

Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in the management of recurrent mucinous cystadenoma of the ovary

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Summary

Purpose: Mucinous cystadenomas (MCA) of the ovary may lead to multiple complications and become recurrent. This study presents the management and long term follow-up of three patients with recurrent ovarian MCA treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS/HIPEC). **Materials and Methods:** A retrospective review of a prospective database of 675 patients treated with CRS/HIPEC at a single institution was conducted. Of 132 patients with gynecological tumors, three patients with recurrent ovarian MCA were identified. CRS/HIPEC was performed with 40 mg of mitomycin-C for 90 minutes. Follow-up for disease recurrence was carried out with computed tomography. **Results:** All patients with recurrent ovarian MCA had a total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH/BSO) as the initial intervention. Two patients recurred twice after the initial procedure and one patient had three recurrences. At the time of CRS/HIPEC, all patients had multiple organ involvement and urinary complications, which resolved after CRS/HIPEC. There were no further recurrences after CRS/HIPEC. Follow-up after CRS/HIPEC was 12, 60, and 72 months. **Conclusion:** The present authors' experience shows that CRS/HIPEC is a feasible and effective treatment for recurrent MCA of the ovary in selected patients.

Key words: Cytoreductive surgery; Hyperthermic intraperitoneal chemotherapy; Mucinous cystadenoma; Ovarian tumor; Recurrence.

Introduction

Most ovarian mucinous tumors are benign (mucinous cystadenoma, MCA) and typically occur during the reproductive years. Nonetheless, MCA may transform into adenocarcinoma in 5-10% of patients. They may reach massive sizes, become recurrent, and lead to complications such as hemorrhage, rupture, adnexal torsion, and pseudomyxoma peritonei (PMP).[1-4] When symptomatic, the management of these tumors depends on patient age, menopausal status, and the size of the cyst, but generally, the standard of care is laparoscopic excision with attempted fertility preservation in patients who desire pregnancy [1, 2]. Patients are then followed periodically to screen for possible recurrences [2]. There are only nine published cases of recurrent ovarian MCA, with no available follow-up data [2-8].

The authors report three patients with ovarian MCA initially treated at outside institutions with a traditional surgical approach, which led to multiple MCA recurrences. These patients were ultimately managed with cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) at this institution, to prevent subsequent recurrences and associated morbidity. The treatment and long term follow-up of these patients is presented.

Materials and Methods

A retrospective review of a prospective database of 675 patients treated with CRS/HIPEC at this institution was conducted. Demographic data and medical history were obtained from chart analysis. Operative reports and patient progress notes were reviewed. Patient age, date of initial diagnosis, tumor histology, date and location of recurrence, description of surgical procedures, and status at last follow-up were extracted.

Of 132 patients with gynecological tumors, three patients with recurrent ovarian MCA were identified. These patients underwent CRS/HIPEC after evaluation by the senior surgical oncologist, who considered functional status as a key component to undergo a major surgical procedure. CT scan of the abdomen and pelvis and tumor markers (CA-125, CEA, and CA-19.9) were obtained prior to CRS/HIPEC.

The CRS/HIPEC surgical technique was performed as previously described [9], using mitomycin-C for 90 minutes, total dose of 40 mg (30 mg given initially and 10 mg added after 30 minutes of perfusion) and temperature 41°C to 42°C. Follow-up for disease recurrence was carried out with physical exam and CT scan of abdomen and pelvis at one month postoperatively, at six month intervals for five years, and yearly thereafter. Clinical descriptive analysis was reported. This retrospective review received Institutional Review Board approval.

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Results

Patient 1

A 46-year old post-menopausal woman was initially diagnosed with an ovarian mass. A total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH/BSO) were performed, and the diagnosis of ovarian MCA was rendered. Two years later she developed another pelvic mass and underwent a second resection via laparotomy. The tumor was classified as recurrent MCA. Four years after initial diagnosis, she presented to this institution complaining of lower back pain, urinary incontinence, and constipation. On pelvic examination, a large midline mass was found pressing down on the anterior vagina displacing the bladder anteriorly. CT scan revealed a complex cystic mass in the pelvis measuring 11.2×11.5×9.7 cm, with thickened walls and septa. Tumor markers were normal.

