Case 2 – Multiple cytoreductive surgeries for metastatic advanced ovarian cancer: a case report

C. Marchetti[1], A. Musella[1], C. Sassu[1], A. Giannini[1], C. Pisano[2]

Abstract
We report the case of a multiple recurrent ovarian cancer (ROC) in a platinum-sensitive patient, 46 years of age, who underwent four cytoreductive surgeries for three recurrences of disease. In selected patients, surgery might represent a useful tool in adjunction to chemotherapy for the management of recurrent ovarian cancer.

Key words: chemotherapy, cytoreductive surgery, ovarian cancer, recurrence, survival

Introduction

Ovarian cancer represents the sixth most common cancer worldwide and it is characterized by the worst prognosis among gynaecological cancers, with a 5-year survival rate of 44.2% since greater than 75% of women present with advanced stage of disease [1]. Overall, 85% of ovarian cancer patients will experience recurrent disease, with virtually no long-term survival after recurrence [2, 3]. Most common sites of recurrence involve pelvic and aortic lymph nodes, bowel, peritoneum or upper abdomen. As most cases of recurrent ovarian cancer (ROC) are multifocal and the prognosis of such patients is rarely curative, the standard management of patients with recurrent disease has been chemotherapy. Acceptance of the role of cytoreductive surgery in the treatment of ROC has not been as high as for primary treatment. Several studies, nearly all retrospective, with highly selected patients, have demonstrated a survival benefit for patients undergoing complete secondary cytoreductive surgery, and current practice differs widely between Institutions. We hereby present the case of a patient affected by advanced ovarian cancer who developed several recurrences, successfully treated by multiple cytoreductive surgeries (Table 1) followed by chemotherapy.

Case presentation

A 46-year-old woman was admitted at our Institution on April 2007 complaining of abdominal distension, abdominal pain and severe weight loss in the last two months. At admission, she was submitted to general and gynaecological examination and pelvic ultrasound, which revealed a fixed, solid pelvic mass of about 10 cm in diameter and ascites. General blood investigations were normal, while the CA 125 value was 843 U/mL. After adequate counselling and informed consent signed, she underwent primary cytoreductive surgery consisting of retroperitoneal hysterectomy according to the Hudson and Delle Piane technique, bilateral salpingo-oophorectomy, sovracolic omentectomy and removal of bowel nodules. Optimal debulking cytoreduction was achieved, without any evidence of macroscopic or microscopic residual tumour (RT=0). The histological analysis documented a poorly differentiated serous papillary ovarian carcinoma, International Federation of Obstetricians and Gynaecologists (FIGO) stage IIIC with positive peritoneal washing. Surgery was followed by 6 cycles of adjuvant chemotherapy with carboplatin (AUC 6) plus paclitaxel 175 mg/m2 every 21 days, with no serious adverse events or significant toxicities except for alopecia. Positron emission tomography-computed tomography (PET-CT), performed at the end of medical treatment, revealed no residual disease. The CA 125 value had returned to normal.

She had negative follows-up, both instrumental and clinical, until October 2009 when a PET-CT revealed a pathologic focal area of about 18 mm diameter in the right hepatic lobe. The CA 125 value reached 293 U/mL. The patient, in good general condition (performance status [PS]=1), after careful counselling, eventually gave

[1]Department of Gynaecological and Obstetrical Sciences and Urological Sciences, Università di Roma "Sapienza", Rome, Italy.
[2]Division of Oncology, Department of Urology and Gynaecology, Istituto Nazionale Tumori IRCCS "Fondazione G. Pascale", Naples, Italy.

Correspondence to: Dr. Claudia Marchetti,
Viale del Policlinico 155, 00161 Roma, Italy.
Phone: +39 338 4652744 – Fax: +39 06 49972564
E-mail: clamarchetti@libero.it

CANCER BREAKING NEWS 2014;2(1):25-28

Table 1. Clinical history and evaluation of criteria for debulking in a patient receiving four cytoreductive surgeries for epithelial ovarian cancer

