Worldwide, ∼225 500 women are diagnosed with ovarian cancer every year and ∼140 000 women die of the disease [1]. It carries the highest mortality of all the gynecological cancers. About 70% of patients with epithelial ovarian cancer present with advanced disease, and long-term survival for these patients is <25% [2]. The treatment of patients with advanced disease requires a combination of cytoreductive surgery and chemotherapy, and the concepts of surgery for advanced ovarian cancer have evolved over the past 35 years. The concept of a primary surgical approach has also been challenged [3].

**historical evolution**

The first report to quantify the benefits of cytoreductive surgery for advanced epithelial ovarian cancer was that of Griffiths in 1975 [4]. In a single institution retrospective study of 102 patients who underwent primary cytoreductive surgery for advanced ovarian cancer, Griffiths reported improved survival if all tumor nodules >1.5 cm in diameter could be removed. A subsequent small prospective study by Griffiths confirmed these findings, whether the surgery was carried out primarily (n = 15), after neoadjuvant chemotherapy (n = 9) or at the time of recurrence (n = 4) [5]. He coined the term ‘optimal’ for a cytoreductive operation in which all tumor nodules >1.5 cm in diameter could be removed. Griffiths reported that the extent of metastatic disease was not of prognostic significance.

In a report from the University of California, Los Angeles (UCLA) in 1983, Hacker et al. demonstrated that cytoreduction to residual nodules 5 mm or less carried an even better prognosis, but also demonstrated for the first time that tumor biology had an independent prognostic significance. Within the ‘optimal’ group, patients having >1000 cc ascites or metastatic nodules >10 cm in diameter had a significantly poorer survival [6]. Most patients in this series were treated with single alkylating agent chemotherapy. The 1986 subdivision of FIGO stage III ovarian cancer into stages IIIA, B, and C, based on the diameter of the metastatic disease, was influenced by this paper.

The prognostic importance of large metastatic disease would be consistent with the Goldie Coldman hypothesis, a mathematical model which assumes that tumors have a spontaneous mutation rate, which will progressively lead to drug resistance [7]. The larger the tumor burden at the start of surgery, the more likely it is that there will already be chemoresistant cell clones present.

A further UCLA study of the significance of tumor biology was reported by Farias-Eisner et al. [8] in 1992. They analyzed 78 patients who had all been cytoreduced to a maximal residual tumor diameter of 5 mm. With the larger numbers in this second report, patients with grade 1 tumors had a significantly better survival. Analysis also revealed that patients who had no residual disease (n = 18) had a median survival of 56.5 months, compared with 30.6 months for those with moderate residual disease (n = 40) and 16.6 months for those with extensive carcinomatosis (n = 20) (P < 0.001).

In a 1992 retrospective review of the surgical reports from GOG Protocol 52 (a chemotherapy study in patients with residual disease of ≤1 cm), Hoskins et al. [9] confirmed the UCLA studies which demonstrated that the extent of metastatic disease before cytoreduction and the number of small residual nodules were of prognostic significance. They stated that ‘This study failed to prove the hypothesis that initial cytoreductive surgery would allow a patient presenting with large volume ovarian cancer to have the same chance for survival as a patient found to have small volume disease (ab initio)’.

**the importance of complete cytoreduction**

The first person to suggest that ‘complete’ rather than ‘optimal’ cytoreduction should be the objective of primary surgery for advanced ovarian cancer was Eisenkop et al. [10] in 1998. Between 1990 and 1996, his team operated on 163 consecutive patients with stage IIIC and IV epithelial ovarian cancer. All visible tumors were resected in 139 (85.3%) patients, residual nodules were ≤1 cm in 22 (13.5%), and 2 (1.2%) had bulky unresectable disease. To achieve complete resection, 85 (52.1%) had an en bloc recto-sigmoid resection, 66 (40.5%) had diaphragmatic stripping or resection, 145 (89%) had peritoneal implant ablation with the argon beam coagulator or cavitron ultrasonic aspirator, and 31 (19%) had miscellaneous operations, such as splenectomy, liver resection, or distal pancreatectomy.

