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Prolonged survival following maximal cytoreductive effort for peritoneal metastases from recurrent granulosa cell tumor of the ovary

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To the editor: Granulosa cell tumor (GCT) of the ovary is characterized by a relatively indolent natural history with a propensity for late recurrence and long-term survival. The median time to recurrence is 4 to 6 years after the initial diagnosis [1]. Disease recurrence often presents within the pelvis as a local mass, in the retroperitoneal lymph nodes, or as disseminated peritoneal metastases [1,2]. There is no standard management for recurrent GCT. Various treatment options include surgery with/without chemotherapy and/or radiotherapy. Patients with peritoneal metastases are often considered inoperable with treatment largely directed at palliation of symptoms. Five patients with recurrent GCT with peritoneal metastases from our institution were treated with cytoreductive surgery (CRS).

The mean (standard deviation) age of five women at the time of CRS was 49 (10) years. Prior to CRS, all five patients were followed-up after initial staging surgery performed by the gynaecologic oncology surgeon. The initial staging surgery was a total abdominal hysterectomy with bilateral salpingo-oophorectomy in the three patients. Two patients required opted for fertility conservation and underwent a unilateral salpingo-oophorectomy. Due to the localized disease in the ovary, none of the patients received adjuvant treatment after the initial surgery. The median disease-free survival after primary treatment was 6 years (range, 6 to 12 years). Treatment of first recurrence involved CRS in patient one and patient three, systemic chemotherapy in patient two, debulking surgery in patient four and systemic chemotherapy with radiotherapy in patient five. The three patients who did not undergo CRS eventually underwent CRS for management of persistent recurrent disease. The detailed summary of the patients' clinical pathway is presented in Table 1.

In total, eight cytoreductive surgeries using peritonectomy procedures were performed in five patients, of which one patient received intraoperative hyperthermic intraperitoneal cisplatin for 90 minutes at 42°C. There was no in-hospitalization treatment related mortality. The median length of operation was 5.3 hours (range, 3.3 to 10 hours). The median length of stay in hospital was 10 days (range, 7 to 87 days). Patients one and two recovered uneventfully. Severe postoperative complications as graded according to the National Cancer Institute's Common Toxicity Criteria occurred in patient three at the time of peritonectomy for the fourth recurrence, in patient four at the time of peritonectomy for the second recurrence, and in patient five at the time of first peritonectomy for treatment for third recurrence. Patient three had a 24 day hospital stay after suffering from a grade III postoperative complication, requiring percutaneous drainage of a retroperitoneal abscess under radiological guidance. Patient four remained hospitalized for 87 days following grade IV postoperative complications with renal impairment secondary to intraperitoneal cisplatin, right pleural effusion requiring chest drain placement, recto-cysto-vaginal fistula and sepsis. Patient five had a 12 day hospital stay after suffering from grade III postoperative complication, requiring percutaneous drainage of a right upper quadrant collection.

Following CRS, patient one, four and five are disease free. However, disease recurrence was seen in patient two and three in whom repeat peritonectomy was performed. Patient two developed recurrence 38 months later, and was treated with repeat peritonectomy. Patient three developed multiple

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Table 1. Summary of clinical pathway of four patients with peritoneal metastases from recurrent granulosa cell tumor of the ovary

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age at diagnosis (yr)	36	53	34	35	25
Primary surgical treatment	Right salpingo-oophorectomy	Total hysterectomy, bilateral salpingo-oophorectomy, omentectomy	Total hysterectomy, bilateral salpingo-oophorectomy	Left salpingo-oophorectomy	Total hysterectomy, bilateral salpingo-oophorectomy
Time to first recurrence (yr)	6	9	12	6	6
Type of first recurrence	Intra-abdominal mass with peritoneal disease	Peritoneal disease	Intra-thoracic mass and Intra-abdominal mass with peritoneal disease	Retroperitoneal nodal mass and few peritoneal nodules	Peritoneal disease
Type of treatment for first recurrence	Omentectomy + splenectomy, pelvic peritonectomy, total anterior parietal peritonectomy, diaphragmatic peritonectomy, total hysterectomy left salpingo-oophorectomy*	Bleomycin, etoposide, carboplatin	Right lower lobectomy, liver resection, right diaphragmatic peritonectomy, right adrenalectomy*	Debulking surgery with excision of peritoneal nodules	Bleomycin, etoposide, carboplatin and radiotherapy
Time to second recurrence (mo)	-	44	30	40	81
Type of second recurrence	-	Peritoneal disease	Peritoneal disease	Peritoneal disease	Single lung metastasis, peritoneal disease
Type of treatment for second recurrence	-	Pelvic peritonectomy*	Pelvic peritonectomy	Pelvic peritonectomy, total anterior parietal peritonectomy, hyperthermic intraperitoneal cisplatin*	Bleomycin, etoposide, carboplatin
Time to third recurrence (mo)	-	38	29	-	91
Type of third recurrence	-	Peritoneal disease	Nodal disease	-	Peritoneal disease and stable lung metastasis
Type of treatment for third recurrence	-	Diaphragmatic peritonectomy, cytoreduction on small bowel surface, stripping of mesentry	Debulking surgery	-	Total anterior parietal peritonectomy, pelvic peritonectomy, right diaphragmatic peritonectomy, stripping of omental bursa with cholecystectomy, cytoreduction on small bowel surface, small bowel resection, anterior resection, right hepatectomy, right adrenalectomy*
Time to fourth recurrence (mo)	-	-	30	-	-
Type of fourth recurrence	-	-	Peritoneal disease	-	-
Type of treatment for fourth recurrence	-	-	Cytoreduction of small bowel surface, small bowel resection, distal pancreatectomy, splenectomy, diaphragmatic peritonectomy	-	-
Survival following peritonectomy (mo)	38	44	95	33	10
Number of recurrence following peritonectomy	0	1	3	0	0
Current disease status	NED	NED	NED	NED	NED