Date diagnosis	Site	PS	CA 125 U/mL	Ascites	Peritoneal carcinomatosis	Radiology	PFI months	Surgery	RT	Complications	Chemotherapy
April 2007	Pelvic mass (10 cm)	0	843	Yes	No	Pelvic ultrasound	–	Hysterectomy, salpingoophorectomy, sovracolic omentectomy, removal of bowel nodules	0	No	Carboplatin (AUC 6) plus paclitaxel 175 mg/m^2 every 21 days
October 2009 1st recurrence/ progression	Right hepatic lobe (18 mm)	1	293	No	No	PET-CT	22	Resection of the 7th segment of the liver	0	No	3-weekly carboplatin (AUC 6) plus paclitaxel 175 mg/m^2
June 2012 2nd recurrence/ progression	Rectal ampulla (35 mm)	0	130	No	No	CT scan	27	Adhesiolysis; removal of sacral lesion. Sigma rectum latero-terminal anastomosis; adhesiolysis	0	Wound dehiscence	3-weekly carboplatin (AUC 4) plus gemcitabine 1,000 mg/m^2 on days 1 and 8
November 2013 3rd recurrence/ progression	Spleen	0	207	No	No	PET-CT	10	Adhesiolysis; splenectomy	0	No	Liposomal doxorubicin 30 mg/m^2 plus trabectedin 1.1 mg/m^2

AUC, area under the curve; CT, computed tomography; PET, positron emission tomography; PFI, progression-free interval; PS, performance status; RT, residual tumour.

her consent for surgical treatment followed by chemotherapy. Therefore, she underwent diagnostic laparoscopy, which confirmed the absence of other sites of recurrence in the abdominal cavity; consequently a second laparotomic cytoreductive surgery with a wedge resection of the 7th segment of the liver was performed. An optimal residual tumour was achieved. Histologic evaluation confirmed the liver as the only site of metastasis. Adjuvant chemotherapy with triweekly carboplatin (AUC 6) plus paclitaxel 175 mg/m2 was administered for 3 cycles, achieving a complete clinical response (CR) with CA 125 <35 U/mL. Subsequent PET-CT scans showed no evidence of disease until June 2012,when she complained of alterations in bowel function plus pain in the lower abdominal quadrants. She immediately underwent a CT scan, which showed a focal pathological area (35 mm diameter) on the right side wall of the rectal ampulla. The CA 125 value was 130 U/mL. In view of her good performance status (PS=1) at relapse diagnosis and previous willingness, we proposed a third cytoreductive surgery. After a careful evaluation of risks and benefits of the procedure, she acquiesced to surgery. She initially underwent a diagnostic laparoscopy which was negative, but was not completely reliable due to severe adhesive syndrome. Therefore, a laparotomy was performed and, after cautious adhesiolysis, a sacral lesion involving rectal serosa was discovered. Thus, an accurate removal of the lesion was performed, requiring rectal resection and sigmarectum latero-terminal anastomosis. An optimal residual tumour was achieved. Definitive histopathological examination confirmed cancer relapse. Postoperative course was regular, but on the sixth postoperative day, wound dehiscence was noted. After medications and complete resolution, the patient received 6 cycles of adjuvant chemotherapy with gemcitabine 1,000 mg/m2 on days 1 and 8 plus carboplatin (AUC 4) on day 1, every 3 weeks.

Post-chemotherapy follows-up were all negative until November 2013, when a PET-CT scan detected splenic lymphadenopathy and high metabolic uptake in the left upper abdominal quadrant, without further evidence of disease or peritoneal carcinosis. The CA 125 level was 207 U/mL. The patient still had good performance status (PS=1), without cardiovascular disease; therefore, we discussed treatment options with our patient, explaining the advantages/disadvantages of the procedure and the absence of certain clinical benefit. Nonetheless, the patient, after discussing with her family, decided in favour of surgery.

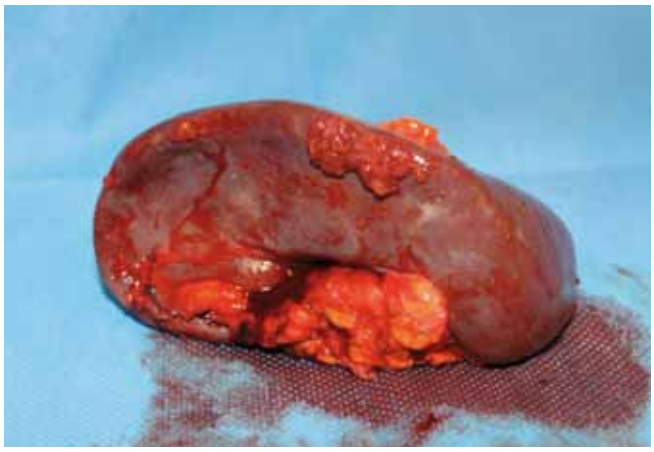

Fig. 1. Spleen with pathologic area.

