

Debulking Surgery for Clear Cell Carcinoma of the Ovary – A Case Report and Literature Review

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Abstract. Ovarian clear cell carcinoma represents a distinct histopathological subtype of epithelial ovarian cancer, with poor outcomes, especially in cases diagnosed in advanced stages of disease. However, even in these cases, it seems that the most effective treatment remains debulking surgery to no residual disease. We present the case of a 56-year-old patient diagnosed with a large pelvic mass invading the rectosigmoidal colon, and ileal loop who was successfully submitted to cytoreductive surgery to no residual disease. The histopathological studies demonstrated the presence of a well-differentiated clear cell ovarian carcinoma of the ovary. At 1-year follow-up there is no evidence of residual disease.

Ovarian clear cell carcinomas represents a rare condition comprising 5% of all ovarian carcinomas and up to 12% of epithelial ovarian malignancies (1, 2). Defined for the first time as a separate entity characterized by the presence of clear cells with solid or tubular pattern of growth in 1973 by the World Health Organization, this pathology is associated with a poor prognosis (3). Moreover, due to the paucity of cases, a standard therapeutic protocol has not been established; however, it seems that the best outcomes are provided by debulking surgery to no residual disease. This aspect is mainly explained through the fact that most often these tumors are platinum-resistant lesions; in consequence, complete cytoreductive surgery remains the option of choice in most cases (3-5). Most authors have demonstrated that ovarian clear cell carcinomas are diagnosed in early stages of the disease due to the fact that they usually present as large pelvic masses (2, 3, 6). Several studies have demonstrated

that ovarian clear cell carcinomas measure in the range of 3-30 cm, the most common sign at the time of diagnosis being the presence of a large pelvic mass (7, 8).

Case Report

We present the case of a 56-year-old patient who presented for diffuse pelvic pain, constipation and abdominal enlargement, symptoms that were observed in the previous 6 months. The clinical examination revealed the presence of a large pelvic mass, while computed tomography confirmed the presence of a tumor invading the rectosigmoidal loop and an ileal loop. The patient was submitted to surgery, the tumor being resected *en bloc* with total hysterectomy, bilateral adnexectomy, rectosigmoidectomy, segmental ileal resection, omentectomy, and pelvic and para-aortic lymph node dissection. The continuity of the digestive tract was re-established through an ileo-ileal end-to-end anastomosis and an end-to-end colo-rectal anastomosis (Figures 1-6). The postoperative course was uneventful, the patient being discharged on the seventh postoperative day. The histopathological studies confirmed the presence of a well-differentiated ovarian clear cell carcinoma. Postoperatively, the patient was submitted to six cycles of carboplatin and paclitaxel chemotherapy. At 1-year follow-up there is no sign of recurrent disease.

Discussion

Clear cell carcinomas of the ovary usually present as large pelvic masses compressing the surrounding organs. An *in vitro* model of ovarian cancer demonstrated the fact that in clear cell tumors, the malignant cells remain attached to the mesothelial layer for more than 18 hours, while cells of serous origin rapidly invade it, explaining the higher propensity of the serous subtype to induce distant metastases; this model also explains why clear cell carcinomas usually present as localized, large lesions (9). However, clear cell subtype tumors are associated with poor outcomes, with high

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rates of recurrence, even if they are initially diagnosed in early stages of disease, and low rates of long-term survival (4). This poor outcome can be related to the poor response to platinum-containing chemotherapy, the main mechanisms involved consisting of a low intracellular accumulation of the drug, increased intracellular detoxification and an increased capacity for DNA repair (10, 11).

Due to these aspects, attention was focused on the possible role of debulking surgery in order to increase long-term survival. Once the benefits of debulking surgery was widely demonstrated in patients diagnosed with advanced-stage and recurrent epithelial ovarian cancer, attention was focused on determining the effectiveness of cytoreduction on other histopathological subtypes which seem to have a poor response to other therapeutic protocols (12-19).

