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Feasibility Evaluation for Selection of Neoadjuvant Chemotherapy before Cytoreduction of Advanced Ovarian Carcinoma

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ABSTRACT Ovarian carcinoma is one of three gynecological neoplasms. It typically develops as an insidious disease, with few warning signs or symptoms, because the ovary is situated at a deep part of the pelvic cavity. Advanced ovarian carcinoma (AOC) is highly malignant, so the prognosis of the patients is poor. Initial debulking surgery, followed by chemotherapy, is currently the main therapeutic choice for AOC. During operations, efforts should be made to excise the tumor and minimize the residual lesion, so as to achieve the optimal cytoreduction and improve the prognosis. As a feasible therapeutic regimen for the patients with primary unresectable AOC, neoadjuvant chemotherapy can improve the surgical condition and can increase the optimality of cytoreduction. It is important therefore to evaluate the feasibility of surgical treatment and make a proper selection of the primary treatment plan and neoadjuvant chemotherapy, so as to enhance the optimality of surgery and to avoid unnecessary exploratory laparotomy. At present, methods of feasibility evaluation for optimal cytoreduction of AOC are as follows: 1) radiography, i.e., CT, PET and MRI scanning; 2) CA-125 value; 3) laparoscopic exploration; 4) other tumor markers such as p53. However, any method lacks the ability to cover all the predicting factors influencing the outcome of cytoreduction, and to evaluate the surgery across the board. Searching for new methods and combining two or more procedures to evaluate the feasibility of cytoreduction may increase the optimality, reduce the residual focus, prolong survival time and improve the prognosis. In this study, recent advances in evaluation of the feasibility for optimal cytoreduction and the selection of neoadjuvant chemotherapeutic regimens were reviewed.

KEYWORDS: advanced ovarian carcinoma, optimal cytoreduction, neoadjuvant chemotherapy.

In 2002, Bristow et al.[1] concluded from a meta analysis that, following cytoreduction of advanced ovarian carcinoma (AOC), there was a correlation and statistical significance between the residual lesion size and median survival rate of the patients. Median survivals increased by 5.5% with a 10.0% addition to the cytoreduction rate. Efforts to reduce the surgical residue have become the goal of surgical treatment for AOC. Multiple studies have shown that neoadjuvant chemotherapy can improve the surgical condition for AOC patients that fail to receive a surgical operation, with enhancement of surgical optimality, reduction of postoperative recurrence and improvement of prognosis etc.[2,3] Neoadjuvant chemotherapy, combined with cytoreduction, has become a selectable regimen for AOC treatment. In this article we have reviewed advances in the preoperative evaluation of AOC cytoreduction. We have considered methods to avoid surgical open and close processes and the progression of disease and drug assistance caused

by unnecessary preliminary chemotherapy. We have examined preoperative appraisement of optimal cytoreduction (OC), in order to enhance the optimality of cytoreduction after the primary operation and neoadjuvant chemotherapy.

Evalution of images

Computed tomography (CT)

CT scans are a common feasible method to evaluate OC for AOC, as it provides an imageological basis for evaluating the AOC treatment plan. After a retrospective analysis of preoperative CT findings from 41 patients with AOC who received surgery as preferred treatment method, Bristow et al.[4] established a predicting score system for evaluating the feasibility of OC (the residual focus was less than 1 cm). This was developed by screening the imageological parameters related to probable surgical outcomes and comparing 25 clinical indices and parameters with the surgical outcomes. The scoring for 9 of the 14 indices in the gynecologic oncology group (GOG) scoring system was 2 (exactness of each index was over 60.0%), including the presence of a thickened peritoneum, and peritoneal seeding. Mesenteric and great omentum foci were all $\geq$ 2 cm, omental lesions were extended to the stomach, spleen or lesser sac of the peritoneal cavity, with a great quantity of abdominal edema. The focus at the abdominal aortic lymph node of the superior renal artery was $\geq$ 1 cm, and the GOG scoring was $\geq$ 2. The scoring for 5 of the 14 indices was 1, including that the focus in the disphragmatic muscle, or at the base of the lung was $\geq$ 2 cm, with confluent plaque, the inguinal focus or inguinal lymphatic focus, as well as the focus at the liver surface were all $\geq$ 2 cm. The focus at the hepatic hilum or cystic crypt was $\geq$ 1 cm, and the focus at, the peritoneal aortic lymph node of the inferior renal artery $\geq$ 2 cm, or it was a focus of the liver parenchyma.

