perfusate. All other drains were taken out intraoperatively. All patients were moved to the intensive care unit for 2 days, and afterward transferred to the wards for recovery.

Postoperative complications following the CRS and HIPEC were evaluated according to the Common Terminology Criteria for Adverse Events—version 4.0.<sup>12</sup>

Following the CRS and HIPEC, all patients were considered for postoperative (adjuvant) systemic chemotherapy. As all patients were previously platinum sensitive, carboplatin and paclitaxel regimen were used. Platinum-resistant patients were defined as patients who did not respond or developed recurrences in less than 6 months following the primary platinum-based systemic chemotherapy.

All patients were followed up regularly. No patient was lost during the follow-up. During the first year following the CRS and HIPEC, patients were followed up every 3 months. During the second year and afterward, patients were followed up every 6 months. The follow-up workup included the following: physical examination, hematological profiles, biochemical profiles (hepatic, coagulation, bone, renal, and electrolyte), serum tumor marker (CA-125), whole-body CT scan, and PET/CT scan (whenever indicated).

## RESULTS

Between November 2010 and September 2013, a total of 6 patients (n=6) with PC from primary and recurrent endometrial carcinoma met the inclusion criteria for considering aggressive CRS and HIPEC. The characteristics of patients at the time of clinical presentation with pri-

mary and recurrent endometrial carcinoma confined to peritoneal cavity are depicted in **Table 1**. The mean age at the time of CRS and HIPEC was 55.5 years (range: 26–64 years). While 2 patients presented with PC from primary endometrial carcinoma, 4 patients presented with PC from recurrent endometrial carcinoma.

All patients with recurrent endometrial carcinoma (n=4) had only 1 prior laparotomy in the form of TAH and BSO. Postoperatively (following the initial laparotomy), 1 patient received abdominopelvic radiotherapy (n=1) while another patient received both abdominopelvic radiotherapy and chemotherapy (carboplatin and paclitaxel). Moreover, 1 patient received only adjuvant chemotherapy (carboplatin and paclitaxel), while 1 patient received no postoperative therapy.

As shown in **Table 1**, the FIGO stages and histopathological types were as follows: IB endometrioid adenocarcinomas (n=1), IC mesonephric (high-grade) adenocarcinomas (n=1), IIIA endometrioid adenocarcinomas (n=2), IIIA papillary serous carcinomas (n=1), and IIIC clear-cell carcinoma (n=1). The mean period from the initial laparotomy to recurrence and performing CRS and HIPEC was 9 months (range: 1–18 months).

The details of the CRS and HIPEC are described in **Table 2**. All 6 patients underwent multiple standard peritonectomies and visceral resections with intent to achieve complete (optimal) cytoreduction. The mean PCI was 19 (range: 9-26). While 5 patients achieved complete cytoreduction (CC-0), 1 patient achieved incomplete cytoreduction of CC-2. The mean duration of CRS and HIPEC combined was 9.5 hours (range: 8-11 hours), and the mean postop-50 days).

The details and grading of postoperative complications are shown in **Table 3**. Overall, postoperative complications were tolerable. Anastomotic leak (grade I) was the most commonly encountered postoperative complication. Two patients developed grade IV complications due to septicemia and pulmonary embolism. No grade V complication occurred.

The details of the postoperative therapy and outcomes following the CRS and HIPEC are demonstrated in **Table 4**. Following the CRS and HIPEC, all 6 patients (n=6) received chemotherapy (carboplatin and paclitaxel). In 1 patient, the complication that was a very aggressive and highly recurrent histological type relapsed within 6-months, developed metastases to hepatic, pelvic, and mesenteric lymph nodes, and eventually died 5 months later. In 1 patient with cytoreduction completeness of CC-2, the disease relapsed within 3 months following HIPEC; the patient developed hepatic metastases, but she was still alive at a follow up of 6 months. The rest of the 4 patients are alive and disease free without evidence