*Refer to time of first peritonectomy.
NED, no evidence of disease.

recurrences 30 months after first peritonectomy, where a repeat peritonectomy was performed. A further disease-free interval of 29 months was achieved before the development of a nodal recurrence which was treated with debulking surgery where lymphadenectomy was performed. Subsequently, the patient developed peritoneal recurrence 30 months later and underwent a third repeat peritonectomy. With a median follow-up of 38 months after the first peritonectomy treatment, all five patients are still alive 10 to 95 months after treatment with no evidence of disease.

Disseminated peritoneal metastasis of GCT is characterized intraoperatively by the extensive presence of macroscopic whitish tumor nodules of variable sizes and consistency that may coalesce to form plaques or masses within the abdominopelvic cavity. These nodules and plaques may also layer out and line the entire peritoneal surface. This phenomenon in recurrent GCT has been previously described [3]. It occurs as a result of direct serosal invasion, perforation or rupture of the primary ovarian tumor. It may also be related to iatrogenic mechanisms during invasive procedures such as fine-needle cytology or spillage of tumor content during surgical intervention. As with other forms of malignancies that disseminate extensively on the peritoneal surface, such as colon cancer, epithelial ovarian cancer and peritoneal mesothelioma, peritoneal metastases has traditionally been regarded incurable and is associated with a poor prognosis. Patients with advanced ovarian cancer have a 5-year survival of less than 25% [4]. In a Korean multicenter study of 113 patients with GCT, FIGO stage predicted for recurrence in patients after initial treatment [5].

Surgical treatment of peritoneal metastases from recurrent GCT is unduly challenging. Conventional debulking surgery is insufficient in attaining complete cytoreduction. Peritonectomy procedures, as described by Sugarbaker [6], is a surgical procedure that involves the removal of the diseased peritoneum as a means of achieving complete cytoreduction. It has brought about a new paradigm into the treatment of peritoneal metastases. We demonstrate the feasibility of employing peritonectomy procedures to achieve complete cytoreduction in the five patients and have demonstrated prolonged disease-free survival ranging from 10 to 95 months. In patients who develop recurrence, repeat peritonectomy is a reasonable option, as shown in patient three, where a disease-free interval of 29 months was achieved after the second peritonectomy. This may be a reflection of the indolent biology of this disease where a long-term survival can be achieved if complete cytoreduction is performed. Nonetheless, severe postoperative complications may occur as a result of the process of aggressive cytoreduction. This must be balanced with any hope of long-term survival this treatment may offer.

Various other treatment modalities are employed in the treatment of recurrent disease; chemotherapy, radiotherapy and hormonal therapy. The common chemotherapy regime used in this setting is a combination of bleomycin, etoposide, and cisplatin. Although, the response rate to this regimen ranges between 51 to 90%, the effectiveness of this treatment remains poor with a median disease-free survival of only 14 to 24 months [7,8]. Outcomes of radiotherapy and hormonal therapy are also poor, with response rates being 43 and 40% respectively. Overall median survival following radiotherapy treatment is 156 months in responders and 12 months in non-responders [9]. Patients treated with hormonal therapy develop progressive disease after 8 months [10]. Therefore, the only available effective treatment that has demonstrated a prolonged survival is surgery [1,3].

From our experience, non-surgical management of recurrent GCT is only employed in the setting of un-resectable disease. In selected patients who are suitable to undergo surgery, maximal cytoreduction with a curative intent that includes tumor resection, retroperitoneal lymphadenectomy and peritonectomy should be considered. Our report is the first to describe the use of peritonectomy procedures to achieve maximal cytoreduction in patients with recurrent GCT, demonstrating the feasibility and safety of this treatment option. We have not begun routinely administering intraoperative hyperthermic intraperitoneal chemotherapy for patients with peritoneal metastases from GCT; however it may be worth considering given the 51 to 90% response rate observed when administered intravenously for which may potentially be higher when administered intraperitoneally. Following evidence from the literature that suggests that maximal cytoreduction is an important aspect of treatment in recurrent GCT [1], we have described the use of peritonectomy to achieve complete cytoreduction in patients with peritoneal metastases from recurrent GCT.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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