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TOPIC HIGHLIGHT

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Neoadjuvant chemotherapy and cytoreductive surgery in epithelial ovarian cancer

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Abstract

Ovarian cancer is one of the leading causes of death among gynecological cancers. This is because the majority of patients present with advanced stage disease. Primary debulking surgery (PDS) followed by adjuvant chemotherapy is still a mainstay of treatment. An optimal surgery, which is currently defined by leaving no gross residual tumor, is the goal of PDS. The extent of disease as well as the operative setting, including the surgeon's skill, influences the likelihood of successful debulking. With extensive disease and a poor chance of optimal surgery or high morbidity anticipated, neoadjuvant chemotherapy (NACT) prior to primary surgery is an option. Secondary surgery after induction chemotherapy is termed interval debulking surgery (IDS). Delayed PDS or IDS is offered to patients who show some clinical response and are without progressive disease. NACT or IDS has become more established in clinical practice and there are numerous publications regarding its advantages and disadvantages. However, data on survival are limited and inconsistent. Only one large randomized trial could demonstrate that NACT was not inferior to PDS while the few randomized trials on IDS had inconsistent results. Without a definite benefit of NACT prior to surgery over PDS, one must carefully weigh the chances of safe and successful PDS against the morbidity and risks of suboptimal surgery. Appropriate selection of a patient to undergo PDS followed by chemotherapy or, preferably, to have NACT prior to surgery is very important. Some clinical characteristics from physical examination, serum tumor markers and/or findings from imaging studies may be predictive of resectability. However, no specific features have been consistently identified in the literature. This article will address the clinical data on prediction of surgical outcomes, the role of NACT, and the role of IDS.

Key words: Advanced stage ovarian cancer; Neoadjuvant chemotherapy; Interval debulking surgery

Core tip: Neoadjuvant chemotherapy (NACT) is an option when the primary surgery is expected to be impossible or suboptimal, or when high morbidity is anticipated. Delayed primary surgery or interval debulking surgery (IDS) is performed in patients who show some clinical response to neoadjuvant or induction chemotherapy. Preoperative clinical data to predict surgical outcomes and selection criteria for primary surgery followed by adjuvant chemotherapy or for NACT followed by IDS will be discussed in this chapter.

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INTRODUCTION

Because of the lack of effective screening procedures to detect early stage ovarian cancer, the majority of patients present with advanced disease (stage Ⅲ-Ⅳ), resulting in a poor overall survival. The current standard management of patients with advanced ovarian cancer (AOC) is "debulking or cytoreductive surgery" followed by platinum-based chemotherapy. The aim of primary debulking surgery (PDS) is to remove as much cancer as possible, since the amount of residual tumor is one of the most important prognostic factors for survival[1,2]. When the cytoreduction is successful, the term "optimal debulking surgery" is applied. The definition of optimal debulking surgery has changed over the past 30 years from a residual tumor sized not more than 1-2 cm to no macroscopic disease[2-4]. However, it is not always possible to debulk tumors in the pelvis and upper abdomen optimally, especially when they have invaded the neighboring viscera. To achieve the goal of no residual disease and improve disease specific survival, "ultra" radical surgical techniques have been developed[5]. However, data on quality of life are not available and the documentation of adverse events is incomplete. Furthermore, many other factors must be considered, such as the patient's status or medical contraindications, morbidity-related treatment, and the reluctance or expertise of some surgeons/centers to practice such an aggressive procedure[4,6-10].

When PDS is not possible or is predicted to be unsuccessful, or where morbidity might be excessively high, chemotherapy prior to PDS is an option; so called "neoadjuvant chemotherapy" (NACT)[10]. The chemotherapy is given after the diagnosis of ovarian cancer, preferably by tissue biopsy. On the other hand, when PDS is incomplete and there is a bulky residual tumor, "induction chemotherapy" is usually given for 2-3 cycles to reduce tumor size. Secondary surgery or so called "interval debulking surgery" (IDS) is considered before continuing more cycles of chemotherapy when there is no evidence of progressive diseases[11].

PREDICTION OF OPTIMAL SURGICAL OUTCOME

The achievement of optimal surgery varies according to the extent of the disease itself and the ability of the surgical team to perform the operation. These factors must be taken into consideration in estimating whether the PDS will be possible and successful. The evaluation should be as accurate as possible, in order to avoid a futile procedure or excessive morbidity and, on the other hand, to offer patients the best opportunity for optimal cytoreduction. The estimation should be based on the combination of a number of factors: clinical characteristics or findings from physical examination, imaging studies, serum markers, or laparoscopic findings.

Serum markers

Some biological markers have been studied in relation to the stage of disease, resectability, and survival. The elevation of these markers is frequently reported in direct association with advanced stage diseases, suboptimal resection of ovarian cancer or decreased survival. Nevertheless, different reports show variation in their diagnostic performance and levels of significance varied.

Inflammatory markers: Recently, the relationship between cancer development and inflammation has been recognized. This relationship is explained through an inflammatory process elicited by cancer cells. Cancer cells can trigger the host inflammatory response with the release of neutrophil-releasing inflammatory cytokines, leukocytic and other phagocytic mediators. These substances induce damage to cellular DNA, inhibit apoptosis and promote angiogenesis around cancer area. This will ultimately result in tumor growth, progression, and metastases[12-14]. Similarly, platelets can release growth factors such as platelet-derived growth factor, platelet factor 4, transforming growth factor β, vascular endothelial growth factor[15-17] and thrombospondin, which function as potent mitogens or as adhesive glycoproteins for various cell types including ovarian surface epithelium[18,19]. These growth factors can stimulate ovarian tumor cell proliferation and adhesion to other cells, leading to tumor growth and metastases, respectively[20].