In contrast with a standard of respective scoring items, clinical manifestation and CT outcome of each patient achieved a total score. Different scores were used as the cut off point of the predictive system to calculate the sensitivity, specificity, positive and negative predictive values and exactness of the predictive system. The 5 indices were respectively 100%, 85.0%, 87.5%, 100% and 92.7%, as the cut off point was 4, and the impertinent non-exploration rate (INER) (the rate of failing to conduct the operation on the patient who should achieve the OC) corresponding to the specificity was 15.0%. The INER was accordingly decreased as the score of the cut of point was enhanced. When the cut off point was 7, the INER was 5.0%, the sensitivity 85.7%, and the unnecessary exploration went up to 13.6%. Generally speaking, the predictive scoring system is good, though no predictive factors such as the preoperative CA125 value and the patient's age were included in a comprehensive evaluation.

Dowdy et al.[5] reported thatneoadjuvant chemotherapy could be considered a preferred treatment if it was found by a preoperative CT scan of AOC that the diameter of all foci larger than 2 cm were infused to sites, such as the spleen or diaphragmatic muscle, surface of the liver, paraaortic lymph node of the kidney, etc., with an extensive thickening of the peritoneum, so that it was untreated by an optimal resection.

Positron emission tomography (PET)

Yoshida et al.[6] performed preoperative CT and PET scans on 15 ovarian cancer patients and compared the intraoperative findings with the pathological outcomes. Results showed that the coincidence between the preoperative staging by a simple CT scan and the surgical staging amounted to 8 cases (53.3%), whereas the coincidence between the preoperative staging by CT in combination with a PET scan and the surgical staging achieved 13 cases (86.7%). The sensitivity of a simple CT scan and combined use of a CT with a PET scan for detection of the lesions was 46.7% and 67.8%; specificity was 90.0% and 92.0%, and positive predictive value 47.0% and 65.0%, respectively. A meta-analysis by Ruiz-Hernandez et al.[7] on 17 studies indicated that in the decisions of doubtful ovarian cancer cases, the sensitivity and specificity of PET was 94.0% and 65.0%, respectively, with a minor false positive rate. In addition, a report of a study involving a small sample number indicated that combined use of PET and CT could improve accuracy of a simple CT scan or PET scan of tumor stages[8].

Magnetic resonance imaging (MRI)

Qayyum et al.[9] conducted preoperative CT (91 cases) or MRI scans (46 cases) on 137 cases with a primary diagnosis of ovarian cancer, and proposed imaging standards for a non-optimal resection: 1) the diameters of implantation metastases were larger than 2 cm at sites, such as the hepatic hilum, fissures of hepatic segments, cystic crypt, subdiaphragmatic region, hepatic and gastric ligament, hepatic and splenic ligament, lesser sac of the peritoneal cavity, or root of the small mesentery; 2) the diameter of retroperitoneal implantation metastasis at the upper renal hilum; 3) there were liver parenchymal metastases or abdominal wall invasions.

The results showed that for comparing the evaluation ability of OC between CT and MRI, the analysis of the imaging evaluations and surgical outcomes

showed that 21of the 137 patients failed to achieve OC (15.3%). Correct preoperative imaging appraisement was conducted in 16 of the total cases. The sensitivity, specificity, positive predictive value and negative predictive value of the preoperative imaging evaluation for the non-optimal cytoreduction were 76.2%, 99.0%, 93.7% and 96.0%, respectively. The same 4 indices with MRI scans were respectively 71.0%, 100%, 100% and 95.0%. There was no significant difference compared to CT scans (P=1.00), i.e., the appraisement capacity of MRI and CT for diagnosis of ovarian cancer and surgical feasibility was similar.