**Table 1.** Characteristics of patients at the time of clinical presentation.

Patient no.	Age (y) at CRS+HIPEC	Primary/ Recurrent endometrial cancer	Current/Original FIGO stage and histology	Number of prior laparotomy	Postoperative radiotherapy and/ or chemotherapy	Time from initial laparotomy to CRS+HIPEC (mo)
1	26	Recurrent	IB endometrioid adenocarcinoma	1	—	1
2	53	Recurrent	IIIA endometrioid adenocarcinoma	1	Abdominopelvic radiation	6
3	62	Primary	IIIC clear cell carcinoma	0	—	—
4	43	Primary	IIIA endometrioid adenocarcinoma	0	—	—
5	55	Recurrent	IC mesonephric (high-grade) carcinoma	1	Abdominopelvic radiation and chemotherapy (carboplatin and paclitaxel)	10
6	64	Recurrent	IIIA papillary serous carcinoma	1	Chemotherapy (carboplatin and paclitaxel)	18

S: Cytoreductive surgery, HIPEC: hyperthermic intraperitoneal chemotherapy, FIGO: International Federation of Gynecology and Obstetrics; y: year; mo: month.

**Table 2.** Details of the CRS and HIPEC.

Patient no.	Peritonectomy and visceral resections	Peritoneal cancer index (PCI)	Cytoreduction completeness (CC)	Duration of CRS+HIPEC (h)	Hospital stay (d)
1	Resection of umbilicus, lesser/greater omentectomy, total peritonectomy, cholecystectomy, subtotal colectomy with iliorectal anastomosis, splenectomy, distal pancreatectomy	20	0	11	26
2	Subtotal/Total peritonectomy, distal 2/3 gastrectomy, appendectomy, cholecystectomy, splenectomy, distal pancreatectomy, partial transverse colon resection, Glisson capsule resection	9	0	8	50
3	Total abdominal hysterectomy with bilateral salpingo-oophorectomy, total peritonectomy, greater omentectomy, splenectomy, distal pancreatectomy, total colectomy and iliorectal anastomosis, resection of terminal ileum, resection of umbilicus	23	0	10	30
4	Total abdominal hysterectomy with bilateral salpingo-oophorectomy, subtotal peritonectomy, lesser/greater omentectomy, splenectomy, right iliac and obturator lymph node dissections, appendectomy, Glisson capsule resection	15	0	8	35
5	Subtotal peritonectomy (right and left abdominal wall), pelvic peritonectomy, lesser/greater omentectomy, cholecystectomy, appendectomy, 4 small bowel resections, extended left colectomy and colorectal anastomosis	26	0	11	33
6	Subtotal peritonectomy, cholecystectomy, total colectomy and iliorectal anastomosis, lesser/greater omentectomy, splenectomy, distal pancreatectomy, resection of vaginal cuff, resection of segment of right ureter and re-anastomosis	23	2	9	23

CRS: Cytoreductive surgery, HIPEC: hyperthermic intraperitoneal chemotherapy.

of recurrence at 35, 34, 19, and 7 months follow-up. The overall range of follow-up after the CRS and HIPEC is 6 to 35 months. Using Kaplan–Meier estimates, the OS rate was 83.3% (Figure 1) whereas the disease-free survival rate was 66.7% (Figure 2).

## DISCUSSION

Roughly 25%<sup>3</sup> and 50%<sup>13</sup> of endometrial cancer-related mortality are attributed to recurrent disease and advanced-stage disease (FIGO stages III and IV), respectively.

Also, 50% to 70% of patients present with recurrence of endometrial carcinoma within 24 months after the primary management.<sup>14</sup> Recurrence rates range from 2% to 15% in patients with an early-stage disease (stage I and II) or with a biologically benign tumor histologic lesion (endometrioid histologic lesion grades 1 and 2). Conversely, recurrence rates can reach as high as 50% in patients with an advanced-stage disease (stages III and IV) or a biologically aggressive tumor histologic lesion (endometrioid histologic lesion grade 3, or non-endometrioid histologic lesion: serous, clear cell, mucinous, squamous, transitional cell, mesonephric, and undifferentiated).<sup>15,16</sup>

The most significant poor prognostic factors in setting of recurrent endometrial carcinoma include the following: shorter disease-free interval from the surgery to recurrence,<sup>17,18</sup> advanced-stage disease,<sup>18</sup> and high-grade endometrioid or non-endometrioid histologic lesion (clear-cell and papillary serous).<sup>17,18</sup> Other factors are as follows: advanced age of patient; lymphovascular invasion; and adnexal, endocervical, lymph node, and peritoneal metastases.<sup>3</sup>

The development of PC from primary or recurrent endometrial carcinoma is not uncommon. The prognosis of patients presenting with advanced or recurrent widespread disease confined to peritoneal cavity is deadly, with an estimated median survival of less than 12 months.<sup>6,7</sup>