Patients having complete cytoreduction had a median survival of 62.1 months, compared with 20 months for those with any residual disease (P = 0.001). In univariate analysis, age >61 years, poor performance status, largest metastasis >10 cm,
ascites >1000 ml, histological type mucinous or clear cell, extensive carcinomatosis, and any residual disease were all significantly poor survival variables, whereas in multivariate analysis, only age, ascites, residual disease, and histologic type remained significant.

In 2002, Bristow et al. [11] reported a meta-analysis of 6885 patients from 81 studies with stage III or IV ovarian cancer treated during the platinum era to evaluate the effect of maximal cytoreduction on survival. They demonstrated that each 10% increase in optimal cytoreduction was associated with a 5.5% increase in median survival. Cohorts with ≤25% maximal cytoreduction had a median survival of 22.7 months, whereas that with >75% optimal cytoreduction had a median survival of 33.9 months. No relationship was found between survival and platinum dose intensity.

The importance of complete cytoreduction was examined by Du Bois et al. [12] in a retrospective review of 3126 patients with stages IIB–IV epithelial ovarian cancer entered on to three prospective randomized trials of chemotherapy (AGO-OVAR 3, 5, and 7). Approximately one-third each fulfilled criteria for complete resection, group A (1046 patients), optimal cytoreduction, (1–10 mm), group B (975 patients), and suboptimal cytoreduction, (>10 mm), group C (1105 patients). Multivariate analysis showed improved progression-free (PFS) and overall survival (OS) for group A (P < 0.0001). The impact of optimal debulking (group B) showed a smaller prognostic impact compared with suboptimal debulking (group C) (P = 0.01). Further independent prognostic factors for OS were age, performance status, grade, FIGO stage, and histologic type (i.e., mucinous worst).

The group from the Mayo Clinic examined the relative impact of disease status, patient status, and the surgical aggressiveness on the resectability of advanced ovarian cancer [13]. They retrospectively reviewed 194 consecutive patients undergoing primary cytoreductive surgery from 1994 to 1998. Variables recorded were age, American Society of Anesthesiology (ASA) score, CA125 titer, ascites (>1000 ml), carcinomatosis, diaphragmatic involvement, mesenteric involvement, and the aggressiveness of the surgeon. Aggressive surgeons were defined as those who carried out ‘radical’ procedures in >50% of their patients. The perioperative mortality was 1.5%, and the mean follow-up was 3.5 years. In multivariate analysis, only ASA score, presence of carcinomatosis, and surgery carried out by a surgeon with a more radical attitude were independently associated with optimal residual disease (defined as <1 cm). Even in patients with carcinomatosis, optimal residual status was obtained significantly more frequently when the patient was operated on by a surgeon with a more radical attitude (75% versus 45.5%), and this translated into median survival differences of 3.5 and 2.1 years, respectively (P = 0.02).

**the role of lymphadenectomy**

In spite of suggestions from retrospective studies that systematic pelvic and para-aortic lymphadenectomy may improve survival in patients with advanced ovarian cancer [14–17], the only randomized, controlled trial to test this hypothesis failed to show any benefit in terms of OS [18]. Patients who had residual nodules ≤1 cm in the peritoneal cavity were randomized between systematic pelvic and para-aortic lymphadenectomy (n = 216) versus resection of bulky nodes only (n = 211). Both arms were well matched for clinical variables. There was a 6-month benefit in PFS (P = 0.02), but no difference in OS. Systematic lymphadenectomy increased the median operating time by 90 min, the transfusion rate by 12%, and increased the incidence of lymphocysts and lymphedema. The subgroup analysis of patients with no residual disease also showed no significant difference in OS, although this was not reported in the paper.

Du Bois et al. [15] retrospectively analyzed the data from three randomized clinical trials (AGO-OVAR 3, 5, and 7) to evaluate the role of systematic retroperitoneal lymphadenectomy in patients with advanced ovarian cancer. The three trials enrolled 3388 patients, and 1942 (57.3%) were eligible for the analysis. In patients with no gross residual disease, patients with and without lymphadenectomy had median survivals of 103 and 84 months, and 5-year survivals of 67.4% and 59.2%, respectively (P = 0.0166). For patients with residual tumor nodules up to 1 cm, the effect of lymphadenectomy barely reached significance (P = 0.0497). For patients with small residual nodules and clinically suspicious nodes, lymphadenectomy improved survival from 17% to 28% (P = 0.0038).

