Advanced ovarian yolk sac tumor: Upfront surgery or neoadjuvant chemotherapy followed by interval debulking?

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Abstract

OBJECTIVE To compare the surgery and survival outcomes between neoadjuvant chemotherapy and primary debulking surgery in patients with advanced ovarian yolk sac tumor (OYST). METHODS In this retrospective cohort analysis, patients with stage III to IV OYST or mixed germ cell tumor containing yolk sac tumor elements and underwent surgery at Peking Union Medical College Hospital between 2010 and 2021 were identified. Nineteen cases were treated with neoadjuvant chemotherapy (NACT) followed by interval surgery. Twenty-one cases were treated with primary debulking surgery (PDS). Data on patient characteristics, treatment and survival were analyzed between the two groups.

RESULTS After NACT, the physical status of patients were significantly improved and tumor burden were decreased, with an optimal cytoreduction rate of 100% at interval surgery. No statistical difference was found in 3-year disease-free survival (DFS) and overall survival (OS) between NACT group and PDS group (Log Rank p=0.461 and 0.935). Patients suffered less blood loss, lower rate of transfusion, shorter operation time, and less severe peri-operative complications at the debulking surgery after NACT, as compared to patients who underwent PDS. CONCLUSION For patients with advanced stage OYST, NACT followed by interval surgery might be an alternative option, especially for those who could not tolerate the primary debulking surgery because of high tumor burden and vulnerable status.

Introduction

Malignant ovarian germ cell tumors (MOGCTs) are rare, accounting for only 1% of all ovarian tumors with an average age of onset < 25 years[1, 2]. Yolk sac tumor (YST) accounts for about 20% of ovarian malignant germ cell tumor (GCT), and is the second most common subtype[3]. Fertility-sparing surgery followed by 3-4 cycles BEP chemotherapy is the standard treatment approach for eligible patients and most of them can reach complete remission (CR)[1].

Due to the malignant behavior including rapid growth, tumor eruption, intra-abdominal bleeding and peritoneal metastasis of YST, approximately 30-40% patients are presented with FIGO stage III to IV at initial diagnosis[4]. The high tumor burden and vulnerable status of the patients have added the difficulties to the primary cytoreductive surgery, as well as increased peri-operative comorbidities[5]. To minimize the surgical complications, the radicality of the primary debulking surgery may be compromised, resulting in sub-optimal tumor reduction and residue tumor[6]. Primary cytoreductive surgery in stage III/IV YST patients remains a challenge nowadays.

Neoadjuvant chemotherapy (NACT) has been successfully used in epithelial ovarian cancer patients with a high tumor burden at presentation or poor performance status[7]. Its feasibility has been explored in advanced ovarian YSTs and the previous results were promising. However, the rarity of this tumor has limited the evidence-based studies such as randomized controlled trials. The oncologic safety of NACT and interval debulking surgery in advanced YST patients remains unclear. The objective, feasible clinical
selection criteria for surgical intervention are lacking. Thus, we reviewed the 10 years’ experience of our institution as the largest referral center of gynecologic germ cell tumor in China. We aim to evaluate the oncologic safety and feasibility of difference treatment sequence, in order to provide optimize the therapeutic approach in patients with advanced YSTs.

Methods

The Peking Union Medical College Hospital (PUMCH) Institution Review Board approved this retrospective cohort study (IRB number: I-23PJ272). The medical records of patients who were diagnosed with stage III to IV ovarian yolk sac tumor (OYST) or mixed germ cell tumor containing yolk sac tumor elements and underwent surgery at PUMCH between January, 2010 to December, 2021 were reviewed. The following information was collected for analysis: the age of diagnosis, physical status, clinical presentation, tumor markers, tumor size, ascites volume, surgical details, chemotherapy details, stage, pathological diagnosis, follow-up, relapse details and outcomes. Patients were staged according to the FIGO classification of ovarian tumors. Tumor tissue was evaluated by central pathology review to confirm diagnosis.

Surgery

Patients underwent debulking surgery or fertility sparing surgery. In patients without fertility preservation requirement, total abdominal hysterectomy and bilateral salpingo- oophorectomy were performed. In patients who desired fertility preservation, the uterus and at least one ovary were preserved. Patients received either unilateral salpingo-oophorectomy (USO) or cystectomy. Regardless of preserving fertility or not, omentectomy, resection of macroscopic lesions, dissection or sampling of the retroperitoneal lymph nodes were performed. Optimal cytoreductive surgery was defined as the residual disease ≤ 1 cm. R0 was defined as the absence of macroscopic residual lesions. R1 was defined as the largest residual tumor was ≤ 1 cm.