Elevation of neutrophils[21], platelets[22-24], lymphocytes as well as of the neutrophil to lymphocyte ratio (NLR)[25,26], and the platelet to lymphocyte ratio (PLR)[27,28] were found to be associated with unfavorable clinico-pathologic features in ovarian cancer. In many early studies thrombocytosis was found to be associated with more advanced disease, inoperable cancer, and to be an independent prognostic factor for survival of epithelial ovarian cancer patients[22-24,28]. A possible prognostic role of NLR was also studied, but with inconsistent results[25,26,28]. One study found that elevated NLR (> 2.6) and cancer antigen (CA) 125 correlated with poor survival[26] while a second study failed to demonstrate any such association and only found significant association between elevated pre-operative NLR and advanced stage or suboptimal surgery[25]. Other studies also explored the role of PLR and found that it functioned better than platelet count[28] or NLR[27,28] as a prognostic factor for poor survival and other unfavorable clinico-pathological factors, such as, advanced stage and suboptimal residual disease.

Despite the association of elevated inflammatory markers with survival and suboptimal surgery, data on the levels of significance are inconsistent among studies. Different number of patients and non homogeneous patients' characteristic (*e.g.*, stage of disease and result of primary surgery) among the series might explain these differences. Larger studies and more homogeneous pop-

Table 1 Studies of cancer antigen 125 for predicting the result of surgery in epithelial ovarian cancer

First author, year	*n*	Preoperative CA 125 (U/mL)		Optimal surgery[3]	Sensitivity	Specificity	PPV	NPV
		Median	Cut-off					
Not clinically useful[1]								
Gemer *et al*[30], 2001	40	341	500	60%	62%	83%	71%	77%
Cooper *et al*[31], 2002	112	893	500	58%	49%	77%	74%	52%
Memarzadeh *et al*[32], 2003	99	-	912	73%	58%	54%	78%	31%
Rossi *et al*[33], 2004	82[2]	1351	500	40%	40%	64%	-	-
Alcázar *et al*[34], 2004	67	730	620	48%	60%	-	-	-
Gemer *et al*[35], 2005	424	495	400	57%	69%	57%	55%	71%
Everett *et al*[36], 2005	56	NA	500	52%	-	-	-	-
Barlow *et al*[37], 2006	164	364	500	47%	66%	59%	64%	36%
Gilani *et al*[38], 2007	90	500	500	47%	68%	62%	64%	35%
Arits *et al*[39], 2008	96	625	330	43%	80%	42%	-	-
Chi *et al*[40], 2009	277	731	500	80%	-	-	-	-
Probably clinically useful[1]								
Chi *et al*[41], 2000	100	819	500	45%	78%	73%	78%	73%
Saygili *et al*[42], 2002	92	494	500	52%	73%	77%	75%	75%
Obeidat *et al*[43], 2004	40	467	500	55%	72%	73%	68%	76%
Eltabbakh *et al*[44], 2004	72	680	500	81%	73%	74%	-	-
Brockbank *et al*[45], 2004	77	397	586	68%	80%	89%	86%	80%
Vorgias *et al*[46], 2009	426	650	500	42%	79%	90%	85%	85%

[1]Studies of not clinical useful and probably useful were arranged according to the comments of the authors in each study; [2]Diagnostic functions of cancer antigen (CA) 125 in the study were of the whole group (22% early stages and 78% advanced stages) while the numbers of patients (*n*) in other studies were of stage Ⅲ or stage Ⅲ-Ⅳ disease; [3]All studies defined residual disease ≤ 1 cm as optimal surgery. NPV: Negative predictive value; PPV: Positive predictive value; NA: Not available.

ulations are needed to validate the role of inflammatory markers as predictors for suboptimal surgery.

CA 125: Serum CA 125 is the most widely used biological marker in ovarian cancer and is abnormally high in more than 90% of patients with AOC[29]. Hence, many studies have attempted to find a reliable cut-off level of CA 125 which could predict the optimal resection of ovarian cancer.

However, the results are inconsistent among studies and it is not possible to define a single reliable cut-off value of CA 125 to predict optimal surgery (Table 1)[30-46]. Some reasons can explain these unsatisfactory results. First, all of these studies were retrospective in nature. Second, the number of patients in each study varied from less than 50 to over 400. Third, the rates of optimal cytoreduction ranged from less than 50% to 80% in the various centers. Fourth, the median value of CA 125 in the studies varied significantly. Most probably, these differences reflect the lack of homogeneity of tumor stages and in the extent of tumor burden, as well as the different criteria for operability adopted in the different centers.

Since the level of CA 125 is directly related to the stage of disease and to the amount of tumor burden, preoperative CA 125 levels in studies with a higher number of optimal cytoreductions should, theoretically, be lower than those in studies with more unresected tumors. Nevertheless, some studies suggest that the aggressiveness of the surgical procedures may be a confounding factor that affects the rates of optimal cytoreduction. One multicenter study by Gemer *et al*[35] reviewed records of 424 patients with AOC and found that clinical applicability of CA 125 for predicting suboptimal surgery was limited. The authors found only a 57% rate of optimal surgery. Although the median CA 125 serum levels in patients with optimally cytoreduced tumor was significantly lower than that in suboptimally debulked cases (304 U/mL *vs* 863 U/mL), the diagnostic accuracy of CA 125 as predictor of optimal debulking was only 62% with the best cut-off identified (400 U/mL). Another large study by Vorgias *et al*[46] also found significant association between CA 125 levels and surgical results in 426 patients: 84% of patients with CA 125 < 500 U/mL achieved optimal cytoreduction compared to only 15% of those with higher CA 125 levels. However, this study reported only a 42% overall rate of optimal cytoreduction. Once again, this might be the result of a less extensive surgical effort for peritoneal carcinomatosis and for metastatic lymph-nodes. The results from 2 other studies by the same groups of authors further demonstrated the importance of the surgical aggressiveness. In their first report in early 2000s, Chi *et al*[41] reported a 45% optimal cytoreduction in 100 AOC patients. The rate of optimal cytoreduction was significantly higher in patients with pre-operative CA 125 ≤ 500 U/mL than those with higher level: 73% *vs* 22%[41]. However, their subsequent study in 277 patients with similar characteristics demonstrated that the patients with a higher CA 125 level required more extensive upper abdominal surgery to achieve optimal surgery (< 1 cm residual tumor) compared to those with a lower CA 125 level, 50% *vs* 27%[40]. There was no CA 125 threshold which could predict the surgical outcome. Of note, their latter study reported a higher rate of cytoreduction (80%). These studies may be affected by selection bias, a com-

