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Case Report
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Rapid Postoperative Growth of Ovarian Cancer- Two Case Reports

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Abstract

When feasible, advanced epithelial ovarian cancer is treated with primary cytoreductive surgery to resect all macroscopic disease followed by Platinum-based chemotherapy to achieve the best survival. It is suggested that chemotherapy be started as soon as possible following surgery, on the basis of theories as well as scientific and clinical evidence of residual microscopic disease progressing more rapidly after surgery than macroscopic disease and being more sensitive to chemotherapy. However, extensive clinical criteria are used to determine when do initiate chemotherapy and the clinical significance of a postoperative increase in the cancer cell kinetic growth rate and prognostic significance of the time to start chemotherapy for ovarian cancer is undetermined. Two cases are presented to address the issues of microscopic disease progression after surgery and additional issues in the investigation and management of ovarian cancer.

Keywords: Ovarian cancer; Postoperative microscopic progression; Time to start chemotherapy; TTC

Introduction

For advanced Epithelial Ovarian Cancer (EOC), Primary Cytoreductive Surgery (PriCRS) resulting in absence of macro scopic residual disease (R0), followed by platinum/taxanes -based chemotherapy with maintenance therapy using paclitaxel or bevacizumab, has produced the best Progression-Free Interval (PFI) and Overall Survival (OS) [1-5]. All macroscopic disease is removed prior to chemotherapy when possible, primarily on the basis of a better PFI and OS consistently reported for R0 patients relative to those with any macroscopic Residual Disease (RD), an inverse relationship between the size of residual metastatic implants up to 1.5 cm in diameter and OS, and theories of treating microscopic RD with chemotherapy being most efficacious [1,2,5-7]. Vascularity associated with microscopic disease is reported to increase chemotherapy levels, while microscopic disease is reported to have a more rapid kinetic growth rate with greater sensitivity to cytotoxic agents, and a reduced probability of baseline and acquired resistance is associated with a reduced population of cancer cells [6-8]. On the basis of theoretical and laboratory evidence of postoperative rapid microscopic progression and sensitivity of microscopic disease to chemotherapy, an early time to start chemotherapy TTC was recommended; although reports of the efficacy of an early TTC and the maximal delay possible without a prognostic compromise are inconsistent.

Two cases are presented to add insight to the clinical significance and theories of microscopic disease progression postoperatively, and additional postoperative issues in the investigation and management of ovarian cancer.

Case Reports

Case 1

A 38-year old black G3P3 female presented to her Gynecologist for follow-up with a several year history of symptomatic leiomyoma's, with increasing pelvic pain and menorrhagia. A pelvic mass diagnosed as gradually enlarging leiomyoma's by ultrasound and a CA-125 of 386 was obtained. She was taken to the operating room to perform a Total Abdominal Hysterectomy (TAH). A stage IIIC EOC with 600 milliliters of ascites was noted and the author was called for an intraoperative Gynecologic Oncology consultation. She was noted to have a 14-16 week leiomyomatous uterus with a complex 8-cm right adnexal mass densely adherent to the pelvic sidewall and confluent extension to the cul-de-sac. The omentum was replaced with metastatic disease; there were several millimeter sized implants on the right diaphragm peritoneum and about 50 1-5 millimeter implants on the mesentery. An extended TAH with radial bilateral salpingo oophorectomy, pelvic peritonectomy,

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Omentectomy (OME), ablation of diaphragm and peritoneal implants with an Argon Bean Coagulator (ABC), and complete Pelvic and Aortic Lymph Node Dissection (PALND) was completed with 5 grossly positive nodes removed, rendering her R0. The pathology report was consistent with benign leiomyoma and Grade 3 serous ovarian cancer; stage IIIC (FIGO 2014). She ambulated and tolerated clear and full liquids but then developed an ileus before anticipated in-house chemotherapy. She was treated conservatively. Fourteen days postoperatively it was necessary to operate due to an intestinal obstruction, which was managed by enterolysis and a small bowel resection with anastomosis. The obstruction was due to progressive confluent disease and 1-3 millimeter miliary implants were noted, and ablated with an ABC or aspirated with a CUSA, leaving her R0 with the possibility of sub-millimeter RD. Chemotherapy was completed 9 days postoperatively with Carboplatin and Paclitaxel without complication.