Chemotherapy

Neoadjuvant chemotherapy was given to patients with ASA 2 and above, high tumor burden at upper abdomen on imaging study who were less likely to achieve optimal primary cytoreduction. The inclusion criteria of NACT group were listed as follows: 1) extensive metastasis of intra-abdominal and pelvic organ, especially upper abdomen; 2) large tumors peri vital organs including liver, kidney, spleen, which were difficult to be resected during initial surgery; 3) massive malignant ascites and carcinomatosis; 4) patients unable to tolerate surgery because of severe underlying illnesses or poor physical performance status. Cisplatin, bleomycin and etoposide (BEP) regimen was preferred regimen for NACT. Patients received for 1-3 cycles before surgery, depending on their response and tolerance to chemotherapy.

After surgery, cisplatin, bleomycin and etoposide (BEP) were given to patients within 14 days. The BEP regimens were cisplatin (100mg/m², divided in d1-3), etoposide (100mg/m², d1-3) every 3 weeks and bleomycin (20IU/ m², maximum 30IU, d2) every week. The PEV regimens were given when patients have reached a lifetime dose of bleomycin or intolerant to bleomycin due to impaired pulmonary function. The PEV regimens were cisplatin (100mg/m², divided in d1-3), etoposide (100mg/m², d1-3) every 3 weeks and vincristine (1-1.5mg/m², d1-2) every 3 weeks. After serum AFP were normalized, another 2-3 cycles of chemotherapy were given for consolidation.

Treatment response

Treatment response was defined according to Response Evaluation Criteria in Solid Tumor (RECIST 1.1)⁸. Complete remission (CR) was defined as the disappearance of all clinical, radiographic, and biochemical evidence of disease. Partial Response (PR) was defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. Progressive Disease (PD) was defined as at least a 20% increase in the sum of diameters of target lesions. Stable Disease (SD) was defined neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

Follow-up
After treatment completion, patients were followed every 2 months for the 1-2 years, 4-6 months for the third year, 6 months for 4-5 years, then annually thereafter[9]. Physical examination, serum tumor markers and radiographic imaging were included in the follow-up. Recurrences were defined as abnormal elevated serum tumor markers or newly-measurable disease on radiographic imaging evaluation. Refractory diseases were documented SD and PD as persistently elevated tumor markers with definitive residual diseases. Disease-free survival (DFS) was defined as the time from diagnosis to disease recurrence (months). Overall survival (OS) was defined as the time from initial diagnosis to death from all causes (months). Data on patients with no evidence of disease recurrence or death were censored at the date of last follow-up.

**Statistics**

Statistical analysis was carried out using SPSS Statistical Package version 26 for MAC (IBM Company, Armonk, NY, USA). Descriptive analyses were conducted using the Chi-squared test or Fisher exact test for categorical variables. Differences in variables with a continuous distribution across categories were assessed using the Mann–Whitney U test. Disease-free survival and Overall survival curves were calculated using the Kaplan–Meier method and compared using the log-rank test. Statistical difference was considered significant when p value was <0.05.

**Results**

**Patient characteristics**

From 2010 to 2021, 40 patients with stage III to IV OYST or mixed germ cell tumor containing yolk sac tumor elements and underwent surgery at PUMCH were identified from the PUMCH Rare Cancer Registry. The median age at diagnosis was 23.5 years old (range 5-73). The major clinical manifestations were abdominal bulging with accidently finding of abdominopelvic mass (35%), abdominal pain (45%) and distension (25%). 28 patients were diagnosed with FIGO stage III (70%) tumor and 12 with IV (30%). 19 (47.5%) of them received neoadjuvant chemotherapy followed by debulking surgery or fertility sparing surgery, others underwent primary surgery directly at initial diagnosis. Table 1 summarizes patient demographics and tumor characteristics.

In the NACT group, the median age at diagnosis was 24 years old (range 5-45). There were 13 patients with FIGO stage III (68.42%) tumor and 6 with IV (31.58%). 16 of them (84.21%) were diagnosed with pure YST while other three (15.79%) were diagnosed with mixed GCT. The median diameter of the tumor was 11.4cm (range 5-22.8cm). In the PDS group, patients’ age, tumor stage, histology and tumor size were similar to the NACT group. The median serum AFP level was significantly higher in the NACT than that in the PDS group (51,140.00 vs. 15,783.00 ng/ml, p = 0.039). In the NACT group, 13 patients’ AFP level were higher than 30,000.00 ng/ml, while six in the PDS group (p = 0.012). There were more patients in the NACT group who presented with massive ascites than that in the PDS group, but the difference was not significant (94.74% vs. 71.43%, p = 0.095).