mon phenomenon in retrospective and in non-randomized prospective trials

It is therefore difficult to make any conclusion regarding the possible role of CA 125 in determining resectability in advanced ovarian cancer patients. One systematic review by Kang *et al*[47] determined the ability of pretreatment CA 125 level to predict optimal cytoreduction in AOC. The authors identified 122 articles in which 15 studies including their own series met the inclusion criteria, and 2192 patients were analyzed in the meta-analysis. The pooled optimal cytoreduction rate and the mean of median CA 125 levels were 53.7% and 580 U/mL, respectively. The authors did not find any significant heterogeneity factor (year of publication, numbers of patients, median CA 125 levels, percentage of stage Ⅳ disease, or rate of optimal cytoreduction) influencing the analysis. The diagnostic performance of CA 125 in predicting suboptimal cytoreduction was analyzed at 3 cut-off levels of 500, 1000 and 1500 U/mL. A direct association between CA 125 levels and likelihood of suboptimal cytoreduction was found. Increasing specificity and odds ratios along with decreasing sensitivity were observed with higher CA 125 cut-off levels. At a cut-off level of 500 U/mL, the odds ratio was 3.69 (95%CI: 2.02-6.73). The authors also demonstrated that the predictive role of CA 125 was not affected by the rate of optimal cytoreduction. The odds ratios were not different among the studies which had optimal cytoreduction rate ≥ 50% *vs* < 50%: 4.0 *vs* 4.5, respectively. Against all the odds, this might suggest that the effort of a surgeon probably has little to do with the accuracy of CA 125 in predicting the result of PDS. It should be noted that, despite the strong association of CA 125 and risk of suboptimal surgery, the meta-analysis showed that CA 125 showed only a low positive likelihood ratio and could not accurately predict the optimal or suboptimal surgery at any cut-off level[47].

From these retrospective studies and from the systematic review, we can conclude that although pre-operative serum CA 125 level is a reliable predictor for the extent of disease, it has limited accuracy in predicting a successful surgical outcome. The sensitivity and specificity in the various studies ranged from 40% to 80% and from 40% to 90%, respectively (Table 1). With a positive predictive value (PPV) of 55%-86% (approximate mean of 73%) an unsuccessful (unnecessary) surgical exploration would be performed in 27% of patients (false negative diagnosis). On the other hand, the negative predictive values (NPV) ranged from 31%-85% (approximate mean of 62%), suggesting that 38% of patients would be falsely interpreted to be inoperable and would miss their chance to undergo a successful operation. Hence, one should not use CA 125 as a single criterion to determine patient management: primary surgery *vs* NACT. Other clinical features, such as ascites or imaging studies, may add value to CA 125 in predicting an optimal cytoreduction. Nevertheless, a high level of CA 125 should warn a surgeon that aggressive surgery will probably be required to achieve an optimal resection. This will ultimately aid in planning the setting or level of the hospital where the operation should be performed.

Imaging studies

Imaging studies are very useful to evaluate the location, nature, and extent of disease. However, some common pitfalls are encountered depending on the location and size of the lesions. Aside from having an important role in the assessment of tumor response during or after the courses chemotherapy, imaging can be used to evaluate the extent or location of disease preoperatively to estimate whether the surgery can be achieved with minimal morbidity and with maximal outcome. An imaging study can be an indicator alone or in combination with other clinical features, such as CA 125, in trying to improve the predictive role of each.

Computed tomography: Computed tomography (CT) scan is a commonly used imaging tool in AOC. Many criteria have been used to select the patients who were unlikely to have a successful surgical outcome and NACT may be a better option. These include carcinomatosis, pelvic sidewall infiltration, ascites, and extensive upper abdominal disease over diaphragm, liver, porta hepatis, mesentery, and bowel[48]. Using spiral CT scan, the reported sensitivity in detecting peritoneal metastases, mesenteric, and diaphragmatic surfaces ranged from 85% to 93%[49,50]. This technique yielded improved sensitivity over previous reports that used 10-mm slice CT scanning, which may miss subcentimetric peritoneal nodules or plague-like lesions[51].

One of the earliest studies of CT scan for predicting optimal surgery in 42 ovarian cancer patients was reported by Nelson *et al*[52]. The authors found that CT scan could detect the presence of ascites, mesenteric, and omental disease. However, it was poor in detecting liver involvement, omental attachment to the spleen, gallbladder fossa disease, and peritoneal nodules smaller than 2 cm. The overall optimal cytoreduction rate was 69%. The sensitivity was as high as 92% with specificity of 79%, while the PPV and NPV were 67% and 96%, respectively. Notably, 8 of the 42 patients had stage Ⅰ / Ⅱ disease. In patients with advanced disease the specificity decreased from 79% to 71%.

A larger study by Salani *et al*[53] who included only stage Ⅲc/Ⅳ disease reported 92% overall rate of optimal cytoreduction in 180 ovarian cancer patients. The authors found varying rates of optimal surgery according to the location and number of lesions identified preoperatively: 91% optimal debulking in the presence of ascites or carcinomatosis, 94% in the presence of lesions over the diaphragm, 85% or 88% with spleen or liver involvement, and only 75% for lesions involving the porta hepatis or the lymph-nodes above the renal vessels. The rates of optimal debulking according to the number of lesions were: 95% for disease involving 1 site, 94% for 2 sites, and 82%, 93%, 80% for 3, 4, and 5 sites, respectively. The authors concluded that none of these features absolutely excluded the possibility of optimal resection.