Considering PC is a locoregional disease, the combination of CRS and HIPEC has been utilized in a chosen series of patients with PC arising from gynecological and non-gynecological malignancies. This novel procedure (CRS and HIPEC) yielded a 5-year survival rate of 54% in patients with PC from ovarian cancers,<sup>9,10</sup> 27% in patients with PC from gastric cancers,<sup>19</sup> 45%

in patients with PC from colon cancers,<sup>20</sup> and 73% in patients with pseudomyxoma peritonei.<sup>21</sup>

A recently published meta-analysis by Barlin et al.<sup>22</sup> proposed that CRS to no gross residual disease offers survival benefits (ranging from 9-35 months) in patients with advanced or recurrent endometrial carcinoma.

Aside from this meta-analysis, Campagnutta and colleagues<sup>23</sup> reported a series of 75 patients undertaking salvage CRS for managing advanced and recurrent disease. Complete resection of gross tumor and tumor resection to <1 cm residual disease were achieved in approximately 64% and 75% of patients, respectively. Optimal salvage (secondary) CRS was coupled with a median survival advantage of 53 months compared to only 9 months for patients left with gross residual disease.

Moreover, Awtrey and associates<sup>24</sup> reported a series

**Table 3.** Postoperative complications following CRS and HIPEC.

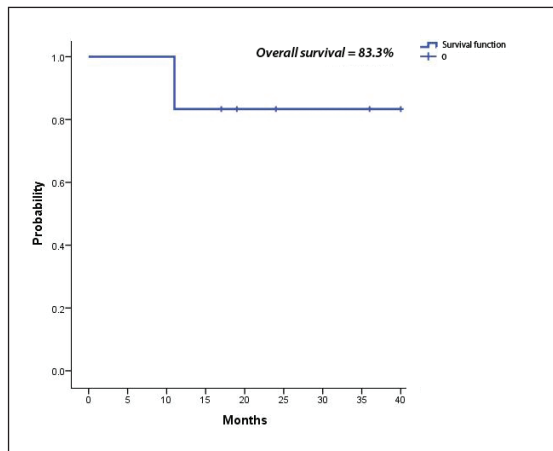
Patient no.	Postoperative complication and grade
1	Anastomotic leak, grade I
2	Anastomotic leak, grade I Right deep vein thrombosis, grade II Pulmonary embolism, grade IV
3	Anastomotic leak, grade I Bilateral pleural effusion, grade II Right hydronephrosis, grade I Intestinal obstruction, grade I
4	Anastomotic leak, grade I
5	Anastomotic leak, grade II Septicemia, grade IV
6	Anastomotic leak, grade I Urinary tract infection, grade II

CRS: Cytoreductive surgery, HIPEC: hyperthermic intraperitoneal chemotherapy.

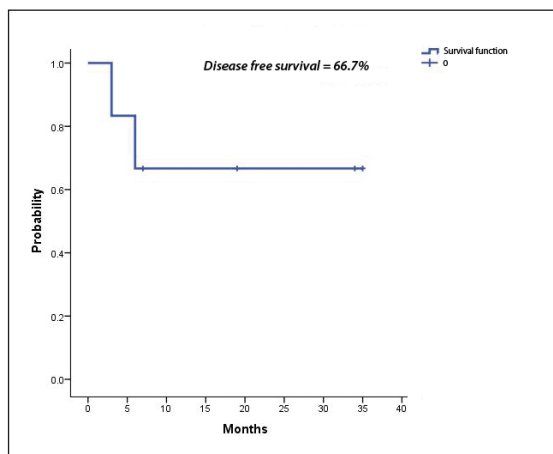
**Table 4.** Postoperative therapy and outcome following HIPEC.

Patient no.	Adjuvant therapy following HIPEC	Time of relapse following CRS+HIPEC (mo)	Site of recurrence	Time since CRS and HIPEC; follow-up (mo)	Current status
1	Carboplatin and paclitaxel	—	—	35	Alive, disease free
2	Carboplatin and paclitaxel	—	—	34	Alive, disease free
3	Carboplatin and paclitaxel	6	Hepatic, mesenteric, and pelvic lymph nodes	11	Died
4	Carboplatin and paclitaxel	—	—	19	Alive, disease free
5	Carboplatin and paclitaxel	—	—	7	Alive, disease free
6	Carboplatin and paclitaxel	3	Hepatic lymph nodes	6	Alive

CRS: Cytoreductive surgery, HIPEC: hyperthermic intraperitoneal chemotherapy.