A recent report from Korea retrospectively reviewed 189 consecutive patients with FIGO stage IIIIC ovarian cancer who underwent primary cytoreductive surgery followed by platinum- and taxane-based chemotherapy between 2000 and 2001 [16]. Patients were classified into those who underwent systematic pelvic and para-aortic lymphadenectomy (n = 135) and those who did not (n = 54). There was a significantly better PFS and OS for patients having the lymphadenectomy in the patients with no residual disease or residual disease of ≤1 cm.

In both studies, mentioned above, lymphadenectomy was not randomized; the decision to perform lymphadenectomy was based on surgeon preference. More aggressive surgeons were more likely to perform lymphadenectomies, but were also more likely to perform more radical upper abdominal surgery, so this may well have biased the results.

**thoracic involvement**

The conventional approach to the evaluation of thoracic disease in ovarian cancer has been chest X-ray or computed tomography (CT) of the chest, but the ability of these modalities to properly determine the extent of pleural and supradiaphragmatic disease has been questioned.

The first person to undertake thoracoscopy to determine the extent of intrathoracic disease was Eisenkop [19]. He also explored the feasibility of intrathoracic cytoreduction. He used mainly a transdiaphragmatic approach, after observing a significant increase in operating time associated with thoracoscopy through the chest wall. Small pleural implants were ablated with the Argon Beam Coagulator, whereas larger implants were excised with long Metzenbaum scissors and the bases then ablated. Among 24 patients with stage IV disease, 11 (45.8%) had no macroscopic intrathoracic disease, 10 (41.7%) had implant ablation/excision or nodal excision, and 3 (12.5%) had unresectable disease. The estimated 5-year survival...
for patients with stage IV disease was 42%. There was a significantly improved median and 5-year survival compared with matched historical controls ($P = 0.05$). He concluded that thoracoscopy improved the ability to achieve complete cytoreduction in some cases, and allowed modification of the intraabdominal cytoreduction in cases with unresectable intrathoracic disease.

Others have subsequently confirmed the ability of video-assisted thoracic surgery (VATS) to improve the assessment of supradiaphragmatic disease. In 2004, Chi et al. [20] reported the use of VATS in 12 patients with moderate-to-large pleural effusions. The thoracoscope was introduced via the chest wall in all cases, biopsies taken, and a chest drain placed. The median operating time was 31 min, and there were no complications attributable to the procedure. Nodules >1 cm were noted in four patients (33%) and <1 cm in 2 (17%). Of the six patients with no gross pleural tumor, the pleural fluid was positive for malignant cells in two (17%) cases. The authors felt that VATS allowed better delineation of the extent of disease, treatment of the effusion, and possibly triage of patients between intrathoracic cytoreduction or neoadjuvant chemotherapy.

A recent paper from Freiburg, Germany, confirmed the ability of VATS to improve the accuracy of FIGO staging, and to assess operability more reliably than through the use of imaging techniques alone [21]. The median operating time for their 17 patients was again acceptable (median 46 min), and there was no perioperative morbidity.

A recent paper evaluated the role of $^{18}$F-fluorodeoxyglucose positron emission tomography (FDG PET)/CT in the staging of patients with advanced ovarian cancer [22]. In 20 of 30 (67%) patients, FDG PET/CT detected supradiaphragmatic lymph node metastasis, compared with 10 of 30 (33%) for the conventional CT scan. The location of the positive nodes was parasternal in 14 (70%) patients, cardiophrenic in 14 (70%), other mediastinal in 8 (40%), axillary in 6 (30%), and subclavian in 1 (5%). The axillary metastases were confirmed in all three patients who underwent fine-needle aspiration cytology. All patients with supradiaphragmatic lymph node metastases had significantly more ascites ($P < 0.01$), and more abdominal carcinomatosis ($P < 0.03$) on preoperative FDG PET/CT, so were a poor prognosis group. The authors felt that the clinical relevance of their findings was currently unclear, and that any change in treatment strategies should await further studies.

**The use of neoadjuvant chemotherapy**

For the past decade, most of the debate has revolved around the indications for neoadjuvant chemotherapy for patients with advanced ovarian cancer.