In accordance with our centre management, the patient underwent a diagnostic laparoscopy and, after confirmation of single site of relapse, she received a laparotomic splenectomy (Figure 1), after extended accurate removal of adhesions between bowel and abdominal wall. Histological examination of the spleen confirmed recurrent neoplastic lesion. No macroscopic residual disease was present after surgery. Thus she was submitted to adjuvant chemotherapy with 6 cycles of pegylated liposomal doxorubicin 30 mg/m^2 plus trabectedin 1.1 mg/m^2, once a month. Further instrumental and clinical follows-up revealed no evidence of disease with a negative CA 125 value in May 2014. She is currently receiving 3-weekly trabectedin 1.1 mg/m^2; her next follow-up is due in July 2014.

Discussion

Despite optimal treatment with complete cytoreduction followed by adjuvant platinum-paclitaxel chemotherapy, 5-year survival for advanced ovarian cancer remains approximately 30% [1] and most patients succumb to their disease. Usually, the disease remains confined to the peritoneal cavity and lymph nodes, but recently some evidences regarding metastatic patterns of ovarian carcinoma have indicated the peritoneum (97–99%) as the most common site of recurrence of ovarian disease, followed by abdominal lymph nodes (74%), bowel (55%) and liver (48%) [4]. Unfortunately, even if primary ovarian cancer is generally successfully treated with cytoreductive surgery, the role of surgery in recurrent disease remains still controversial [2]. Our patient was optimally debulked at primary surgery and she was considered to be a fully platinum-sensitive recurrent patient, partially explaining her encouraging survivorship and, moreover, confirming the role of residual tumour as the strongest prognostic factor for prolonged survival [5].

In addition, she met the majority of predictive criteria for tumour resectability at recurrence such as good PS, optimal RT at previous surgery, absence of ascites according to the AGO score and pre-surgical serum CA 125 values, localization of disease, and treatment-free interval according to minor reports. She also always received chemotherapy after cytoreductive surgery and this would probably have improved her overall survival, consistent with data reported by Fotopoulou et al., who demonstrated that optimal cytoreduction plus chemotherapy in recurrent disease has a significant impact on overall survival [6].

Nonetheless, if optimal debulking is the strongest predictive factor of survival in patients with epithelial ovarian cancer, multiple surgeries should be performed only in highly specialized centres, by highly specialized gynaecological oncologists, in order to achieve optimal cytoreduction while minimizing morbidity rate. This is of crucial importance, but not adequately shared; in fact it should be underlined that still less than half of the patients suffering from advanced-stage ovarian cancer are operated on by gynaecological oncologists in European countries [7].

In conclusion, while waiting for the results of two randomized trials (DESKTOP III and GOG 213) assessing the role of chemotherapy and/or surgery in ROC, which should provide definitive evidence, we strongly believe that surgery might represent a useful adjunct to chemotherapy in the management of accurately selected patients affected by epithelial ovarian cancer if performed in referral centres by expert gynaecological oncologists.

Commentary

This is the case of a patient gaining benefit from multiple surgical interventions for recurrent ovarian cancer. In all the relapses, isolated areas of recurrence were present. The authors conclude that "multiple surgeries should be performed only in highly specialized centres, by highly specialized gynaecological oncologists, in order to achieve optimal cytoreduction while minimizing morbidity rate". I fully agree with this conclusion, but I would add that multiple surgeries should also be performed in "highly selected patients". I don't believe that the final message for the readers of our journal should be that multiple surgeries can always or can frequently be performed in the recurrence

setting. In this setting, surgery remains experimental (as it is for the first recurrence surgery), even if in general practice in some European countries (i.e. Germany, Italy) about 15-20% of patients receives surgical intervention at their first recurrence.
This patient was highly selected since in all the recurrences, the location of disease was isolated (single liver lesion, spleen, pararectal node). In particular, isolated liver metastasis and splenic disease have a very favourable outcome after surgery. This clinical situation occurs in about 2-3% of recurrences, since in most cases, multiple areas of recurrence are present with associated peritoneal carcinosis. I believe that this is the only case where a PET-CT scan is highly indicated in ovarian cancer, being more sensitive for the pre-surgical staging.
Another point of discussion is the non-aggressive behaviour of the disease in this patient. This is quite rare for a serous high-grade tumour. The classification of serous ovarian cancer has been recently changed with the added classification as high-grade or low-grade. The clinical behaviour in this case is more typical of a low-grade serous ovarian cancer, but of course this is not a general rule. Which were the histology features at time of recurrence? Were all the recurrences undifferentiated?
In conclusion, as stated by the authors, while we wait for the results of DESKTOP III and GOG 213, surgery may be proposed in selected patients affected by epithelial ovarian cancer.

Sandro Pignata

Division of Oncology, Department of Urology and Gynaecology
Istituto Nazionale Tumori IRCCS, "Fondazione G. Pascale", Naples, Italy
E-mail: s.pignata@istitutotumori.na.it

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