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Survival of large volume recurrent endometrial cancer with peritoneal metastases treated by cytoreductive surgery, HIPEC and EPIC. Report of a case

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ABSTRACT

INTRODUCTION AND IMPORTANCE: Endometrial cancer may disseminate through lymphatic channels to pelvic and retroperitoneal lymph nodes, through the bloodstream to the lungs, or through the peritoneal space to peritoneal surfaces. However, not all endometrial cancers involve all 3 sites for metastatic disease.
CASE PRESENTATION: A patient with large volume of symptomatic recurrence of peritoneal metastases from endometrial cancer was subjected to additional surgery and both regional and systemic chemotherapy. All aspects of her disease and its treatment were studied.
CLINICAL DISCUSSION: The primary malignancy was treated by a laparoscopic hysterectomy and bilateral salpingo-oophorectomy followed by intravaginal radiation. Large volume recurrent disease limited to the abdomen and pelvis was treated by complete cytoreductive surgery (CRS), hyperthermic intraperitoneal chemotherapy (HIPEC) and early postoperative intraperitoneal chemotherapy (EPIC). After recovery from surgery, systemic chemotherapy with cisplatin and paclitaxel was administered. The patient is now 25 months following treatment for recurrent cancer and free of disease.
CONCLUSIONS: The possibility of complete resection of recurrent endometrial cancer combined with HIPEC, EPIC and systemic chemotherapy is a treatment option for selected patients.

1. Introduction

Endometrial cancer is confined to the corpus uteri at the time of diagnosis in a large majority of patients [1,2]. Also, most of these patients are cured of disease by hysterectomy with or without pelvic and para-aortic lymph node dissection. Radiation therapy, usually recommended in the past, is less frequently or not used at all [3]. Combination chemotherapy is increasingly used by systemic administration. A regional (intraperitoneal chemotherapy) treatment has seldom been used in the past. This lack of enthusiasm for a regional route of administration may be questioned in that the most common sites of disease dissemination in patients thought to have uterine-confine disease is the peritoneal space. Positive peritoneal cytology was documented in 12%, 5% had adnexal involvement and 6% had gross intraperitoneal metastases [4]. These patients with early peritoneal disease at the time of primary resection will most commonly fail treatment within the peritoneal cavity [5]. Therapies may be individualized by determining the most likely sites for metastatic disease documented by careful follow-up [6].

Although not mentioned in the standard textbooks, surgery for recurrent endometrial cancer has been reported with some success. Papadia and coworkers reported a 5-year disease-free survival of 42% in 42 patients with optimal cytoreduction [7]. Cornali and coworkers added HIPEC with cisplatin to a cytoreductive surgery for 33 patients with peritoneal metastases from recurrent endometrial cancer. The 5-year overall survival was 30% (median survival was 33.1 months) [8]. The completeness of cytoreduction was the only significant factor independently influencing overall survival ($p = 0.016$). Goere et al. reported on 20 patients who underwent CRS and HIPEC for recurrent endometrial cancer [9].

In this case report, a patient with extensive recurrent endometrial cancer confined to the abdomen and pelvis was treated with a complete CRS, multiagent HIPEC and EPIC paclitaxel. She remains disease-free at 25 months after her intervention for recurrent disease. The ramifications of this outcome for patients who have a high propensity for progression of peritoneal metastases is discussed.

2. Patient presentation

Data on this patient was prospectively recorded and then retrospectively reviewed at an academic institution. This research work has been reported in line with the SCARE 2020 criteria [10]. This