One of the largest studies on this topic was conducted by Takano *et al.* and published in 2006 (20). The study involved 254 patients diagnosed with clear cell ovarian carcinoma who were submitted to surgery between 1992 and 2002. All cases were submitted to total hysterectomy, bilateral adnexectomy, peritoneal washing, omentectomy, and pelvic and para-aortic lymph node dissection. At the time of initial diagnosis, The International Federation of Obstetrics and Gynecology (FIGO) classification revealed the presence of stage IA tumors in 33 cases, IB in three cases, IC in 89 cases, II in 33 cases, IIIA-B in five cases, IIIC in 75 cases and IV in 16 cases. The main adjuvant therapeutic regimens included cyclophosphamide, doxorubicin and cisplatin, or a combination of irinotecan and cisplatin, mitomycin or etoposide repeated at every 4 weeks. The therapeutic response was considered a complete one in cases in which all lesions disappeared for at least 4 weeks, and a partial one if the tumoral volume decreased by at least 50% for at least 4 weeks; in cases with absence of tumoral modifications during treatment, a diagnosis of stable disease was established, while cases presenting new lesions or an increase of up to 25% of the initial tumoral volume were categorized as progressive disease. The authors defined the time to progression as the interval between primary surgery and recurrence development or progression of the disease. After debulking surgery, 176 cases presented no visible lesions, 18 cases had residual disease of less than 1 cm, while the remaining 60 cases had a residual tumoral volume larger than 1 cm. Postoperatively, a good therapeutic response to the adjuvant treatment was reported in 16% of cases submitted to cyclophosphamide, doxorubicin and cisplatin; in 32% of cases submitted to paclitaxel and platinum; but none among patients submitted to irinotecan-based regimens. The long-term outcomes were significantly influenced by the initial stage at diagnosis and lymph node status, as well as by the completeness of cytoreduction. After a median follow-up period of 47.4 months, the median progression-free survival period was 39 months among

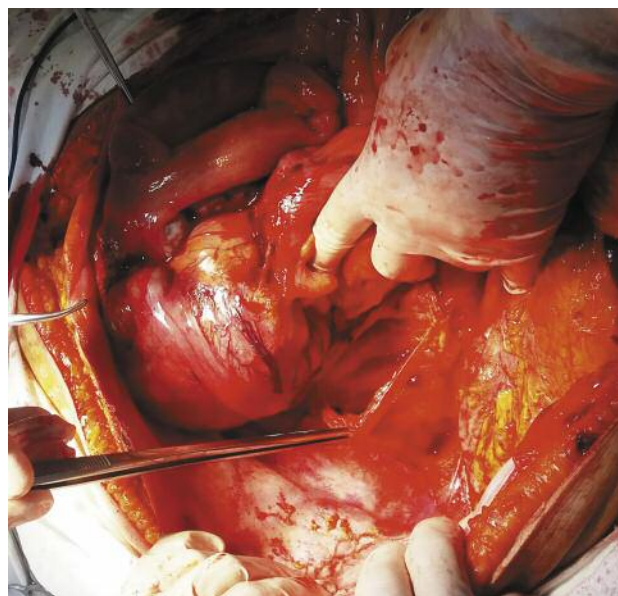


Figure 1. Large pelvic mass with rectosigmoidal and ileal invasion – dissection of the left ureter.