**Figure 1.** Kaplan–Meier estimate for the overall survival (OS) rate.



**Figure 2.** Kaplan–Meier estimate for the disease-free survival (DFS) rate.

of 27 patients undergoing non-exenterative CRS for recurrent endometrial carcinoma. The complete resection of macroscopic tumor and tumor resection to <2 cm residual disease were accomplished in nearly 56% and 67% of patients, respectively. Optimal CRS was associated with a much longer median survival interval of 43 months compared to 10 months for patients with sub-optimal CRS and residual disease ( $P < .05$ ).

Furthermore, Bristow et al<sup>25</sup> reported a series of 61 patients commencing secondary (salvage) CRS for recurrent endometrial carcinoma. Complete resection of macroscopic tumor without residual disease was attained in approximately 66% of patients. Optimal CRS was linked to a median post-recurrence survival benefit of 39 months in contrast to only 13 months for patients with macroscopic residual disease ( $P = .0005$ ).

In all studies, the volume of residual disease was the

most important predictor of post-recurrence progression-free and OS.<sup>23-25</sup>

The use of CRS and HIPEC for managing PC from primary and recurrent endometrial carcinoma is rather limited to 2 studies only.<sup>7,26</sup>

Recently, Bakrin et al<sup>7</sup> explored the combination of CRS and HIPEC for managing recurrent endometrial carcinoma confined to the peritoneal cavity. The study included 5 patients and showed promising results. Complete CRS (CC-0) was achieved in all patients. HIPEC was performed with cisplatin and mitomycin C. Postoperative complications were well tolerated. Two patients developed early recurrences at 2 and 10 months, respectively, and both died afterward. The rest of the 3 patients were alive and disease free at 7, 23, and 39 months from the time of CRS and HIPEC with a good performance status.

Another study by Helm et al<sup>26</sup> showed promising results in 5 patients with recurrent endometrial carcinoma limited to peritoneal cavity. One patient developed recurrence carcinoma and eventually died. Two patients were alive and disease free at 28 and 32 months from the time of CRS and HIPEC with a good performance status. The remaining 2 patients were alive with disease at 12 and 36 months.

The rationale for utilizing HIPEC is principally based on the direct heat-enhanced deep penetration, cytotoxicity, and synergism of varying cancer chemotherapeutic agents on neoplastic cells.<sup>27,28</sup> Following the aggressive CRS, intraperitoneal chemotherapy is directed at microscopic residual foci, which are the principal sources of surgical management failures.<sup>23-25</sup> Intraperitoneal, as opposed to intravenous, chemotherapeutic administration offers much higher local concentrations and much lower unnecessary systemic toxicities and side effects.<sup>29</sup> These advantages of HIPEC make the combination of the CRS and HIPEC very attractive and worth-experimenting modality for managing primary and recurrent endometrial carcinoma limited to the peritoneal cavity.

The preference of chemotherapeutic agents for HIPEC should be based on scientifically and clinically confirmed elevated heat-boosting effects on anticancer agents. Such anticancer agents include cisplatin,<sup>30</sup> doxorubicin (adriamycin),<sup>31</sup> and mitomycin C.<sup>32</sup> The most frequently used regimen in HIPEC is cisplatin and doxorubicin. When doxorubicin is contraindicated for cardiotoxicity reasons,<sup>33</sup> cisplatin and mitomycin C are the alternative chemotherapeutic regimens in HIPEC.

A recent systematic review by Chua et al<sup>34</sup> demonstrated that the morbidity rate following the CRS and HIPEC extend from nearly 12% to 52% in high-volume institutions. In our series, the most frequently

reported postoperative complication was anastomotic leak, and this finding mirrored other studies published in the peer-reviewed published reports.<sup>35,36</sup> Cisplatin has been studied to fail/interrupt anastomotic healing in animal studies.<sup>37</sup> Moreover, it has been suggested that delaying fast restoration of gastrointestinal tract (by keeping patient NPO [nothing per oral]) is highly advised,<sup>35</sup> and this results in reduced rates of anastomotic impairments.<sup>38</sup> Other severe complications such as sepsis, intrabdominal abscess, or postoperative hemorrhage requiring immediate interventions are uncommon.<sup>35,36</sup> In our series, only 2 patients developed life-threatening complications requiring urgent interventions, namely pulmonary embolism and sepsis.