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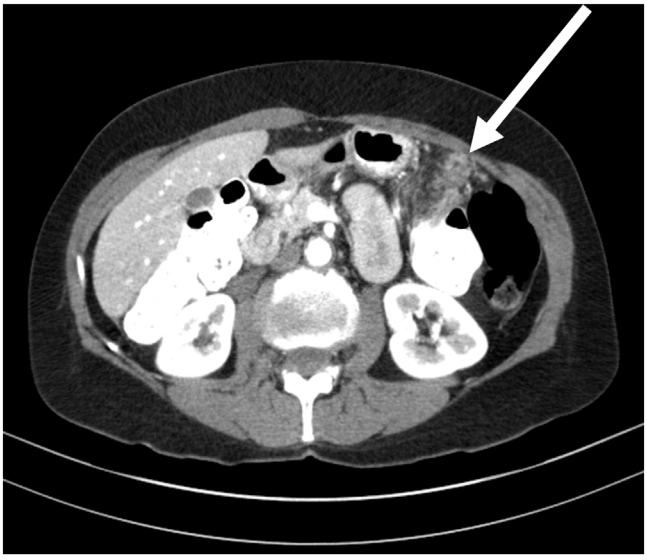

Fig. 1. CT scan through the upper abdomen shows cancer infiltration of the greater omentum.

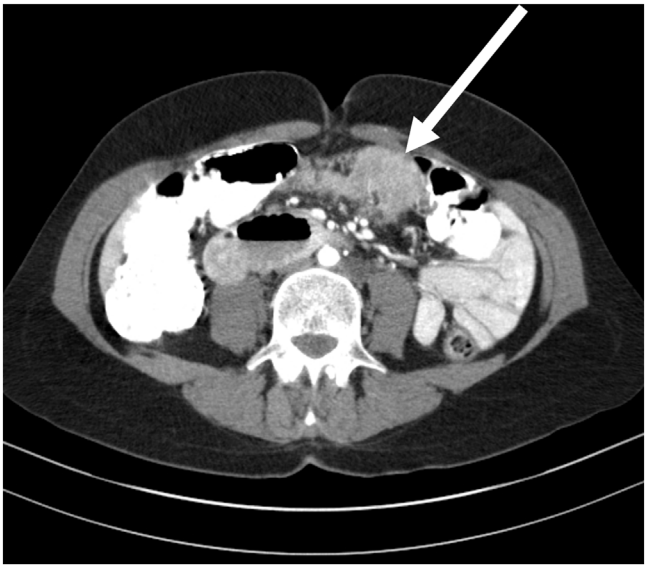

Fig. 2. At the level of the umbilicus, CT shows an 8 cm mass associated with the mid-transverse colon. No bowel obstruction is evident.

study was registered as a case report on the www.researchregistry.com website with UIN 6481.

September 2016: At age 57, this woman developed postmenopausal bleeding. A Pap smear revealed malignant cells.

January 2017: A laparoscopic total abdominal hysterectomy and bilateral salpingo-oophorectomy was performed by a gynecologic oncologist. Right and left sentinel pelvic lymph nodes were negative as were biopsies from right and left para-aortic lymph nodes. The endometrioid adenocarcinoma of the endometrium was FIGO grade 2 of 3. The tumor size was 3.5 cm in diameter. The histologic type was endometrioid adenocarcinoma with focal squamous differentiation. The patient underwent 5 cycles of intravaginal chemotherapy.

September 2018: The patient had an episode of urinary retention with severe discomfort upon urination. A CT scan showed disease within the greater omentum (Fig. 1), a mass associated with the transverse colon (Fig. 2) and a nodule between right and left common iliac vessels thought to be a para-aortic lymph node (Fig. 3).

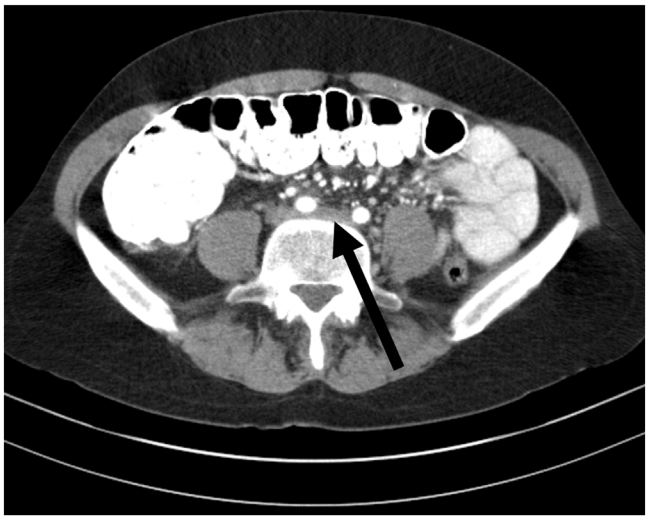

Fig. 3. A nodule interpreted as a lymph node at the bifurcation of the aorta is seen between the right and left common iliac vessels.