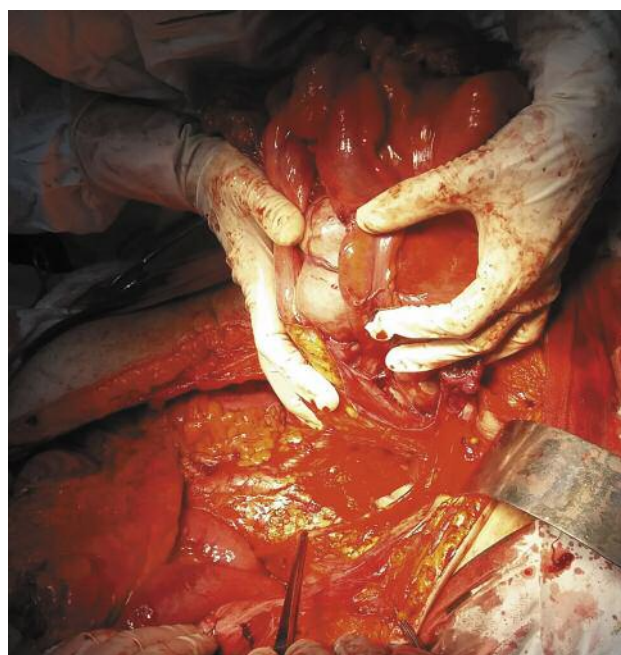


Figure 2. Mobilizing the tumor en bloc with rectosigmoidal resection and segmental enterectomy.

patients with no residual tumor, 7 months for cases with residual tumor of less than 1 cm and only 5 months in cases with larger residual tumoral volumes. However, when comparing the impact of adjuvant therapy on survival in

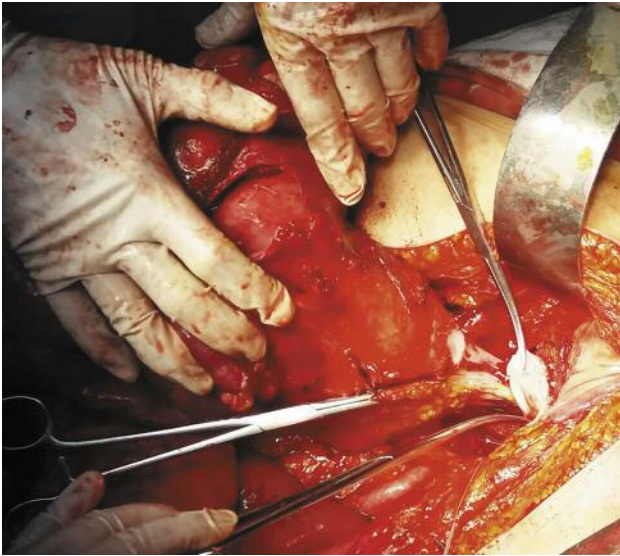


Figure 3. The pelvic mass was completely mobilized. The aspect after sectioning the vagina.



Figure 5. The aspect after completing the para-aortic lymph node dissection.

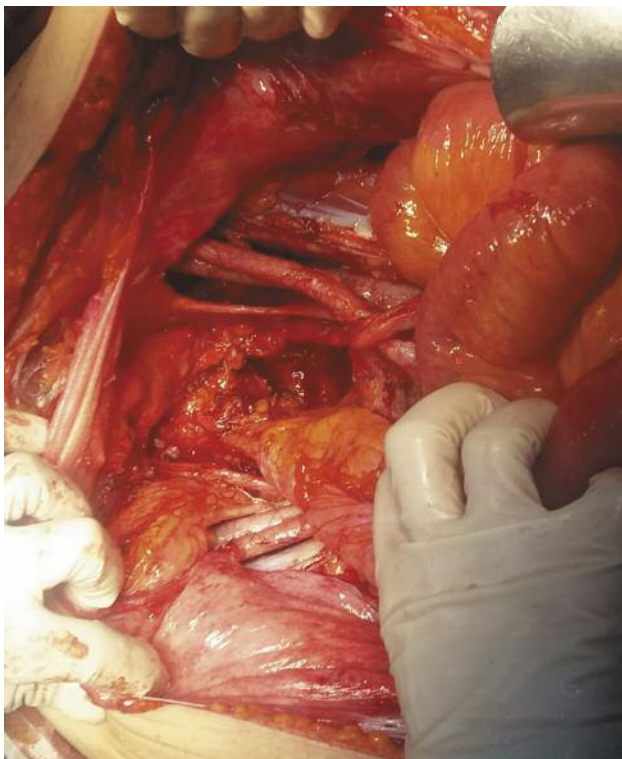


Figure 4. The final aspect after resection and pelvic lymph node dissection. The continuity of the digestive tract was re-established through an end-to-end colorectal anastomosis.