In 2006, Bristow and Chi [23] published a meta-analysis of 22 cohorts of patients with stages III and IV ovarian cancer (835 patients) identified from articles in Medline (1989–2005). The median OS for the group was 24.5 months. They reported that each 10% increase in maximal cytoreduction was associated with a 1.9-month increase in median survival ($P = 0.027$). Each incremental increase in chemotherapy cycles was associated with a decrease in median survival time of 4.1 months ($P = 0.046$). They concluded that neoadjuvant chemotherapy was associated with inferior OS compared with primary surgery.

This would be consistent with the fractional cell kill hypothesis of Skipper, which assumes that a constant proportion, rather than a constant number, of cells are killed with each cycle of chemotherapy [24]. The larger the tumor burden at the start of chemotherapy, the more cycles that would be required to eradicate the tumor, and the greater likelihood of spontaneous mutation to drug resistance [7].

A subsequent meta-analysis from South Korea was unable to confirm that the number of cycles of neoadjuvant chemotherapy influenced survival ($P = 0.701$), and they questioned the statistical methods used in the Bristow study [25]. They reported that neoadjuvant chemotherapy was associated with an increased rate of optimal cytoreduction, but the latter did not translate into improved survival.

Both these conclusions could have been predicted. If a patient has chemosensitive disease, small tumor nodules, such as those on the diaphragm and bowel, will completely disappear after three cycles of chemotherapy. This will commonly leave only large volume disease to be resected, such as in the ovaries and omentum, and this can usually be achieved much more readily than resection of disseminated carcinomatosis. Hence, complete resection of all macroscopic disease after neoadjuvant chemotherapy has a very different significance than complete cytoreduction at primary surgery.

In 2008, Vergote et al. presented the results of a randomized EORTC–NCIC study of primary debulking surgery (PDS) versus three cycles of neoadjuvant chemotherapy followed by interval debulking surgery in patients with stages IIIC–IV ovarian, fallopian tube and peritoneal cancer at the 2008 meeting of the International Gynecologic Cancer Society in Bangkok. The results were published in 2010 [3]. There were 718 patients enrolled and 670 were randomized. Optimal cytoreduction (largest residual $\leq 1$ cm) occurred in 41.6% of patients having primary cytoreduction, and 80.6% of patients having neoadjuvant chemotherapy. Perioperative morbidity and mortality tended to be higher in the group having primary surgery, but OS and PFS were similar in both groups. The median OS was 29 months after primary surgery and 30 months after neoadjuvant chemotherapy, and the median PFS was 12 months in each group. Complete resection of all macroscopic disease was the strongest independent predictor of OS in both groups.

This study has been criticized by the German and Austrian Gynecologic Oncology Groups [26]. The major points of criticism were as follows: (i) the study required patients to have metastatic disease at least 2 cm in diameter outside the true pelvis, so patients with stage IIIC disease on the basis of positive retroperitoneal nodes, with or without small extrapelvic metastases, were excluded. They suggested that this selection bias was reflected in the very low median survivals: 29 months compared with 43.3 months in the AGO-OVAR-3 study and 49 months in AGO-OVAR 9, (ii) a variety of chemotherapy regimens were allowed, but 72.3% of patients in the primary surgery arm received platinum and a taxene, compared with 84.7% in the neoadjuvant chemotherapy arm, (iii) the surgical outcome was heterogeneous, with complete resection rates after primary surgery ranging from 3.9% in the Netherlands to 62.9% in Belgium. They felt that there was a potential bias with respect to the different surgical effort in different countries. This would
be consistent with data from the Mayo Clinic on the importance of the aggressiveness of the surgeon [14]; (iv) there was also heterogeneity with respect to outcome for different postoperative residuals. There was an advantage for primary surgery in patients with no residual disease (median survival of 45 versus 38 months) or residual disease up to 1 cm (32 versus 27 months). Only the cohort with residual disease >1 cm showed no difference between the two arms, and this was the largest cohort in the primary surgical arm. (v) in subgroup analysis, patients with metastatic disease up to 5 cm had a better survival after primary surgery (P < 0.05).