The patient underwent CRS/HIPEC as her third surgery which involved lysis of adhesions, a partial cystectomy, vaginectomy, and low anterior resection, along with resection of the tumor. Intraoperatively, the patient received mitomycin-C for a total of 90 minutes, with an initial dose of 30 mg plus 10 mg, 30 minutes later. Gross examination of the tumor revealed a 7.5×6.5×6.5 cm saccular mass filled with mucinous fluid, adherent to surrounding structures, including rectosigmoid colon, perivaginal soft tissue, and urinary bladder wall. Microscopic examination revealed mucinous epithelium associated with ovarian-like stroma without atypia.

The length of hospital stay was eight days without complications. The patient remains free of disease and asymptomatic six years after CRS/HIPEC.

Patient 2

A 57-year-old post-menopausal woman was initially diagnosed with an ovarian tumor. She underwent a TAH/BSO and the pathology report revealed an ovarian MCA. Two years later, the patient developed a large, multiloculated pelvic mass, and underwent debulking surgery at that time. She presented to this surgical oncology clinic three years after initial diagnosis with a history of constipation, decreased appetite, pelvic pain, urinary frequency, and urinary incontinence. She had a palpable mass in the lower abdomen. CT scan revealed a large cystic mass in the pelvis measuring approximately 10 cm in diameter and compressing the bladder and sigmoid colon, with significant bilateral hydronephrosis. Tumor markers were negative.

After consultation, CRS/HIPEC was recommended. With surgery pending, the patient presented to the emergency department with worsening pelvic pain, urosepsis, and acute renal failure. At that time, the authors proceeded with CRS/HIPEC. Resection of the pelvic mass, along with low anterior resection and partial vaginectomy were performed. Significant extrinsic obstruction of the rectosigmoid and ureters was noted. The patient received HIPEC with mitomycin-C for a total of 90 minutes, at a reduced dose of 20 mg initially and 5 mg 30 minutes later, due to renal insufficiency. Gross examination of the tumor revealed a 10×8×7 cm encapsulated and multiloculated cystic mass attached to the serosa of the distal colon and perivaginal soft tissue. The final pathology report described mucinous epithelium associated with ovarian-like stroma without atypia.

The postoperative hospital course (16 days) was uncomplicated and both urosepsis and acute renal failure which resolved. The patient remains free of disease and is asymptomatic five years after CRS/HIPEC.

Patient 3

A 60-year-old postmenopausal woman was initially diagnosed with ovarian MCA and underwent a TAH/BSO. Recurrence was detected one year later, when a second resection of the pelvic tumor was required. Five years after diagnosis, a second recurrence with tumor involving the right ureter required a third procedure which was complicated by right ureteral injury with repair and stent placement. She later developed right kidney hydronephrosis secondary to ureteral fibrosis, which required the placement of a nephrostomy tube. Eleven years after diagnosis, the patient presented to the this surgical oncology clinic with constipation, decreased appetite, abdominal pain, and fullness. CT scan revealed a septated cystic mass in the pelvis measuring 10×12×8.3 cm which anteriorly displaced the sigmoid colon. Tumor markers were negative.

The patient underwent her fourth surgery (initial CRS/HIPEC) for resection of the pelvic tumor. The following resections were performed in the presence of severe tumoral adherence and multiple intra-abdominal adhesions: rectosigmoid, segment of right internal iliac and external iliac vessels, distal right ureter, segment of jejunum and partial cystectomy. HIPEC was performed with mitomycin-C using 30 mg initially with 10 mg added 30 minutes later. Perfusion time was shortened from 90 minutes to 45 minutes due to intraoperative hypotension. Gross examination of the tumor revealed a multilocular cystic structure measuring 10.1×9.7×6.0 cm filled with hemorrhagic mucoid material. Histopathologic examination revealed multiple simple mucinous cysts with associated ovarian-like stroma, involving the subserosal tissue of the colon.