An encounter summary performed in the Cancer Institute recorded no drug history, no family history of cancer, and a totally normal psychosocial history.

Physical examination showed a prominent mass in the left upper quadrant which extended transversely along the abdominal wall. On pelvic exam, there were masses on the left side of the pelvis and at the apex of the vagina.

The results of the evaluation for recurrent endometrial cancer including the masses by physical examination and the marked progression of disease by CT were discussed with the patient. The possible options for treatment were discussed at a combined surgical oncology/gynecologic oncology multidisciplinary team (MDT) meeting. Given the patient's young age and lack of comorbid conditions, a reoperative surgery plus HIPEC was recommended. This information was again, at a separate visit, communicated to the patient and her family. The possibility for adverse events and their incidence were discussed. The patient elected to move toward the cytoreductive surgery which was scheduled within 10 days. The patient was treated as part of an ongoing performance improvement project with extensive data monitoring.

October 2018: An 11-h cytoreductive surgery was performed with HIPEC by a surgical oncologist (PHS). Procedures performed included greater omentectomy, splenectomy, cholecystectomy, lesser omentectomy, peritonectomy of the undersurface of the right hemidiaphragm, partial peritonectomy of the left hemidiaphragm, transverse colectomy with anastomosis, pelvic peritonectomy and bilateral ureterolysis. The apex of the vagina was resected for approximately 4 cm because of disease at that site [11]. All specimens except the gallbladder were positive for metastatic high-grade carcinoma. The nodule at the bifurcation of the aorta was removed and submitted as a separate specimen. It was a nodule of high-grade carcinoma but was not thought to be within a lymph node. Fig. 4 shows the peritoneal cancer index.

The patient received hyperthermic intraperitoneal chemotherapy for 90 min with cisplatin 80 mg, doxorubicin 24 mg, and intravenous ifosfamide 2080 mg. Mesna was given prior to ifosfamide infusion, 4 h after completion of chemotherapy and 8 h after completion of chemotherapy at 416 mg. Temperature within the peritoneal space was approximately 42.5–43.5 °C [12].

Postoperatively, the patient received EPIC paclitaxel at 32 mg/day in 1 L of hetastarch solution for 5 consecutive days. The