Other studies have used several radiographic findings in combination to develop a score model to predict surgical outcomes. Dowdy *et al*[54] reported the role of CT scans in predicting suboptimal cytoreductive surgery in 87 patients with stage Ⅲ/Ⅳ ovarian cancer. The optimal cytoreduction rate was 71%. Among many radiographic criteria from CT scans, only diffuse peritoneal thickening was independently associated with suboptimal resection. Using this single criterion, the PPV and NPV were 57% and 85%, respectively. The PPV increased to 68% when ascites was added as a feature, and 79% with added ascites and diaphragmatic diseases. Interestingly, the authors made specific note that the predictive ability of CT criteria was dependent on other factors, especially the effort of the surgeon to perform extensive surgery[54]. Another study by Meyer *et al*[55] used a 10-score model composed of a score of 0 to 2 for a disease at each site of the following: omentum, liver, para-aortic nodes, diaphragm, and small-bowel mesentery. The rate of optimal cytoreduction or of having residual diseases ≤ 2 cm was 57%. Score ≥ 3 had sensitivity of 58% and a specificity of 100% in predicting residual disease > 2 cm. The area under the curve (AUC) was 0.94. Of note, nearly 40% of the patients in this study had early stage disease, and again, this may have led to overestimation of the role of pre-operative CT scan. Another study by Fujwara *et al*[56] created two models using various features of diffuse peritoneal thickening, infrarenal para-aortic or pelvic lymph node involvement, a bowel encasement tumor or bowel mesenteries or omental cake ≥ 2 cm, and ascites fluid. The two models using either 4 or 6 disease sites as criterion yielded greater than 90% accuracy in predicting suboptimal surgery.

Combined CT scan and clinical data: Some studies have evaluated the combined use of CT scans with clinical data, including CA 125, to improve the doctor's ability to predict the results of surgery. However, the results of these attempts to predict optimal cytoreduction were inconsistent[7,55,57-61].

As mentioned earlier, Meyer *et al*[55] used a 10-point scoring system from CT scan features and found an AUC of 0.94 in predicting a suboptimal surgery. The AUCs were not improved when the authors added age, ascites, or CA 125 to their index, with AUC scores of 0.91, 0.93, and 0.97, respectively[55]. A study by Byrom *et al*[57] evaluated CT scan findings in 51 ovarian cancers (49% having residual diseases). The sensitivity and specificity of the CT scan using a full model (the 4 CT features of ascites, omental cake, mesenteric disease, and diaphragmatic deposits) or a reduced model (only omental cake and mesenteric disease) in predicting residual disease were the same: 88% sensitivity, 98% specificity, 95% PPV, and 94% NPV. The specificity and PPV, at 98% and 95% respectively, were not improved by the addition of age and CA 125.

In addition to the chronological age of an individual, the performance status of a patient may affect the treatment outcome. One study by Aletti *et al*[7] examined the resectability of ovarian cancer by considering disease factors as well as patient status and the effort of the surgeon. Data taken into account were age, performance status, CA 125, ascites volume, carcinomatosis, diaphragmatic or mesenteric involvement, and the surgeon category (radical surgery in less than *vs* more than 50% of cases). Only performance status, carcinomatosis, and surgeon were independently associated with surgical outcome. The authors focussed on the surgical effort of the surgeon. Among the patients with high-risk factors of poorer performance status or with carcinomatosis, the rates of optimal cytoreduction varied from 42% to 67% depending on the willingness of the operating surgeons to perform aggressive surgery[7].

Another study by Bristow *et al*[58] included as many as 25 radiographic features from CT scans as well as clinical features including performance status and pre-operative serum CA 125 to predict optimal cytoreduction in 41 ovarian cancer patients. Based on the statistical probability of each factor in predicting cytoreductive outcome, performance status and 13 imaging features were selected for the final assessment model. Performance status ≥ 2, peritoneal thickening, ≥ 2 cm tumor implants on the peritoneum, small or large bowel mesentery, ≥ 1 cm suprarenal para-aortic lymph nodes, omental extension (spleen, stomach, or lesser sac), and pelvic sidewall involvement and/or hydroureter, which were most strongly associated with surgical outcome, had a score of 2 while the other CT features had a score of 1. Scores ≥ 4 had the highest overall accuracy at 93%, with 100% sensitivity, 85% specificity, 88% PPV, and 100% NPV. However, the predictive function of this model was not confirmed in other similar cross-validation studies[59,60]. Axtell *et al*[59] found disease over the diaphragm and large bowel mesentery as independent predictors of suboptimal cytoreduction. The authors also applied a different 14-criteria radiographic-based model to the original cohort of Bristow *et al*[58] as well as to the other cohorts, but found lower sensitivity, specificity, and accuracy. Another study by Gemer *et al*[60] compared the validity of four predictive CT scan models reported by Nelson *et al*[52], Dowdy *et al*[54], Bristow *et al*[58], and Qayyum *et al*[62]. Only the Dowdy study's criteria for predicting the results of surgery were confirmed. The predictive performances of the other models were lower.

Finally, one recent prospective study by Ferrandina *et al*[61] used several features from CT scans combined with clinical data to develop a predictive index. The CT scan features were: peritoneal thickening or implants > 2 cm, bowel mesentery involvement, omental cake, pelvic sidewall involvement and/or hydroureter, suprarenal aortic lymph nodes > 1 cm or infrarenal aortic lymph nodes > 2 cm, superficial liver metastases > 2 cm and/or intraparenchimal liver metastases of any size, and ascites > 500 mL. Clinical data included age, CA 125, and ECOG-performance status. Radiographic and clinical features which yielded a specificity > 75%, PPV and NPV > 50%, and accuracy > 60% in predicting surgical outcomes were assigned a score of 2. The AUC was 0.78 using only radiographic features and 0.81 using both radiographic and clinical data. The

Table 2 Studies of computed tomography scan with or without clinical features to predict surgical outcome in epithelial ovarian cancer