Hospital stay was ten days and the patient recovered uneventfully with full return of previously altered renal function. Twelve months after surgery, there is no evidence of hydronephrosis or tumor recurrence.

Discussion

Only nine cases of recurrent ovarian MCA have been reported in the literature and the long term follow-up of these patients is unknown [2-8]. The estimated recurrence rate of ovarian MCA is 7.1% according to a series of 42 patients

Table 1. — Cases of recurrent ovarian mucinous cystadenoma reported in the literature.

First author, year	No. of patients	Patient's age (y)	No. of recurrences	Surgery #1	Surgery #2	Surgery #3
Olesen, 2001	1	11	1	No data	Ovarian cystectomy (laparoscopy)	N/A
Gotoh, 2004	1	31	2	Bilateral ovarian cystectomy	Bilateral ovarian cystectomy	TAH, BSO
Baksu, 2006	1	20	2	Left oophorectomy, right ovarian cystectomy (laparotomy)	Right ovarian cystectomy (laparotomy)	TAH, right SO
Mittal, 2008	1	25	1	Ovarian cystectomy (laparoscopy)	Left SO (laparoscopy)	N/A
Turkyilmaz, 2009	1	27	1	Ovarian cystectomy (laparotomy)	Left SO (laparoscopy)	N/A
Ben-Ami, 2010	3	21.7 ± 4.5 (mean ± SD)	1	Ovarian cystectomy (laparoscopy)	No data	N/A
Sanaullah, 2011	1	26	1	Left SO (laparoscopy)	Tumor resection (laparoscopy)	N/A

SD: standard deviation, TAH: total abdominal hysterectomy; SO: salpingo-oophorectomy; BSO: bilateral salpingo-oophorectomy; N/A: not applicable.

Table 2. — Characteristics of the patients in the present case series.

Patient's age at Dx (years)	No. of recurrences	Surgery #1	Surgery #2	Surgery #3	Surgery #4	Other organs involved*	Complications†
46	2	TAH, BSO	Tumor resection	CRS, HIPEC	N/A	Rectosigmoid, bladder, vagina	Urinary incontinence
57	2	TAH, BSO	Tumor resection	CRS, HIPEC	N/A	Rectosigmoid, vagina	Bilateral hydronephrosis, urosepsis, acute renal failure
60	3	TAH, BSO	Tumor resection	Tumour resection	CRS, HIPEC	Rectosigmoid, right internal and external iliac vessels, right ureter, jejunum, bladder	Right ureteral injury, hydronephrosis

Dx: diagnosis; TAH: total abdominal hysterectomy; BSO: bilateral salpingo-oophorectomy; N/A: not applicable; UTI: urinary tract infection.

* Adherence of the tumor to organs other than ovaries or fallopian tubes. †Complications due to the tumor itself or derived from previous surgical procedures.

[3]. Table 1 [2-8] summarizes the characteristics of recurrent ovarian MCA reported in the literature. Patient age ranged from 11 to 31 years; therefore, the preferred initial intervention for eight patients was ovarian cystectomy in order to preserve fertility. However, four of these patients ultimately underwent salpingo-oophorectomy.

The characteristics and management of the present patients differ considerably from the previously reported cases. The three patients were post-menopausal and underwent total TAH/BSO as the initial intervention (Table 2). They had tumor involvement of adjacent organs and complications at time of recurrence. The follow-up of the present patients ranged from 12 months to six years after CRS/HIPEC, all without further complications or recurrence of MCA, indicating CRS/HIPEC as a definitive management strategy. Unfortunately, the present authors are unable to make comparisons as there is no available data regarding the long term follow-up and status of the patients previously reported in the literature.