The group at Memorial Sloan-Kettering Cancer Center in New York identified all patients undergoing primary treatment of advanced ovarian, tubal, or peritoneal cancer at their institution between September 1998 and December 2006 [27]. This was the same time period in which the EORTC–NCIC trial was conducted, and the same inclusion and exclusion criteria were used. Of 316 eligible patients, 285 (90%) underwent PDS and 31 (10%) received neoadjuvant chemotherapy. Of the 285 patients, 93 (33%) underwent extensive upper abdominal procedures. No residual disease was attained in 24% of patients, compared with 19.4% in the EORTC–NCIC study, whereas residual disease of ≤1 cm (optimal cytoreduction) was attained in 47% of patients (versus 22%). Eight (2.5%) patients died within 28 days of surgery. The median PFS and OS were 17 and 30 months. The patients were all 65 years or older and were identified from the Surveillance, Epidemiology, and End Results (SEER)-Medicare database. Of these women, 479 (12%) failed to receive chemotherapy, 2527 (72%) initiated treatment within 6 weeks of surgery, 838 (24%) within 6–12 weeks, and 147 (4%) >12 weeks after surgery. In a multivariate model, older patients, those with comorbidities, mucinous tumors, and stage IV neoplasms were more likely not to receive chemotherapy (P < 0.05). Extended cytoreduction and the occurrence of postoperative complications were not associated with omission of chemotherapy, but were associated with delay of chemotherapy. The occurrence of more than two perioperative complications and initiation of chemotherapy >12 weeks after surgery were associated with decreased survival.

Another population-based mortality study of 5475 patients with stages III–IV ovarian cancer undergoing primary cytoreductive surgery reported a 30-day mortality of 8.2% [31]. The patients were all 65 years or older and were classified from the SEER-Medicare database between 1995 and 2005. Women admitted electively had a significantly lower mortality rate than those admitted emergently (5.6% versus 20.1%; P < 0.001). Increasing age, stage, and comorbidity score were all associated with an increased 30-day mortality (P < 0.05).

In an analysis of perioperative morbidity and mortality from 564 consecutive patients from Mayo Clinic, Johns Hopkins University, and Memorial Sloan-Kettering Cancer Center undergoing primary cytoreductive surgery for advanced ovarian cancer, Aletti et al. [32] reported that the strongest predictors of 30-day mortality were preoperative serum albumin of <3.5 g/dl (P < 0.001), ASA score of 3 or 4 (P = 0.008), and complexity of surgery (P < 0.001). Age (P = 0.002) and ASA (P = 0.001) independently predicted mortality.

**Postoperative morbidity and mortality**

The Nationwide Inpatient Sample was used by Wright et al. [29] to identify 28 651 women who underwent surgery for ovarian cancer in the USA from 1998 to 2007. The postoperative complication rate increased with age from 17.1% in those under 50 years, to 29.7% in those 70–79, and 31.5% in those 80 or older (P < 0.05). The number of extended procedures was also a predictor of morbidity, with complication rates increasing from 20.4% for patients having no extended procedures to 34% for those having one, and 44% for those having two or more (P < 0.0001). Extended procedures included splenectomy, small or large bowel resection, and resection of liver, diaphragm, or bladder. In multivariate analysis, age, comorbidity, and the number of procedures carried out were the strongest predictors of outcome. Perioperative morbidity rates increased from 0.5% in patients under 50 years to 4.1% in patients over 80. Other factors influencing perioperative morbidity and mortality were race, treatment in a teaching hospital, number of comorbidities, and ovarian cancer volume of the treating institution.

The same authors examined the effect of radical cytoreductive surgery and its associated perioperative morbidity on the omission and delay of chemotherapy [30]. They identified 3991 women aged 65 years and older from the Surveillance, Epidemiology, and End Results (SEER)-Medicare database. Of these women, 479 (12%) failed to receive chemotherapy, 2527 (72%) initiated treatment within 6 weeks of surgery, 838 (24%) within 6–12 weeks, and 147 (4%) >12 weeks after surgery. In a multivariate model, older patients, those with comorbidities, mucinous tumors, and stage IV neoplasms were more likely not to receive chemotherapy (P < 0.05). Extended cytoreduction and the occurrence of postoperative complications were not associated with omission of chemotherapy, but were associated with delay of chemotherapy. The occurrence of more than two perioperative complications and initiation of chemotherapy >12 weeks after surgery were associated with decreased survival.