First author, year	*n*	OS	CT criteria ± clinical feature	Sensitivity	Specificity	PPV	NPV	Accuracy
Using 2 cm as criteria for OS								
Nelson *et al*[52], 1993	42[1]	69%	1 of 8 disease site	92%	79%	67%	96%	86%
Meyer *et al*[55], 1995	28[1]	57%	5 disease sites	58%	100%	100%	55%	79%
Byrom *et al*[57], 2002	51	51%	Full/reduced models (same values)	88%	98%	95%	94%	-
			CT with age and CA 125 (not useful)	88%	92%	85%	94%	-
Qayyum *et al*[62], 2005	137	15%	Either CT (n = 91) or MRI (n = 46)	76%	99%	94%	96%	95% (CT), 96% (MRI)
Using 1 cm as criteria for OS								
Dowdy *et al*[54], 2004	87	71%	3 disease sites (CA 125 not useful)	44%	95%	79%	81%	-
Fujwara *et al*[56], 2011	98	86%	4 or 6 disease sites (similar values)	-	-	50%	97% or 99%	91% or 94%
Bristow *et al*[58], 2000	41	49%	13 disease site (predictive index ≥ 4) (age and CA 125 not useful)	100%	85%	88%	100%	93%
Axtell *et al*[59], 2007	(3 cohorts)		2 disease sites					
	65	78%	Cohort A	79%	75%	-	-	77%
	48	41%	Cohort B	15%	32%	-	-	34%
	71	87%	Cohort C	72%	56%	-	-	64%
Gemer *et al*[60], 2009	123	73%	Nelson's criteria	64%	64%	-	-	64%
			Qayyum's criteria	67%	57%	-	-	60%
			Bristow's criteria	70%	64%	-	-	66%
			Dowdy's criteria	79%	60%	-	-	65%
Ferrandina *et al*[61], 2009	195	44%	9 disease sites ± age, CA 125, PS	AUC 0.78 for CT only and 0.81 when added with PS				

[1]19% of the patients in the study of Nelson *et al*[52] and 36% in the study of Meyer *et al*[55] had stage Ⅰ-Ⅱ diseases while all other studies included only advanced stage disease. OS: Optimal surgery; CT: Computed tomography; PPV: Positive predictive value; NPV: Negative predictive value; PS: Performance status; CA: Cancer antigen; MRI: Magnetic resonance imaging; AUC: Area under the curve.

authors concluded that adding performance status led to improvement in the diagnostic performance in predicting suboptimal surgery.

Magnetic resonance imaging: Magnetic resonance imaging (MRI) is not as commonly used as CT scans in ovarian cancer and there are fewer studies examining its role in predicting surgical outcome in patients with AOC. Qayyum *et al*[62] compared the possible role of CT scans (91 patients) and MRIs (46 patients) in predicting ≥ 2 cm suboptimal cytoreduction in 137 epithelial ovarian cancer patients. Using criteria from 14 different peritoneal and nodal diseases, the diagnostic performances of CT scan and MRI in predicting suboptimal diseases were similar, and optimal cytoreduction was achieved in 85% of the cases. However, these findings should be interpreted with caution because 32 patients in this study had early stage disease and only approximately one third of the patients underwent MRI. Furthermore, the results compared the findings from the two radiological techniques in all patients, rather than an individual comparison. Until we have a larger number of studies on the role of MRI in predicting surgical outcome, this technique cannot be recommended in place of CT scan as the first radiological imaging study.

Positron emission tomography and CT scans: The combined used of positron emission tomography and CT scans (PET/CT) has become more common in current clinical practice. This combination enables both sequential functional and anatomical imaging. In the primary treatment setting, the PET/CT combination is used to evaluate the extent of disease, to predict the surgical outcome, and to evaluate the response of a tumor to chemotherapy[63,64].

The few studies which compared PET/CT imagings with other imaging tools found that PET/CT was superior to previous methods for diagnosis of malignant ovarian tumors[65,66]. The results of PET/CT were the same as operative findings in 69% to 78% of the patients. One advantage of PET/CT over other imaging methods was that it could reveal extra-abdominal ovarian tumors or co-existing malignant tumors at other sites[65,66]. We found only one prospective study by Risum *et al*[67], which evaluated risk using a malignancy index comprising of 10 features from PET/CT to assess 54 patients with AOC. Large bowel mesentery implants, pleural effusion or ascites, and peritoneal carcinomatosis identified from PET/CT were predictive factors of suboptimal cytoreduction. However, large bowel mesenteric implant was the only independent predictor. The authors concluded that findings from PET/CT scans should not be used to exclude patients from primary cytoreductive surgery. Nevertheless, the identification unsuspected extra-abdominal metastases by PET/CT scan (which were found in approximately one-third of all patients or half of apparent stage Ⅲ patients) gave important information for making a decision on how to manage these patients[67].

Studies using a CT scan either alone or combination with other clinical features to predict the results of PDS are presented in Table 2[52,54-62]. The sensitivity and specificity of imaging studies from various studies ranged from 15% to 92% and 32% to 100%, respectively. The PPV of 50%-100% (approximate mean of 82%) could suggest that 18% of the patients had a false negative diagnosis and that the expected optimal cytoreduction

Table 3 Studies using laparoscopy to predict surgical outcome

Study	*n*	PDS (*n*)	Optimal surgery[1]	Criteria of residual diseases (cm)	Sensitivity	Specificity	PPV	NPV	Accuracy
Angioli *et al*[71], 2006	87	53	96%	0	-	-	-	-	-
Deffieux *et al*[72], 2006	15	11	91%	0	-	-	-	-	-
Fagotti *et al*[73], 2006[2]	64	61	67%	1	30%	100%	100%	70%	74%
Fagotti *et al*[74], 2008[2]	113	91	50%	1	30%	100%	100%	60%	75%
Brun *et al*[75], 2008[2]	55	26	69%	1	46%	89%	89%	44%	60%

[1]Percentage of optimal surgery was obtained only in the patients who had primary debulking surgery; [2]Diagnostic performance predictions in these studies used score ≥ 8 as cut-off value from the model of the study. PDS: Primary debulking surgery; NPV: Negative predictive value; PPV: Positive predictive value.

could not be achieved. On the other hand, the NPVs which ranged from 55%-100% (approximate mean of 89%) or false positive diagnosis would indicate that 11% of patients could miss their chance of successful PDS.

In conclusion, although some radiological features can predict the possibility of optimal or suboptimal resection, aggressive surgery also has impact on the surgical outcome regardless of the extent of diseases. Hence, a predictive model derived from imaging findings (which does take the effort of the surgeons into account) may not be applicable in all advanced stage ovarian cancer patients in different settings.