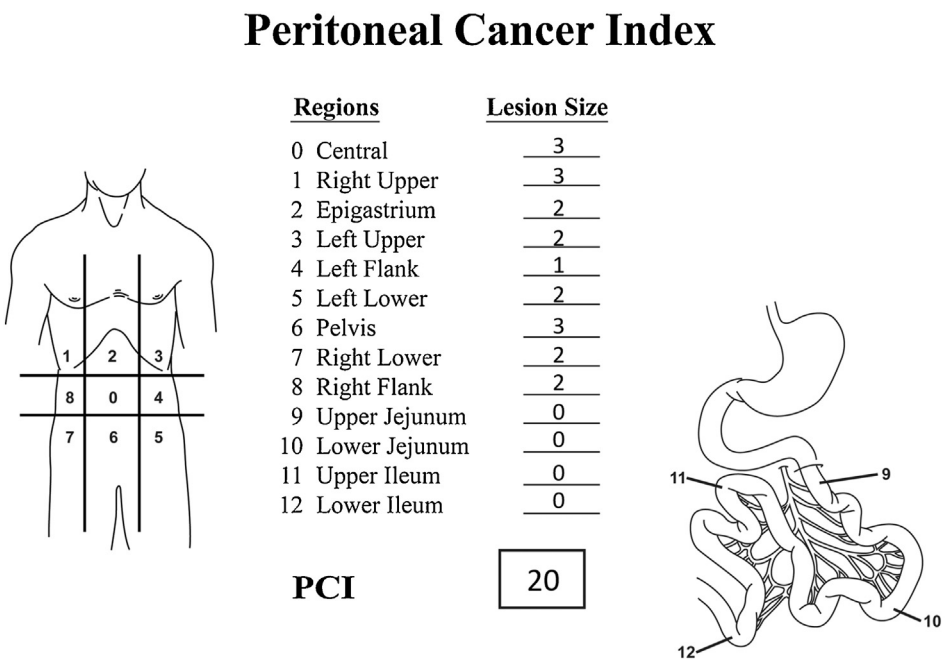

Fig. 4. The peritoneal cancer index (PCI). The PCI combines size and distribution parameters to determine a numerical score. The lesion size (LS) is used to quantitate the size of the peritoneal nodules with the 13 abdomino-pelvic regions. LS-0 indicates no tumor seen, LS-1 indicates tumor implants up to 0.5 cm, LS-2 indicates tumor implants between 0.5 and 5 cm, and LS-3 indicates tumor implants larger than 5 cm or a layering of cancer. The PCI in a 59-year-old woman undergoing surgery for recurrent endometrial high-grade carcinoma is shown in the diagram. The PCI was 20.

total dose of paclitaxel was 160 mg [12]. The patient developed a wound infection which was treated with antibiotics and opening of the lower 3 cm of the abdominal incision. The patient was discharged on her 21st postoperative day. There were no class 3 or 4 adverse events. The HIPEC and EPIC were well tolerated.

The patient received 5 cycles of systemic chemotherapy using cisplatin and paclitaxel delivered by a medical oncologist. A planned sixth cycle of systemic chemotherapy was withheld because of cumulative cisplatin toxicity.

Postoperatively, CT have been performed on a 6 monthly basis.

At 25 months postoperatively, a CT scan of the chest, abdomen and pelvis showed no progression of disease. CA-125 tumor marker was negative prior to surgery and has not shown elevation. The patient is maintained on oral nutrition without supplements and is maintaining here preoperative weight. No pain medicines are required.

3. Discussion

3.1. Treatment and prevention of peritoneal spread is possible

This case report illustrates that peritoneal metastases from endometrial cancer, even of large volume, can be controlled with a combination of complete resection and combined regional and systemic chemotherapy. Other reports attempt to convey the same message [8,9]. It is important to realize that the timing of the two components of this treatment strategy are crucial to its success. The surgery must remove all visible evidence of disease using a combination of peritonectomy procedures and visceral resections [11]. Then before stray cancer cells have the opportunity to become fixed within a fibrinous matrix, they must be washed by a chemotherapy solution to remove them mechanically and initiate chemotherapy-induced apoptosis. The current treatment option to supplement complete cytoreduction is HIPEC or HIPEC plus EPIC as was used in this patient [12]. Success in the management of peritoneal metastases from endometrial cancer is possible.

3.2. Careful study of the primary cancer may reveal the natural history of treatment failure

As published by Creasman and coworkers in a Gynecologic Oncology Group study, positive peritoneal cytology and/or peritoneal metastases are present in approximately 20% of primary endometrial cancers. The extent of the peritoneal spread and its documentation is not available from the pathologist for approximately one week following the surgical procedure. Morrow and coworkers have suggested that there is a relationship between the surgical-pathologic risk factors and the patient's outcome [13]. Also, Mariani and coworkers more specifically showed that the findings within the resected endometrial cancer specimen can predict later progression of peritoneal metastases [5]. If CRS and HIPEC were utilized to eliminate peritoneal dissemination in patients at high risk for this type of treatment failure, an improved outcome is expected.

3.3. A new and expanded role for the pathologist in patients with endometrial cancer

Currently, a large amount of crucial information regarding the outcome of cancer patients is provided by the pathologist. The resected specimen is placed in formalin to be prosected by the pathologist at a later and convenient time. For interventions that occur at the time of cancer resection, such as CRS and HIPEC, this information is "after the fact." Of course, very interesting, but not of benefit to the patient who may be in need of preventative treatment for subsequent progression of peritoneal disease. For peritonectomy procedures to be used to resect peritoneal metastases at a particular site, the anatomic site of disease must be documented histopathologically in the operating theater. Return to perform a second-look at a later time is not a realistic plan. Also, results of peritoneal cytology are needed while the patient is in the operating room to make a decision regarding HIPEC or HIPEC with EPIC.