**Results of NACT**

In the NACT group, 7 patients experienced one cycle of chemotherapy, 10 patients experienced 2 cycles and only 2 patients received 3 cycles. The mean number of NACT cycles was 1.74±0.65. The tumor responses were evaluated according to the CT imaging before and after NACT. The median diameter of tumor was 11.40cm before NACT while 8.00cm after NACT (p = 0.006). The serum AFP level was significantly declined after NACT (51,140.00 vs. 1141.00ng/ml, p < 0.001). Among the 18 patients with massive ascites at initial diagnosis, four patients had completely eliminate ascites and others had decreased ascites volume after NACT. Table 2 compared the tumor status before and after NACT. Tumor status, surgery and adjuvant chemotherapy were also analyzed in patients with different cycles of NACT (Table 3).

**Results of surgery**

Totally, 80% patients underwent fertility-sparing surgery. The rate of optimal cytoreduction was 100% in the NACT group, including 12 patients with no visible residual disease (R0) and 7 with residual disease [?]1cm (R1) after surgery. In PDS group, 14 patients achieved R0 and four achieved R1. There were 3 patients with residual tumor [?]2cm, mainly located in peri rectum, upper abdomen and
abdominal para-aortic lymph nodes. There was no significant difference of the optimal cytoreduction rate between two groups (100% vs. 85.71%, \( p = 0.233 \)). Peri-operative and post-operative parameters between the NACT and PDS groups were compared in Table 4. The mean amount of surgical blood loss in the NACT group was significant less than in the PDS group (328.42 vs. 1285.71 ml, \( p = 0.029 \)). The blood transfusion rate of two groups was similar, however, the PDS group had significantly more transfusion volume of both red blood cells (RBC) and plasma (\( p = 0.011 \) and 0.014). The operation time was less in NACT group, but the differences were not significant. Compared with the PDS group, the incidence rate of surgical complications was lower in NACT group (\( p = 0.032 \)). In NACT group, only one patient had abdominal infection, two patients had moderate anemia and received blood transfusion. In PDS group, six patients received blood transfusion due to moderate to severe anemia or hemorrhagic shock, one patient had abdominal infection, one patient had fever with no confirm evidence of infection, one had incomplete intestinal obstruction, and one 34-year-old woman had abdominal compartment syndrome and died in 7 days after surgery. The rate of transfer to intensive care unit (ICU), ICU length of stay and hospital of stay after surgery were similar between the two groups.

Results of chemotherapy

Table 5 demonstrated the characteristics related to chemotherapy of the NACT and PDS groups. After a median of 1.88\( \pm \)0.99 and 2.53\( \pm \)1.07 cycles, post-surgical serum AFP level fall into normal range in NACT and PDS groups, respectively (\( p = 0.093 \)). The total number of chemotherapy cycles was 6.84\( \pm \)2.24 in the NACT group and 4.95\( \pm \)2.1 in the PDS group (\( p = 0.003 \)). The time to initiate post-operative chemotherapy was longer in the PDS group of 8.8 days, as compared to the NACT group of 5.3 days (\( p = 0.024 \)). The rate of developing pulmonary dysfunction and achieving lifetime dose of bleomycin were similar between the two groups.

Results of follow-up

The median follow-up time was 38 months (range 15-147) in NACT group and 52 months (range 4-107) in PDS group. The recurrence or progression rate were 10.53% and 20%, respectively. In NACT group, one patient had tumor recurrence at peritoneum 10 months after chemotherapy and died 5 months after recurrence, one patient experienced disease progression during chemotherapy and received radiofrequency ablation of liver lesions followed by second surgery was died 2 months after salvage chemotherapy. In PDS group, one patient died due to severe surgical complication of compartment syndrome 7 days after surgery, and three patients had disease recurrence or progression. One patient had uncontrolled disease progression and died 6 months after surgery. The other two patients had recurrent disease at liver, presacral and pelvic 4 months and 36 months after finishing chemotherapy. Both of them received secondary cytoreductive surgery followed by chemotherapy and were remain disease free till the last follow-up. Table 6 showed the details of patients with disease recurrence or progression. There was no statistical difference of disease-free survival (DFS) and overall survival (OS) between NACT group and PDS group (follow-up time censored at 72 months, Log Rank \( p = 0.461 \) and 0.935) (Figure 1 and 2).