Selection of neoadjuvant chemotherapy before cytoreduction is an important progress in treatment of AOC. The sensitivity of patients to chemotherapeutic agents is different, because the mode, course of treatment and chemotherapeutics of the neoadjuvant chemotherapy varies. Therefore, evaluation of the curative effect of neoadjuvant chemotherapy is needed to provide a basis for determining the opportunity of conducting the cytoreduction after neoadjuvant chemotherapy, i.e., the interval debulking surgery, so as to achieve the optimal cytoreduction and to avoid possible drug resistance. At present, the response evaluation criteria for solid tumors (the RECIST standard) are the most frequently-used standards for preoperative appraisement of cytoreduction following neoadjuvant chemotherapy. Shibata et al.[10], using the RECIST standards, appraised the effect of neoadjuvant chemotherapy on 29 patients with Stage III and IV ovarian cancer who underwent an operation. The results showed that there were two cases with complete remission among these patients with a diameter of their surgical residues being less than or equivalent to 2 cm. The diameter of the surgical residues was less than or equivalent to 2 cm in 13 of the 18 cases with partial remission. In the 9 cases without progression of disease nor aggravation, no diameter of the surgical residue was less than or equivalent to 2 cm.

CA125 evaluation

CA125 is a tumor marker used for clinical detection of ovarian cancer. It is also used for working up chemotherapeutic regimens, as well as to evaluate the curative effect and feasibility of OC.

Brockbank et al.[11] performed a comparative analysis between the preoperative serum CA125 level and surgical outcome of 97 ovarian cancer patients. In 20 Stage-I and II patients, the preoperative CA125 level was lower than 586 U/ml and OC was achieved. In 77 Stage-III and IV patients, preoperative CA125 was lower than 586 IU/ml in 33 (72.7%) cases, among which 24 achieved OC. Eight of the 44 remaining cases (18.2%), with a preoperative CA125 level over 586 IU/ml, achieved OC. In the 77 cases, the cut off point was 586 IU/ml, the overall specificity 88.5%, sensitivity 80.0% and positive predictive value 85.7%. The researchers suggested that neoadjuvant chemotherapy could be a treatment choice for the patients with AOC if enforcement of OC is uncertain.

Saygili et al.[12] analyzed the preoperative CA125 level and surgical outcomes of 92 patients with ovarian cancer at Stage IIIc or over and found that 36 of the 47 patients whose preoperative CA125 level was lower than 500 IU/ml (76.6%) achieved OC, while only 12 of the 45 with a preoperative CA125 of over 500 IU/ml (26.7%) reached OC (P<0.05). In various studies, the cut off point value of the CA125 for evaluating feasibility of OC was different. Zhao et al.[13] chose 750 IU/ml as the critical value, and they predicted that the sensitivity of the OC was 64.7%, the specificity was 65.4%, positive predictive value 55.0% and negative predictive value 73.9%.

In addition, CA125 can also be used for preoperative evaluation of cytoreduction after neoadjuvant chemotherapy. Tate et al.[14] conducted neoadjuvant chemotherapy on 50 patients with AOC enlisted in the group. They performed CA125 assays before each course of treatment from the first day of chemotherapy, until normalization of the CA125 level (CA125 < 35 IU/ml) or up to the day of operation. A correlation coefficient between the CA125 value and the number of days (of measurement) was calculated. If the correlation coefficient was less than -0.039, it was regarded as a responder, otherwise it meant a non-responder.. The results showed that 1) following neoadjuvant chemotherapy, OC was achieved in 32 cases of total responders (32/33) and 14 cases in non-responders (14/17), and 2) the overall 3-year survival rate of the patients was 59.3%, with 70.5% in the responder group and 43.3% in the non-responder group. There was a significant difference between the two groups (P=0.012).

Recently, Rustin et al.[15] put forward a standard for a chemotherapeutic reaction and for a definition of CA125, i.e. a standard of 50.0% reaction and 75.0% reaction. Several findings have indicated that there was no difference in evaluation of the chemotherapeutic efficacy between the CA125 reaction standard and the RECIST standard[16]. There have been no reports on the appraisement of the OC feasibility in applying the CA125 reaction standard, and much more studies are needed to determine if the commonly-used RECIST standard can be replaced or combined, in order to guide a latter therapeutic regimen.

Laparoscopic approach

After a retrospective study of 285 patients with AOC, Vergote et al.[17] indicated that a laparoscopic approach is one of the favorable methods for a final diagnosis and evaluation of OC feasibility. They also brought up the following indications for neoadjuvant chemotherapy: 1) absolute indications include a) patient with Stage-IV ovarian cancer; b) metastasis of over 1 g, or a metastasis at the sites, such as the hepatic hilum or mesenteric artery etc., where residuals may remain because of the failure of total resection. 2) concerning the patients with an accumulative metastasis of over 100 g, the relative indications include the following: a) incalculable peritoneal metastases (more than 100 sites); b) an estimation for all metastases of over 1,000 g; c) the lamellar infiltration of over 10 g occurring at the diaphragmatic region or at other peritoneal sites; d) an ascites amount of over 5 L, and e) the WHO scoring of 2 to 3 points.