Laparoscopy

In the absence of any absolutely reliable preoperative imaging studies or serum markers to predict surgical outcomes in AOC, other means have sought. Laparoscopy (LPS) is an emerging technology which has become more widely practiced in gynecological oncology. Laparoscopic procedures have been practiced in early stage ovarian cancer for many years[68,69]. The minimally invasive nature of LPS yields an advantage over a laparotomy in terms of the rapid recovery of the patient. A balance between comprehensive surgery and maintenance of a locally confined ovarian tumor in early stage disease must be exercised. In recent years, LPS has also been applied in AOC[70]. A direct visualization before laparotomy of tumor location and other pathological findings in the peritoneal cavity will assist a surgeon to better assess the possibility of surgery, particularly for optimal cytoreduction.

Few studies have evaluated a role of LPS to predict the outcome of PDS. Angioli *et al*[71] in 2006 performed LPS on 87 women with AOC before making the decision for laparotomy. NACT was the alternative option in the presence of viscera lesions. As much as 96% of patients, whose tumors were deemed resectable from LPS, were actually optimally debulked by PDS, yielding an 80% rate of optimal cytoreduction. It should be noted that the definition of optimal surgery in this study was "no gross residual disease". This might have led to a higher frequency of NACT use compared to a scenario where 1 or 2 cm residual disease was used as the criterion for optimal cytoreduction. In the same year, two other studies also reported on the role of LPS in AOC[72,73]. Deffieux *et al*[72] estimated by LPS that 11 out of 15 AOC patients would have resectable peritoneal carcinomatosis. Ten of them actually had no residual disease from PDS. Another study by Fagotti *et al*[73] reported the results from their prospective study evaluating lesions over the omentum, diaphragm, peritoneum, mesentery, liver, bowel, and stomach in predicting the surgical outcomes in AOC. The rate of optimal cytoreduction was 67%. Using a scale of 0 to 12, a score ≥ 8 had PPV of 100%, NPV of 70%, and accuracy of 75% for optimal cytoreduction. This was confirmed by a subsequent validation study by these authors who used the same scoring model in 113 women with stage Ⅲ/Ⅳ disease[74]. The rate of optimal cytoreduction in this series was 56%. The PPV, NPV, and overall accuracy were 100%, 60%, and 93%, respectively. The authors concluded that a score ≥ 8 was the appropriate cut-off for predicting suboptimal cytoreduction in 100% of patients. The rate of futile exploration was only 40%. Of note, another cross-validation study by Brun *et al*[75], who used a score of ≥ 8 in predicting optimal surgery in stage Ⅲ/Ⅳ disease, reported an accuracy of only 60% with 89% PPV, 44% NPV, 46% sensitivity, and 89% specificity. The authors simplified the original Fagotti-scoring system and found a score ≥ 4 to be as accurate as Fagotti's score in predicting resectability. Table 3 shows studies which have determined the role of LPS to predict surgical outcome prior to PDS or NACT and IDS[71-75].

The limitations noted in the predictive role of LPS score across a number of studies were probably due to the involvement of different surgeons with various intentions and skills in that particular setting. Nevertheless, a direct visualization of disease by LPS should theoretically offer the best prediction of surgical outcome compared to other preoperative markers or imaging studies. Unnecessary laparotomies can probably be avoided with more confidence. One ongoing multicentre trial will randomize 200 patients with AOC to have a diagnostic LPS prior to a planned PDS[76]. Patients who are evaluated by LPS to have disease expected to be resectable to < 1 cm will undergo PDS followed by platinum based chemotherapy while the other patients will have NACT and IDS before continuing chemotherapy. The primary outcome will be the proportion of suboptimal surgeries in each arm of the study.

NACT: INDICATIONS AND SELECTION CRITERIA

As already mentioned, the standard treatment of advanced epithelial ovarian cancer (FIGO stage Ⅲ-Ⅳ) is a staging laparotomy with PDS, followed by platinum-based chemotherapy. The extent of tumour cytoreduction is considered to be the most relevant prognostic factor. The definition of optimal debulking has changed over time and it is currently defined by many authors as "no macroscopic residual tumour"[2]. In the last decade the dogma of PDS as the preferred "one-size-fits-all" approach to the primary treatment of AOC has been challenged by NACT, that is chemotherapy delivered prior to any attempt at surgical debulking.

Two meta-analysis[77,78] and two systematic reviews[79,80] addressed the question of the timing of surgery before or after chemotherapy in AOC patients. The Bristow and Chi meta-analysis included only phase Ⅰ/Ⅱ and retrospective studies involving 835 patients from 21 studies using platinum-based NACT after a primary surgery attempt[77]. The results showed that survival of patients who had NACT followed by IDS was inferior to those who had PDS. Furthermore each incremental chemotherapy cycle after the third course of NACT resulted in a 4.1-mo decrease in survival. This meta-analysis is, however, affected by severe methodological limitations as recognized by the authors themselves. In particular, the results are confounded by major selection biases (no information is given about criteria to establish NACT duration), by a large variety of different chemotherapeutic agents and administration schedules, and by the fact that prognostic factors such as performance status were not examined. It is also worth-noting that because of the limited number of studies the authors did not apply the multiple linear regression model and it is possible that one or more statistically significant variables associated with survival on simple linear regression could be irrelevant if interaction among variables were taken into account. In another meta-analysis on the same 21 studies conducted by Bristow *et al*[77], the random effect meta-regression analysis was used instead of simple linear regression[78]. The year of publication (more *vs* less recent), the stage (Ⅲ *vs* Ⅳ), the use of a taxane (*vs* not), and the optimal cytoreduction (*vs* not) were associated with a better overall survival. The detrimental effect of duration of NACT was not confirmed, indicating that the allocation of poorer prognosis patients to NACT and to a greater number of chemotherapy courses is a general phenomenon in non-randomized studies, leading to a severely confounding selection bias.

A systematic review of randomized controlled trials of chemotherapy *vs* surgery for the initial treatment in AOC patients was conducted by the Cochrane collaborative group in 2007[81] and was recently updated[80]. The first version of the review[81] identified only one randomized trial by Liu *et al*[82]. Patients were randomized to NACT by the intra-arterial route before IDS or conventional PDS followed by adjuvant chemotherapy. This study randomized just 85 women and could not demonstrate any significant difference in overall survival between the two treatment arms. However, optimal cytoreduction was achieved more often in the NACT/embolisation group, and this group had a shorter operating time, less blood loss and fewer blood transfusions. The updated review excluded this trial because the study findings might have been attributable to NACT, the iliac artery embolization, or both.