Discussion

In the present study, we observed a better surgical performance in OYST patients with advanced disease who received NACT and interval debulking surgery (IDS), as compared to patients who underwent PDS. There were less blood loss, transfusion rate, severe peri-operative complications and shorter operation time in interval debulking surgery than in primary surgery. The survival outcomes of patients who received NACT followed by debulking were similar to those who received PDS.

Advanced-stage OYSTs were rarely presented at the initial diagnosis. The principle of management advanced-stage OYST has been extrapolated from experience with epithelial ovarian cancer\(^1\). Primary cytoreductive surgery aiming to achieve complete resection of tumor is recommended, since residual tumor has been proved to be a prognostic risk factor by several studies\(^10\-13\). Removing as much gross tumor as possible is essential to disease cure\(^14, 15\). However, it is difficult to achieve optimal cytoreduction and avoid severe peri-operative complications in advanced OYST patients due to high tumor burden. Talukbar
et al.[16] reported that only 9 of 43 (20.9%) advanced MOGCT patients had none or [?]2cm residual tumor after primary debulking surgery. Optimal cytoreduction rate of PDS in advanced OYST patients ranges 50% to 84% in previous studies[17, 18]. In our study, 18 of 21 (85.71%) patients who underwent primary cytoreductive surgery had achieved optimal goal of residual tumor [?]1cm. However, the peri-operative complications were high among patients undergoing PDS, including fever, abdominal infection, intestinal obstruction, severe anemia and hemorrhagic shock. One patient died from multiple organ failure due to compartment syndrome after prolonged, devastating surgery (4.76%, 1/21). The high comorbidity rate of PDS and excellent chemosensitivity of OYST have led to an altered surgical approach of NACT with interval debulking surgery.

There was no consensus on NACT and interval surgery approaches for advanced-stage OYST. The tumor response to pre-operative BEP chemotherapy is favorable given the high chemosensitivity of OYST. A study[19] focusing on BEP chemotherapy in the treatment of extensively advanced YST showed that clinical partial tumor regression was achieved in 17 of 18 patients and their ECOG scores were all 1 or less at the completion of NACT. One patient with clinical stable disease received laparotomy after one cycle of NACT, and her radiologically unaltered tumors were revealed to be composed mainly of necrotic tissues or fibrotic streaks on her final pathological examination[19]. Similar results were observed in our NACT group. The serum AFP level of most patients decreased by 10 times each course of BEP chemotherapy. In the meantime, the tumor shrank and ascites decreased or disappeared after NACT. One patient’s AFP level decreased to 102 ng/ml after first cycle of NACT but elevated to 452 ng/ml after second cycle of BEP. One patient’s tumor enlarged from 10.6 cm to 15 cm after one cycle of NACT. Both of them were refractory to chemotherapy, and experienced disease progression after cytoreductive surgery and standardized BEP chemotherapy. The response to NACT may be a prognostic factor for advanced OYST.

NACT obtains surgical opportunities for advanced patients and reduce surgical risks and complications. Previous study from our institution[17] showed that NACT followed by IDS was associated with better optimal rate and less peri-operative complications, but the difference was not significant compared with PDS. Another study[18] reported that the optimal cytoreduction rate was improved in patients received NACT compared with that in patients received initial surgery (83.3% vs. 50.0%). Our study has similar results. Better surgical outcomes were observed in NACT group. 100% patients underwent optimal cytoreductive surgery (R0 or R1) while 85.71% of patients in PDS group with no significant difference, likely due to the limited population. Compared with the PDS group, the incidence rate of surgical complications was significantly lower in NACT group, and most of the peri-operative complications are mild in NACT group.

The safety of NACT was well evaluated in our study. For these young female patients, chemotherapy side effects and quality of life are important factors to consider during treatment. Pulmonary toxicity is one of the most frequent complications in patients receiving bleomycin-containing chemotherapy regimen[20, 21]. Our study showed that total cycles of chemotherapy in NACT group were slightly more than those in PDS group, which may be related to the presence of the progressive cases in NACT group. However, the incidence of pulmonary function decline was similar in two groups, which means patients were well tolerated by chemotherapy in NACT group. In this study, days from surgery to post-operative chemotherapy was shorter in NACT group comparing to PDS group. YST grows rapidly and delayed adjuvant chemotherapy may compromise the treatment effect in advanced-stage OYST. Studies of epithelial ovarian cancer suggested, patients who underwent NACT and IDS experience enhanced post-operative recovery and are more tolerable to early adjuvant chemotherapy soon after surgery[22]. In our study, the recurrence or progression rate was lower in NACT group, we did not observe survival differences in DFS and OS between patients undergoing NACT with IDS and those received PDS.