Case 2

A 59-year old white G4P4 female presented with a pelvic mass, pain, distension consistent with ascites and noted the symptoms to be increasing for three months. The CA-125 was 836 and a CT of the abdomen and pelvis with contrast showed a 12-14 cm mostly solid central pelvic mass, the omentum replaced by metastatic disease, with pelvic and aortic lymphadenopathy. She was taken to the operating room for a PriCRS and 1.2 liters of ascites was suctioned, the pelvic organs were encased with metastatic disease, the lesser omentum replaced by metastatic disease, the mesentery involved with 6 1-3 millimeter implants, and the retroperitoneal nodes were grossly involved with metastatic disease, consistent with stage IIIC (FIGO 2014) EOC. A frozen section was consistent with ovarian cancer. A modified poster exenteration with low rectal anastomosis, OME, ablation of implants with the ABC, and PALND were completed with 36/42 pelvic and aortic nodes being grossly positive/confluent and she was R0. Minimal adipose tissue or possible sub-millimeter grossly normal nodal tissue remained adherent to vasculature. The final pathology report was predominantly Grade 3 serous ovarian cancer, with mixed components of clear cell and endometroid. On postoperative day-17 there was a leakage from the low anastomosis and she was taken to the operating room to repair the leakage and perform an ileostomy. While performing enterolysis and mobilization of the bowel that was adherent to the retro peritoneum due to the extensive PALND a solitary 2.5 cm lymph node was noted adherent to the anterior lower inferior vena cava and removed where all grossly positive nodes were previously removed. The pathology report confirmed the node to be replaced with metastatic disease. Chemotherapy was completed 14-days postoperatively with Carboplatin and Paclitaxel without a complication, and the ileostomy was reversed 4.5 months later, at which time she was visibly and pathologically disease-free with multiple peritoneal and retro peritoneum biopsies.

Discussion

The current cases reports illustrate how microscopic disease can rapidly progress after surgery. Case 1, who was R0, had disease progress to 1-3 mm miliary disease and regional confluent disease 14-days postoperatively. Case 2, who was R0 and had all grossly enlarged positive retroperitoneal nodes removed, developed a 2.5 cm preaval positive node 17-days postoperatively, where only minimal adipose tissue or possible sub-millimeter nodal tissue remained. An enlarged node was not overlooked during PriCRS. In both cases, rapid progression before the TTC occurred.

The cancer cell Gompertzian kinetic growth rate is reported to increase after surgery by both basic science data and biologic factors associated with surgery; such as concomitant tumor resistance cessation, stress related steroid production, and intraoperative hypothermia [9-12]. However, the consistency and relative significance of a micro scopic metastatic disease growth increase and period of time over which the increase in growth for EOC patients continues is unknown, but of potential clinical significance.

It is usually not feasible to evaluate disease progression prior to chemotherapy for EOC, as a CA-125 will rise due to inflammation as exemplified by endometriosis, and Gynecologic Oncologists may initiate chemotherapy at the time of discharge or shortly thereafter [13]. A recent review of CT findings was completed for GOG-218 patients, who had PriCRS for EOC with operative outcomes of R0, <1 cm RD and >1 cm RD; and were randomized to receive Carboplatin and Paclitaxel with bevacizumab vs placebo to determine efficacy of bevacizumab, with the PFI as the primary endpoint [14,15]. Baseline CT scans were done a mean of 26 days postoperatively to confirm the largest size of metastatic disease as a baseline. The CT review study was limited to Stage III patients with <1 cm RD [15]. For 40% of the patients the maximal size of RD disease on CT scan was >1 cm. It was concluded that the finding was due to inaccuracy of the surgeons in interpreting the sizes of RD rather than disease progression, as the time from PriCRS to baseline CT scan, examined as a continuous and discordant variable (using the mean number of days to do the scan), and was not significant. However, the series did not determine radiologic changes in R0 patients, as R0 patients in GOG-218 were limited to Stage IV [14].

A controversial topic in the management of EOC is whether the TTC has an impact on the PFI and OS. The TTC following PriCRS is inconsistently reported to influence the PFI and OS [16-21]. An inverse relationship between the TTC and OS with a TTC range of 1-6 weeks was reported as secondary endpoint in the context of GOG Group study, comparing chemotherapy regimens in 1989 [16]. Subsequently, reports have been inconsistent, with a tendency for series using TTC as a categorical or dichotomous variable with an early TTC for R0 patients to be efficacious, while series using the TTC as a delayed dichotomous variable for all patients report the PFI and/or OS to be compromised or not impacted [17-23].

These case reports confirm that progression can occur immediately postoperatively, although the frequency amongst patients with advanced EOC rendered R0and duration of rapid progression are unknown. Given the findings of the current cases, reported theories and explanations for postoperative tumor growth, and efficacy of early TTC reported selectively for EOC and established for breast and colon cancer; it would be informative to evaluate baseline CT scans with contrast specifically for R0 patients who are on Phase III trials for progression of microscopic disease, and evaluate efficacy of early TTC categorically and dichotomously prospectively for R0 patients [6-12,19]. Studies are necessary to determine the consistency and duration of immediate progression as well as predictability using biomarkers.

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