3.4. Intraoperative surgical-pathological collaboration

In order to make the prediction of high risk for peritoneal recurrence/progression relevant to an individual patient, information must be made available in the operating theater. Immediately after the specimen is removed, it must be oriented by the surgeon for the pathologist. All peritoneal or Fallopian tube biopsies suspicious for peritoneal metastases must be presented to the pathologist. The peritoneal cytology results must be determined. The uterus specimen must be examined for peritoneal infiltration. Together the surgeon and pathologist need to make a decision regarding the subsequent risk of the individual patient for peritoneal metastases. If there is a risk, peritonectomy of selected anatomic sites may be required. Also, HIPEC or HIPEC plus EPIC administration requires an intraoperative judgment to proceed. In addition, prior consent for these interventions are required. By cryostat sections, the histopathological information needs to be available in the operating theater to administer the individualized treatments that are indicated in a timely manner.

3.5. CRS and HIPEC failures despite treatment

In the patient in this case report, the small bowel and its mesentery were observed to be free of peritoneal metastases. This is a favorable observation that indicates long-term success may be possible even with large masses of tumor distributed on the parietal peritoneum. Cytoreduction of small bowel and its mesentery is especially difficult. Extensive resection of small bowel is to be avoided. Also, tumor nodule removal on the bowel surface places the patient at risk for postoperative fistula. Removal of tumor from the mesentery creates a risk for small bowel ischemia. This is a major concern if tumor nodules are at the junction of small bowel with its mesentery. The mechanism for persistence and then subsequent progression of peritoneal metastases on visceral peritoneum has not been elucidated. However, incomplete resection combined with rapid removal of cancer chemotherapy with a generous blood supply within the small bowel may combine to cause the poor result. Small bowel sparing is important to the long-term success of CRS and HIPEC.

3.6. Bidirectional chemotherapy with HIPEC and EPIC for prevention or treatment of resected endometrial cancer with peritoneal metastases

For the chemotherapy agents used in this patient with peritoneal metastases from endometrial cancer, drugs with known response for this disease were selected. For HIPEC, the intraperitoneal drugs were moderate dose cisplatin and doxorubicin. Both of these drugs have activity for endometrial cancer and both are augmented in their cytotoxicity by heat. Both drugs have a favorable area under the curve ratio of intraperitoneal to systemic drug concentration. They are both acute phase agents and produce their full cytotoxic effect within the 90-minute HIPEC treatment [14]. A single systemic agent is ifosfamide. Our pharmacologic studies show that the same concentrations of intravenous and intraperitoneal ifosfamide are present almost immediately after intravenous infusion [15]. The intravenous ifosfamide has been shown to gain access to peritoneal tumor nodules.

For EPIC, paclitaxel was selected. This drug has a prolonged dwell time within the peritoneal space because of its large molecular weight. Also, it is a non-vesicant drug and well tolerated by the peritoneum without causing fibrosis [16]. Markman and coworkers demonstrated a 61% complete response rate in 28 patients with microscopic residual disease [17].

Declaration of Competing Interest

Paul H. Sugarbaker has no conflicts of interest to declare.

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Ethical approval

MedStar Health Institutional Review Board has determined that a case report of less than three (3) patients does not meet the DHHS definition of research (45 CFR 46.102(d)(pre-2018)/45 CFR46.102(l)(1/19/2017)) or the FDA definition of clinical investigation (21 CFR 46.102(c)) and therefore are not subject to IRB review requirements and do not require IRB approval.

Consent

Written and signed consent was obtained from the patient.

Author contribution

Paul H. Sugarbaker: study concept or design, data collection, data analysis or interpretation, writing the paper.

Registration of research studies

This study was registered as a case report on the www.researchregistry.com website with UIN 6481.

Guarantor

Paul H. Sugarbaker, MD

Provenance and peer review

Not commissioned, externally peer-reviewed.

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