In the same study by Chua et al,<sup>34</sup> with respect to mortality associated with the CRS and HIPEC, it has been shown to range from 1% to 6%. In our series, no patient died intraoperatively or developed grade V postoperative complications resulting in death.

Glehen et al<sup>39</sup> and Elias et al<sup>21</sup> documented that the degree of morbidity and mortality following the CRS and HIPEC are largely influenced by expertise of health care center in managing PC. Plus, it has been shown that learning curve of CRS and HIPEC is a significant factor to minimize the incidence of postoperative complications.<sup>40,41</sup> An average of 135 cases are anticipated to be sufficient to significantly reduce morbidity and mortality following the CRS and HIPEC.<sup>40,41</sup> In our tertiary care center, till date, more than 160 cases of CRS and HIPEC were performed by surgeons from the departments of surgical oncology and gynecologic oncology. In our current study, the presented 6-patient series is just a subgroup analysis.

Systemic chemotherapy remains the gold standard for managing patients with advanced-stage and recurrent endometrial carcinoma. The 2 most frequently used regimens are AP (doxorubicin and cisplatin) and TAP (paclitaxel, doxorubicin, and cisplatin). These 2 regimens were studied in phase III clinical trial by Gynecologic Oncologic Group (GOG) protocol 177 (AP versus TAP in managing patients with advanced-stage, metastatic, or recurrent endometrial carcinoma).<sup>42</sup> The TAP regimen was coupled with an improved overall response rate (ORR) (57% versus 34%;  $P < .01$ ), progression-free survival (PFS) (median, 8.3 versus 5.3 months;  $P < .01$ ), and OS (mean 15.3 versus 12.3 months;  $P = .37$ ). Conversely, TAP versus AP regimen yielded increased occurrence of severe (grade 3) peripheral neuropathic toxicity (12% versus 1%, respectively;  $P < .01$ ).

In view of the TAP-associated toxicity, the combination of paclitaxel and carboplatin (TC) remains the most frequently utilized regimen. Its administration

is supported by phase III trial by the GOG protocol 209 (TAP versus TC in management of patients with advanced, metastatic, or recurrent endometrial carcinoma).<sup>43</sup> Approximately 50% of TAP and TC patients showed objective ORR, and roughly 30% experienced stable disease. Both TAP and TC patients had fairly comparable median PFS of 13 to 14 months. However, OS was a bit higher in TAP compared to TC patients (38 versus 32 months; no statistical significant difference:  $P > .05$ ). Conversely, in patients receiving TAP versus TC, there were statistically significant decreases in the occurrence of peripheral neuropathic toxicity grade 2 or higher (19% versus 26%), vomiting (4% versus 7%), diarrhea (2% versus 6%), thrombocytopenia (12% versus 23%), and metabolic imbalances (8% versus 14%).

Salvage radiotherapy (RT) is largely effective in managing isolated central pelvic recurrences confined to the vaginal region.<sup>44</sup> For patients with locoregional endometrial carcinoma recurrences, utilization of salvage RT in managing naïve and previously irradiated fields is still debatable.<sup>22</sup> It must be noted that with additional RT schedules (sessions), patients will be at relatively high increased risks for developing severe radiation-induced toxic side effects, such as fistulas, strictures, proctitis urinary/bowel incontinence, and others.

Limitations to this study comprise the retrospective study design, relatively small sample size (case series of 6 patients), comparatively short period of follow-up, lack of uniform histopathological types, and lack of control group. Such limitations hinder our study to draw definitive and solid conclusions.

Thus, we conclude that, aggressive CRS supplemented with perioperative HIPEC emerges to be a well-tolerated, achievable, and feasibly promising treatment modality that yields favorable results in managing patients with PC from primary and recurrent endometrial carcinoma. Meticulous patient selection with highly optimal postoperative care is greatly recommended to prevent occurrence of undesirable complications associated with this novel treatment modality. Further research (uniform large-sized patient series and probably randomized clinical trials with control groups and longer follow-up data) is needed to draw definitive and concrete conclusions and validate the efficacy of this novel modality for managing PC from endometrial carcinoma.

#### Acknowledgments

*Authors sincerely acknowledge the editorial assistance of Ms. Evelyn Dinio, Academic and Training Affairs, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia.*

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