**Interpretation of current literature on cytoreduction for advanced epithelial ovarian cancer**

Patients with advanced ovarian cancer require a combination of cytoreductive surgery and platinum-based chemotherapy, and there is a clear survival benefit in all contemporary studies for complete resection of all macroscopic disease [3, 10, 12–14]. This should now be considered the gold standard for cytoreduction. Optimal cytoreduction (maximal residual tumor diameter up to 1 cm) portends a significant, though smaller survival advantage [13, 28]. Resection of a large pelvic tumor...
and a large omental mass may offer quality-of-life advantages to the patient, but will provide no survival advantage if there is larger residual disease.

The EORTC–NCIC study of neoadjuvant chemotherapy versus primary surgery demonstrated that neoadjuvant chemotherapy does not improve survival, in spite of increasing the incidence of complete tumor resection [3]. This is not surprising, as small tumor nodules on the peritoneal surfaces will disappear after neoadjuvant chemotherapy if the disease is chemosensitive, so the two patient groups are not comparable.

Recent literature makes it clear that surgery must be carried out by surgical teams with the necessary expertise and commitment to undertake radical resection of disease from both the pelvis and the upper abdomen [32], and this was not always the case in the EORTC–NCIC study. The surgery must also be carried out with acceptably low morbidity, so that there is no significant delay in initiating chemotherapy [29, 30]. This means that surgery for patients with advanced ovarian cancer should be limited to centers with the necessary infrastructure, surgical and medical expertise, and volume of referrals [33].

The value of resecting disease above the diaphragm is yet to be proven, but better understanding of the extent of supradiaphragmatic disease may allow modification of the ablative resection, or the use of neoadjuvant chemotherapy [21, 22]. There is no proven benefit to systematic pelvic and para-aortic lymphadenectomy [19], but another randomized trial would be justified in patients with no macroscopic intraperitoneal disease [16].

The EORTC–NCIC study [3] demonstrated less morbidity in the neoadjuvant chemotherapy arm, and this is consistent with the author’s experience. However, patients who are likely to experience postoperative morbidity can usually be predicted preoperatively. They are older patients (75 or older), those with comorbidities, and patients with a poor nutritional (low albumin levels), and/or performance status [29, 34]. Such patients often have a large volume of ascites or a moderate-to-large pleural effusion, and if they have chemosensitive tumors, their effusions will dry up after two or three cycles. Their nutritional and performance status will then improve significantly, and they will be in a much fitter state to undergo major surgery.

Another advantage of neoadjuvant chemotherapy in patients with a poor performance and/or nutritional status is that it allows chemosensitivity to be tested. Patients who have chemoresistant disease can be spared the physical and psychological trauma of major surgery. A few of these patients will have non-ovarian primaries, e.g. metastatic pancreatic cancer, and would not benefit from the surgery.

In this author’s experience, neoadjuvant chemotherapy often makes the surgery more difficult, because of the inflammatory reaction and fibrosis around the tumor, a fact acknowledged by the authors of the paper [3]. It frequently eliminates small nodules from the diaphragm or other peritoneal surfaces, but rarely obviates the need for recto-sigmoid resection in patients with tumor in the Pouch of Douglas invading the bowel or its mesentery.

In view of the above, it is the author’s view that the gold standard for patients with advanced ovarian, fallopian tube, or peritoneal cancer should be primary cytoreductive surgery, with the aim of complete tumor resection. Neoadjuvant chemotherapy and interval debulking should be reserved for a subgroup of patients with significant comorbidities, particularly if they are elderly, or with a poor performance and/or nutritional status. These will usually be patients who have large volume ascites or a moderate-to-large pleural effusion.

**disclosure**

The author has declared no conflicts of interest.

**references**


27. Chi DS, Musa F, Dao F et al. An analysis of patients with bulky advanced stage ovarian, tubal, or peritoneal carcinoma treated with primary debulking surgery (PDS) during an identical time period as the randomized EORTC-NCIC trial of PDS vs neoadjuvant chemotherapy (NACT). Gynecol Oncol 2012; 124: 10–14.