The method of neoadjuvant chemotherapy can be preferred if 2 of the 5 relative indications are apparent. In the study, 77 patients with ovarian cancer underwent a laparoscopic approach. Based on the contrast standard during the operation, a surgical operation was conducted in 28 cases and residuals of less than 0.5 cm remained in 22 of the total (78.6%). Neoadjuvant chemotherapy and cytoreduction were performed in 31 of the remaining patients, among which residuals of less than 0.5 cm were found in 26 cases (83.9%). It is thus clear that evaluation of OC feasibility using a laparoscopic approach enjoys a high sensitivity and specificity, and it is a satisfactory method of evaluating surgical feasibility[18].

Fagotti et al.[19] employed a laparoscopic approach for 64 cases with AOC to evaluate OC feasibility, showing that 1) with the findings of exploratory laparotomy as the gold standard, the exactness of a laparoscopic approach amounted to 90.0%, a positive predictive value of 87.0% and a negative predictive value of 100%; 2) it was suggested that in the patients receiving a laparoscopic approach, 12 of them were unable to accomplish OC, because of metastases in the peritoneum and disphragmatic muscle (8/12, 66.7%), and mesenteric shrinkage (5/12, 41.7%). In addition, it was uncertain as to whether 10 of the cases could achieve OC. It was indicated that during the laparoscopic approach, the number of the cases failing to receive surgery or to ascertain OC feasibility was more than that with exploratory laparotomy. Exploration by laparoscopy at some anatomical positions might be hindered by extensive growth and adhesions of the tumor tissue; 3) the accuracy rating of the indices during the laparoscopic approach was between a range of 80.0% to 100%; the exactness of laparoscope evaluation of the lymph node hyperplasia was the lowest (80.0%). It was found in the study that the preoperative imaging examination plus laparoscopic approach evaluation of OC feasibility could not significantly increase the overall positive predictive value (the patients who could achieve OC were not regarded as a negative outcome, and a high positive predictive value could avoid delaying the surgical opportunity by providing unnecessary preliminary chemotherapy, resulting in progress of disease). Other reports indicated that application of laparoscopy may increase metastasis of the cancer at the incision[20], with an incidence rate of approximately 0% to 7.8%. Nevertheless, application of laparoscopy, as a method for OC evaluation, has a good prospect.

Other procedures

The means for evaluating OC feasibility have continuously expanded, such as cytological examinations, detection of expression of various factors, and assay of proteins, etc. Eltabbakh et al.[21] analyzed the expression level of apoptotic regulatory factors, including p53, p21, Bcl2, Bclx and Bax, to evaluate the ability for OC (with the residuals of less then 1 cm) in 72 patients with Stage-III and IV ovarian cancer or peritoneal cancer. The results showed there was significance only in evaluation of p53 to assess for OC, i.e., 50.0% of the patients with a weak or medium p53 expression achieved OC, whereas only 15.3% of the patients with a strong p53 expression achieved OC. There was a significant difference between the above two groups (P=0.003). Ferrandina et al.[22] compared the surgical and chemotherapeutic results with p53 expression in 168 AOC cases, and found that there was a related tendency between the positive p53 nuclear expression and the achievement ratio of a preferred operation (P=0.065). Further studies on p53 are expected since it has been used in the past to evaluate for OC in AOC cases.

Evaluation for an optimal resection before cytoreduction provides a basis to choose between a thereapeutic regimen and a preferred operation and neoadjuvant chemotherapy. In addition, it aids in finalizing an opportunity for cytoreduction after neoadjuvant chemotherapy. To summarize the above, the exactness of presently-used clinical evaluation means are insufficient, because they are only localized on one respect, and they fail to include all the meaningful predictive factors for an aggregate analysis. Conduction of a comprehensive evaluation of the cytoreduction feasibility by searching for new methods or a cross application of two or more means can enhance the

success rate of cytoreduction and minimize residuals. Improved procedures will help us reach our goal of extending the life time of the ovarian cancer patients, and to improve the prognosis of those suffering from advanced diseases.

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