As a consequence the only RCT included in the Cochrane 2012 review is the Intergroup Study from Europe, Canada and South America (EORTC 55971/NCIC OV13). This is the only published randomized trial comparing NACT (3 courses) followed by surgery and by 3 more courses of adjuvant chemotherapy with PDS followed by 6 courses of adjuvant chemotherapy (with or without IDS)[10]. The trial randomized 718 patients with stage Ⅲc-Ⅳ AOC, primary peritoneal cancer or fallopian tube cancer with the goal of evelauting the NACT *vs* the control arm in terms of overall survival (primary end-point). Secondary end-points were progression-free survival, surgical morbidity and mortality, quality of life and adverse effects. Among 670 evaluable patients, no significant differences in terms of overall survival (HR 0.98; 95%CI: 0.82-1.18) or progression-free survival (HR 1.01; 95%CI: 0.86-1.17) were found, even though the complete resection rate was higher in the NACT group (52% *vs* 20%, RR 2.56; 95%CI: 2.00-3.28). Grade 3 and 4 haemorrhage, venous thromboembolism and infection were more frequent in the control arm. No differences were observed in the need for blood transfusions, operating times and quality of life.

The definition of selection criteria for NACT or PDS in clinical practice remains a matter of heated debate[83-85]. The supporters of PDS state that optimal debulking surgery can be achieved in most cases and must be pursued even when major debulking procedures and ultra-radical surgery are needed, restricting NACT to a minority of patients with diffuse extraperitoneal disease and/or too sick and elderly to tolerate a major debulking procedure[83]. According to this view, the lack of surgical skills among gynaecological oncologists is a critical issue that should be modified in order to improve the survival of ovarian cancer patients. The major criticism of this position is that it is based only on biased retrospective data and has never been prospectively validated in the context of a randomized controlled trial.

On the other hand, some are concerned about the feasibility of extensive surgery in a real clinical practice[84]. According to the EORTC/NCIC trial, the Leuven selection criteria for NACT[85] include: tumours larger than 2 cm around the superior mesenteric artery or behind the porta hepatis, or intrahepatic (multiple) metastases or several extra-abdominal metastases (excluding resectable inguinal or supraclavicular lymph nodes), or poor general conditions (*e.g.*, over 80 years of age), or extensive serosal invasion necessitating bowel resections greater than 1.5 m

or women who cannot be easily debulked to no residual tumor (*e.g.*, more than one bowel resection, expected operating time greater than 4 h). The last two Leuven criteria are probably the most controversial.

Even if the level of evidence in favour of NACT as a treatment option for patients with bulky stage Ⅲc-Ⅳ AOC is limited (one single RCT), the level of evidence in favour of major debulking surgery and ultra-radical surgery is even lower (retrospective data only). Supporters of NACT believe that it is not recommended to submit patients to the risk and costs of major surgical procedures based on such a low level of evidence.

Three more prospective randomized trials are comparing NACT *vs* PDS in AOC: the small Indian trial results[86] were partly presented in 2007 and in 2009 and should be published shortly (the anticipated results are similar to those of EORTC/NCIC trial). The Japanese trial JCOG0602 accrued 301 patients from November 2006 to October 2011, while the CHORUS trial recruited over 500 patients from March 2004 to July 2010 and the results are awaited[87,88]. All of these trials are investigating a short-term platinum-taxane NACT (3 courses in the Indian and in the CHORUS trials, 4 courses in the JGOG trial).

Hence, we can state that NACT can be considered as an option in patients whose disease appears to be extensive and when the PDS is not possible, expected to be suboptimal or requiring extensive surgical demolitions. NACT should not replace PDS whenever there is a chance for a patient to have a successful standard treatment by PDS followed by adjuvant chemotherapy.

IDS: SELECTION CRITERIA AND OPTIMAL TIMING

NACT has been promoted in order to avoid non-useful surgical procedures in patients expected to have a suboptimal surgical staging after establishing a diagnosis of AOC[89]. IDS or delayed PDS will be performed when the tumors have responded to induction or NACT in terms of complete or partial response as well as stable disease. Most studies to date have demonstrated that the advantage of NACT is the higher rate of optimal cytoreduction at IDS compared to PDS[11,79,90,91]. The possible benefit of IDS on survival is more controversial. Several non-randomized trials which attempted to evaluate the association of IDS and patient survival had inconsistent results. Some studies showed similar survival outcomes between patients who underwent IDS and those patients who had PDS[92-95]. Other studies reported significantly longer survival of patients who had IDS[90,96] and some showed lower survival rates for patients having IDS than for those having optimal PDS[97]. To date, only three randomized trial have focused on the prognostic role of IDS[98-100], and these trials did not agree on the benefit of IDS on survival outcomes. Two trials found similar survival rates between patients who had IDS and those who had conventional treatment[98,100], while the third showed significantly longer survival in the IDS group[99]. The positive effects found in the Van der Burg study persisted after a 10-year follow-up[101]. The Cochrane Collaboration Group conducted a systematic review and meta-analysis (including the three trials just noted) involving 853 women (781 evalauble)[11], and found no statistically significant difference of overall survival (HR 0.80, 95%CI: 0.61-1.06) and progression-free survival (HR 0.88, 95%CI: 0.57-1.33) between the patients who had or did not have IDS. IDS appeared to be beneficial when the PDS was not performed by a gynaecological oncologist or when the PDS was less extensive (HR 0.68, 95%CI: 0.53-0.87).

