Selected Summary

Secondary Surgical Cytoreduction for Advanced Ovarian Carcinoma

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SUMMARY

This randomized study was conducted by Gynecologic Oncology Group to evaluate the role of secondary cytoreductive surgery in advanced epithelial ovarian carcinoma (EOC). Between June, 1994 to Jan, 2001, 550 patients of stage III and IV epithelial ovarian cancer with residual intraperitoneal tumour more than 1cm after primary debulking surgery were enrolled in the study. Postoperatively patients received 3 cycles of chemotherapy using cisplatin and paclitaxel. Following this, 448 patients were randomized either to secondary cytoreductive surgery followed by 3 cycles of chemotherapy (n=226) or 3 cycles of chemotherapy alone (n=222). 102 of 550 patients did not undergo randomization either due to disease progression (n=26), died (n=16), medical contraindications (n=20), declined (n=18), presence of extra peritoneal tumour >1cm(n=16), excessive delay before randomization (n=4) or other reasons (n=2). After randomization, 24 patients were found ineligible (10 in surgery-chemotherapy arm, and 16 in the chemotherapy alone arm either due to inappropriate primary cancer (n=10), inappropriate stage (n=7), detection of second primary cancer (n=3), or incomplete pre-study work up (n=4). Thus, out of 424 randomized eligible patients, 216 were assigned to cytoreductive surgery followed by chemotherapy arm and 208 to chemotherapy alone. During secondary surgery, maximal effort was made to resect all gross tumours and surgery was performed within 6 weeks of completion of 3rd cycle of chemotherapy. Patients were reassessed after 6 to 9 weeks of completing protocol with history, physical examination, routine haematological and biochemical tests, CT scan and CA125. Among 216 patients in the surgery-chemotherapy group, 201 patients underwent debulking surgery, 15 had no debulking surgery. At a median follow up of 46.6 months, 151 patients had died, 47 were alive with recurrent disease and 18 were alive without recurrence. In the chemotherapy alone arm, among 208 patients, 145 had died, 35 were alive with recurrent disease and 28 were alive without recurrence at a median follow up of 47.6 months. Thus, a total of 296 patients have died of which 151 belonged to secondary surgery arm and 145 to chemotherapy arm (p=0.34). The median time to progression or death was 10.5 months in secondary surgery plus chemotherapy arm and 10.7 months in chemotherapy alone arm. The risk of progression to death in secondary surgery arm was 7% higher than in chemotherapy alone arm (HR-1.07; 95%CI-0.869 to1.31; p=0.54). The median overall survival was 33.9 months and 33.7months in secondary surgery and in chemotherapy arm, respectively (HR-0.989; 95%CI-0.786 to 1.24; p=0.92) indicating that secondary cytoreductive surgery did not appreciably increase overall survival after initial maximal surgical cytoreduction. Comparison of adverse effects of chemotherapy in 2 arms revealed, higher risk of peripheral neuropathy of =>grade 2 in chemotherapy alone arm (16% vs. 26%, p=0.01) and higher gastrointestinal toxicity in secondary surgery arm (7% vs. 4%).

COMMENTS

Epithelial ovarian cancer (EOC) is the most common gynaecological malignancy. About 70-75% of patients present with advance disease (stage III-IV). Initial debulking surgery followed by paclitaxel and platinum based chemotherapy is currently, the standard treatment approach.[1] Survival is directly proportional to the amount of residual tumour following primary debulking surgery;[2-4] patients with optimal cytoreduction (residual tumour <1cm) have superior survival compared to those with sub-optimal cytoreduction (residual tumour>1cm). However, optimal debulking (<1cm) rate varies from 20% to 40% in most studies, only few studies have reported a higher debulking rate[5]. In an effort to achieve optimum cytoreduction, many investigators have attempted secondary cytoreduction following 3-4 cycles of platinum based chemotherapy among patients in whom initial cytoreduction was sub-optimal. Van der Burg et al for the European Organization for Research and Treatment of Cancer (EORTC) have earlier reported the results of a similar, randomized study. There was significant increase in median progression free survival (18 vs. 13 months, p<. 013) and overall survival (26 vs. 20,p<. 012) among patients who underwent suboptimal debulking followed by secondary surgery after three cycles of cisplatin and cyclophosphamide.[6]

Present study was designed on the lines of EORTC study[7], but results of two studies are not in complement with each other. A close look reveals certain differences between two trials e.g. stage IV disease (6% vs. 22% in the EORTC study), papillary serous carcinoma (76% vs. 57%), and presence of residual tumour of >5cm in 44% vs. 72% in the EORTC study. It is thus possible that benefit of secondary debulking surgery in the EORTC study may have been due to presence of high tumour volume after primary surgery. More importantly, EORTC study used a combination of cisplatin and cyclophosphamide compared to paclitaxel and cisplatin in the present study. The superiority of paclitaxel & platinum over cisplatin and cyclophosphamide combination have been shown in patients with advanced EOC, both in the setting of primary optimal and sub-optimal debulking surgery.[8-9] Whether use of paclitaxel and cisplatin in the present GOG study may have negated the survival benefit of secondary debulking surgery remains speculative! Information on pathological responses in secondary surgery arm was not available; this could have helped to know the role of chemotherapy.

Thus, for a newly diagnosed patient with advanced EOC initial aggressive surgery (with aim for optimal debulking) should be followed by paclitaxel and platinum based chemotherapy. Findings of present study do not support use of routine secondary debulking. Recently, the role of neoadjuvant (pre-operative) chemotherapy is being investigated in patients with advanced EOC; two such randomized trials (neoadjuvant chemotherapy followed by interval debulking surgery followed by 3 cycles of chemotherapy vs. upfront primary debulking surgery followed by chemotherapy) are under progress; one by EORTC group and another at our institute.[10]

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