A study conducted by Ben-Ami *et al.*, revealed that intraoperative cyst rupture and cystectomy instead of adnexectomy are two risk factors for recurrence of MCA [3]. In

fact, all except one case reported in the literature, have been recurrences after cystectomy and there has been only one case of recurrence reported after an oophorectomy [8]. It is remarkable that the patients who presented to the present clinic had multiple recurrences after an initial TAH/BSO. This implies that inadvertent cyst rupture occurred or microscopic ovarian tissue was left behind during the initial procedure, although complete removal of the ovaries was performed. Laparoscopic excision of the adnexal mass with concomitant laparoscopic hysterectomy has been reported as a risk factor for intraoperative cyst rupture [10]. Although not yet described, the same may be true for laparotomy, based on the surgical history of the three patients who presented to our institution.

Management of symptomatic MCA depends on the patient's age, menopausal status, and the size of the cyst [2, 3]. The standard of care is laparoscopic excision, with as much fertility preservation as possible for patients who desire pregnancy [1, 2]. Cystectomy is preferred over oophorectomy in younger patients without a previous history of cancer, even in cases of adnexal torsion [1], while adnexectomy is the preferred surgical procedure in post-

menopausal women [3]. In borderline ovarian neoplasms, laparoscopy is only recommended when tumors are < 10 cm to prevent rupture [11]. However, in benign ovarian tumors such as MCA, laparoscopy has been shown feasible with adnexal masses larger than 10 cm [3].

In the past, CRS/HIPEC has not been used for the management of recurrent ovarian MCA. CRS consists of a complete resection of all visible disease from the abdominal cavity, including affected viscera. Subsequently, HIPEC is administered in order to eliminate tumor cells that remain viable in the abdominal cavity after CRS [12, 13]. The current indications for CRS/HIPEC are pseudomyxoma peritonei, primary peritoneal carcinoma, peritoneal mesothelioma, and peritoneal carcinomatosis of appendiceal, colorectal, and ovarian origin [13, 14]. Disseminated peritoneal adenomucinosis (DPAM), which used to be considered a benign condition, is also an indication for CRS/HIPEC [14].

Although ovarian MCA is not an indication for CRS/HIPEC, this procedure was deemed beneficial by the present surgical oncology team because the patients were suffering from a recurrent disease that was previously uncontrolled by conventional techniques. Moreover, two patients experienced significant morbidity with MCA recurrence, including hydronephrosis and renal failure. Similar to DPAM, ovarian MCA in these patients behaved aggressively despite the presumed benign histopathology. The goal of CRS/HIPEC in these patients, in addition to removing the visible recurrent tumor, was to eradicate microscopic residual tumor and free floating tumor cells in order to prevent further recurrences.

As a major surgical procedure, CRS/HIPEC is known to be associated with postoperative complications. The most common complications are wound infection, small bowel perforations, anastomotic leaks, prolonged ileus, hematological toxicity, pleural effusion, and pneumonia [15]. Despite the risk of morbidity and mortality associated with CRS/HIPEC, the incidence is lower when the procedure is performed by an experienced team, with extensive knowledge and technical expertise [15]. It is important to note that none of the aforementioned complications occurred in the present patients.

Conclusion

In summary, ovarian MCA can reach massive sizes, resulting in severe complications, and become recurrent despite the benign histopathology. The patients who presented to the present center had a history of multiple recurrences following initial TAH/BSO, in addition to significant morbidity caused by excessive tumor growth, mechanical compression, and involvement of adjacent structures. CRS/HIPEC was performed to eliminate the disease and prevent further recurrences. While the present authors cannot conclude that CRS/HIPEC should be used routinely in recur-

rent ovarian MCA, their experience shows that CRS/HIPEC may be offered as a definitive management in patients with high morbidity from this disease.

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