Figure 6. The specimen of total hysterectomy with bilateral adnexectomy, en bloc with rectosigmoidal resection and segmental enterectomy.

patients diagnosed with advanced stages (FIGO stage III-IV), no benefit was observed (20). These data suggest that although they are more aggressive malignancies, ovarian clear cell carcinomas can be successfully submitted to debulking surgery, the completeness of cytoreduction being one of the most important long-term prognostic factors.

A recent study published in Taiwan also demonstrates that patients with clear cell carcinomas have a poorer outcome when compared to those with serous carcinomas and that the

only therapeutic option which might improve their prognosis consists of debulking to no residual disease (21). The study included 169 patients with clear cell ovarian cancer and 351 patients with high-grade serous ovarian cancer who were submitted to debulking surgery followed by adjuvant chemotherapy with taxanes and platinum salts. The demographic analysis showed that patients with clear cell carcinomas were significantly younger when compared to those with serous tumors; moreover, they were usually diagnosed in earlier stages of the disease and were more often amenable to debulking to no residual disease. In regard to the long-term outcomes, the authors demonstrated that among patients diagnosed with early stages (FIGO stage I and II), the survival rates were similar for those with serous and those with clear cell tumors; however, these results were not found in those with advanced stages: patients diagnosed with FIGO stage III had a 5-year survival rate of 47.3% in those with high-grade serous carcinoma and 22.3% for those with clear cell carcinoma. The difference was even higher in patients with stage IV disease, none of the cases diagnosed with clear cell carcinoma being alive at 5-year follow-up, while the 5-year overall survival rate among patients diagnosed with high-grade serous tumors was 24.4%. Moreover, patients with advanced-stage clear cell tumors and submitted to taxane- and platinum-based chemotherapy had a significantly poorer outcome when compared to their serous counterparts, demonstrating the inefficacy of this chemotherapeutic regimen. In multivariate analysis, the overall survival was significantly influenced by the histopathological subtype (clear cell *vs.* serous subtype), FIGO stage at diagnostic (IV, III, II *vs.* I) and by the presence of residual tumoral volume larger than 1 cm (21). Moreover, the study demonstrated the necessity of further evaluating other chemotherapeutic agents in order to improve the long-term outcomes of cases with clear cell ovarian carcinoma (21).

A similar conclusion was also presented by the study conducted by Chan *et al.* involving 1,411 patients with clear cell carcinomas (22). The study included 26,671 patients diagnosed with ovarian cancer between 1988 and 2001, 5% of them presenting a clear cell subtype. Patients presenting with clear cell tumors were younger, more frequently diagnosed with an early stage of disease and more often submitted to surgery as first therapeutic intention. Due to the fact that patients with clear cell carcinoma were diagnosed more often with early-stage disease, they had a higher overall survival rate when compared to patients with other histopathological subtypes. However, after adjusting for FIGO stage, patients with clear cell carcinomas had poorer outcomes for all stages. On multivariate analysis, older age at diagnosis, advanced stage of disease, high tumor grade, lack of surgical treatment and clear cell histopathological subtype were associated with a significantly poorer outcome (22).

A promising agent in these cases seems to be gemcitabine, a multicenter Italian trial demonstrating a response rate of 66% for clear cell carcinomas, significantly higher when compared to other chemotherapeutic regimens (23).

Conclusion

Clear cell carcinoma of the ovary is a rare histopathological subtype which is most often associated with poor prognosis. Due to the fact that most often these are chemoresistant tumors, cytoreductive surgery to no residual disease remains the best therapeutic approach in order to obtain improved long-term survival. However, further studies are still needed in order to determine which chemotherapy regimen is the most efficient for consolidating the results of debulking surgery.

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