Our study showed that the serum level of AFP at initial diagnosis in NACT group was significantly higher than PDS group, but the tumor size was similar in two groups. Compared to PDS group, more upper abdominal lesion, carcinomatosis and omentum cake were detected during surgery in NACT group. In PDS group, 3 patients had residual disease >2cm after debulking surgery. Macroscopic residual lesions were mainly located between the liver and diaphragm or around the liver in the upper abdominal cavity, and on the
surface of rectum and intestine. One patient also had enlarged para-aortic lymph nodes difficult to remove. For patients with high tumor burden and extensive metastasis, tumor size is not the key factor to determining the difficulty and risk of surgery, the main difficulty of initial surgery is to remove upper abdominal lesions and carcinomatosis. NACT may be appropriate for patients with extensive tumor implantation and upper abdominal disease thus IDS can achieve an optimal resection with acceptable surgical comorbidities.

Appropriate number of NACT cycles varies in previous studies. Zhang et al.[19] suggested that 1 to 2 cycles of BEP regimen would be sufficient to render a patient with extensively advanced YST operable. Lu et al.[17] recommended that the optimal number of NACT cycles was no more than three since three cycles were enough for the patients to achieve the optimal effects of NACT and the volume of remaining tumor and necrosis tissue would no longer shrink with NACT more than three cycles. 4 cycles and even 6 cycles were also been reported in previous cases[23]. In our study, the serum AFP level was significant lower after 2 or 3 cycles of NACT. More NACT cycles seems to increase the rate of achieving R0 with surgery, but there was no significant difference. In reviewing the information of our center, we considered two cycles of NACT was appropriate to reach optimal general condition with lower risks. Both of the two patients who received 3 cycles of NACT switched regimen during postoperative adjuvant chemotherapy due to decline of pulmonary function or reach lifetime dose of bleomycin. These problems were also observed in patients received one or two NACT cycles. In those patients who have likely to develop bleomycin induced lung toxicity, whether omit bleomycin in NACT and keep it for post-operative chemotherapy needs further evaluation.

The strength of this study is that a single institution was able to collect the number of cases reported of a rare disease, which allowed for analysis of detailed information and long-term follow-up. However, there are several limitations to our study. It is a retrospective study with unavoidable, inherent biases. The sample size was small because of the low incidence of this disease.

In conclusion, for patients with advanced-stage OYST, NACT followed by interval debulking surgery may be an alternative option, especially for those who could not tolerate the primary debulking surgery due to high tumor burden or frail physical status. No differences in survival outcomes were identified between patients who underwent NACT with IDS and those who received PDS.

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Declaration of competing interest
The authors have declared no conflict of interest.

Reference


**Legends of figures and tables**

Table 1. Characteristics of NACT vs PDS group
Notes: AFP, Alpha-fetoprotein

Table 2. Characteristics of patients before NACT and after NACT

Table 3. Comparison in patients who received different NACT cycles
Notes: *Significant difference was observed between group 1 and 2, 1 and 3, but group 2 and 3 had no statistical difference.

Table 4. Peri-operative and post-operative parameters between the NACT and PDS groups.
Notes: CRS, cytoreductive surgery; ICU, intensive care unit; *Surgical complications were classified according to the Clavien-Dindo Classification

Table 5. Chemotherapy between the NACT and PDS groups.

Table 6. Details of patients with disease recurrence or progression
Notes: BEP, cisplatin, etoposide and bleomycin; PVB, cisplatin, vincristine and bleomycin; PEV, cisplatin, etoposide and vincristine; PEI, cisplatin, etoposide and ifosfamide; TIP, paclitaxel, ifosfamide and cisplatin; DIP, doxorubicin, ifosfamide and cisplatin; EMA/CO, etoposide, methotrexate, Dactinomycin and cyclophosphamide, vincristine; EMA/EP, etoposide, methotrexate, Dactinomycin and etoposide,cisplatin; ACS, abdominal compartment syndrome; NED, no evidence of disease.

Figure 1. DFS of patients of NACT group vs PDS group

Figure 2. OS of patients of NACT group vs PDS group

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