The timing of performing IDS is another unresolved issue. Previous studies reported the number of induction or NACT cycles ranging from 2-10, with the most common being 3-4 cycles[10,11,90,91,102]. Many reasons were proposed for the earlier timing of the IDS. First, chemotherapy induced fibrosis is less extensive after 3 than after 6 cycles[103]. Second, some tumor clones may develop chemoresistance after 6 cycles[104]. Lastly, indirect evidence from an earlier study investigating the role of tumor debulking at the time of second-look surgery after 6 cycles of chemotherapy did not show any survival improvement[8]. To date, only a few studies with data comparing early with late (after 6 cycles) IDS after NACT are available. One French multicenter study investigated the results of NACT in 54 AOC patients presenting with primary unresectable tumors[105]. The authors found a higher complete response rate from late (after 6 cycles) compared to early IDS (after 3-4 cycles), 61% *vs* 45%. However, the survival rates were the same in both groups at 22 mo. These results were consistent with the data of Stoeckle *et al*[106] who compared outcomes of AOC patients who were treated with platinum-based chemotherapy and underwent early (after 3 cycles) or late IDS (after 6 cycles). The authors also found a higher complete resection rate in the late IDS groups than that in the early IDS gropus, 58% *vs* 36%. These findings suggest that the chance of achieving an optimal debulking increases in a direct relationship with the number of cycles before surgery. However, one randomized trial which was unable to demonstrate different response rates or rates of optimal surgery (residual tumors ⩽ 1 cm) between 2 cycles and 3 cycles of NACT[107]. With inconsistent results regarding the benefit of more cycles of NACT, it should be noted that higher rates of responses and optimal debulking were not translated into an improved rate of survival[105,106]. Hence, based on the EORTC randomized trial[10], limiting NACT to 3 cycles is a reasonable practice until further data prove otherwise. Longer NACT treatment should be explored in the context of clinical trials.

Generally when the disease shows some response to induction chemotherapy or NACT, IDS can be performed unless clinical signs of progressive disease are evident. Criteria for selection of patients who are likely to have successful IDS are also important[9,108]. Patients who are still deemed inoperable or cannot have optimal IDS may be better receiving a new chemotherapy regimen. To

Table 4 Laparoscopic parameters assigned a predictive index score

Predictive index parameter	Point value	Sensitivity	Specificity	PPV	NPV	Accuracy
Omental cake	0	72.7%	68.3%	55.8%	82.0%	69.9%
Diaphragmatic carcinosis	0	77.1%	71.2%	61.4%	84.0%	73.4%
Mesenteral retraction	2	64.3%	98.2%	94.7%	85.0%	87.2%
Bowel infiltration	2	69.7%	86.0%	74.2%	84.1%	80.8%
Stomach infiltration	2	17.6%	100%	100%	67.4%	69.6%
Superficial liver metastasis	2	22.8%	100%	100%	68.9%	71.6%

NPV: Negative predictive value; PPV: Positive predictive value.

predict the results of IDS, Rodriguez *et al*[91] studied the role of CA 125 in 103 AOC patients who were treated with platinum-based NACT followed by IDS. Ninety-nine patients (96%) had optimal cytoreduction, defined as residual disease ≤ 1 cm (47 patients or 48% had no residual disease). There was no statistical difference in CA 125 at diagnosis between those without residual disease and those with optimal surgery but with macroscopic disease. However, the CA 125 level before IDS was significantly lower in patients with no residual disease than that in patients with optimal but macroscopic disease, 92 U/mL compared to 233 U/mL ($P = 0.001$). Using CA 125 of ≤ 100 U/mL as a cut-off level, a significantly higher percentage of patients without residual tumors had low pre-IDS CA 125 than the group with macroscopic residual disease, 80% *vs* 63%. The authors suggested that patients with pre-IDS CA 125 ≤ 100 U/mL were likely to have successful optimal cytoreduction to no residual disease. Another study by Bland *et al*[109] evaluated and constructed 3 algorithms using CA 125, CT scan, and LPS findings in 128 AOC women after initial chemotherapy but before surgery. The authors found that failure of CA 125 to decline dramatically was significantly associated with suboptimal surgery: 89% of the patients with optimal surgery had a decline of CA 125 > 50% compared to only 57% in the suboptimal group[109]. In the same vein, a significantly higher percentage of patients with suboptimal surgery had more small-bowel mesentery disease identified from by CT scan than found in those with optimal surgical outcome, 38% *vs* 6%. Other findings which were missed in pre-operative CT scans and were found in patients with suboptimal surgery were diseases on the liver surface, small-bowel surface, large-bowel mesentery, bladder peritoneum, spleen, and diaphragm. Finally the authors proposed a predictive algorithm for identifying patients most likely to have suboptimal surgery following chemotherapy using criteria: < 50% reduction in CA 125, stable or progressive disease on CT scan, and diseases on the bladder peritoneum or liver surface identified at the time of LPS[109]. However, the number of patients in this study having either serum CA 125, CT scan, or LPS surgery before exploration was limited and further study is required to confirm these data.

In addition to tumor markers and imaging studies, a recent study by Fagotti *et al*[9] reported a role for LPS in AOC patients who had partially stable/stable disease after NACT. The authors set a predictive index score based on various features identified from staging LPS to select patients who were likely to have successful IDS (Table 4). The LPS parameters of mesentery retraction, bowel and stomach infiltration, and superficial liver metastasis were strongly associated with unresectable diseases. Using a staging LPS after serological response with NACT, the authors found the rate of inappropriate exploration was reduced from 18% to 0%. Moreover, a predictive index score > 4 could absolutely predict the probability of optimally cytoreduction at laparotomy in all patients.

Unlike the important prognostic role of the size of residual disease after PDS[2], only limited information regarding the size of residual disease after IDS is available. Most studies have used the same traditional definition of "optimal cytoreduction" in IDS as that in PDS. A recent randomized study and one retrospective study found that complete resection of all macroscopic disease at the time of IDS was the single most important independent prognostic factor in AOC[10,110].

In conclusion, standard management of advanced ovarian cancer is primary surgery followed by adjuvant chemotherapy. The aim of surgery should be a removal of all gross visible tumors because this is one of the most important prognostic factors. Prediction of surgical outcome is crucial especially when the benefit of optimal surgery and the risk of extensive surgery are equivocal. NACT followed by surgery is an alternative option with less morbidity and comparable survival outcome. IDS is another approach for patients who have suboptimal primary surgery and who have no progressive disease after induction chemotherapy. This interval surgery yields survival benefits particularly in patients who have had less extensive primary surgery or less than maximal efforts made by an expert surgeon.

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