Royal College of Obstetricians & Gynaecologists

Optimum Surgery in Advanced-stage Ovarian Cancer

Scientific Impact Paper No. 25

June 2011

Optimum Surgery in Advanced-stage Ovarian Cancer

1. Introduction

In advanced-stage ovarian cancer, the evidence base from randomised controlled trials on the role of extensive radical surgery to improve survival is limited.[1–4] Different interpretations of existing trials have led to variation in surgical practice, not only internationally but also within the UK. A recent randomised controlled trial of 632 women focused on the timing of surgery in advanced-stage ovarian cancer and indicated that there was no detriment to survival in performing primary surgery after three cycles of (neoadjuvant) chemotherapy compared with primary surgery performed before the commencement of any chemotherapy.[5] Perioperative morbidity was shown to be less after neoadjuvant chemotherapy. Other trials have shown conflicting results when further surgery was performed as an interval procedure after suboptimal cytoreduction at primary surgery.[6,7] Further robust trials are therefore needed to clarify the role of surgery and optimise the timing and extent of surgery in women with advanced-stage ovarian cancer.

2. Current surgical practice

As stated above, the absence of robust and consistent evidence has led to considerable variation in surgical practice. For example, in the study by Vergote et al.,[5] the range of complete cytoreduction rates at primary laparotomy among the various recruiting countries was between 3.9% and 62.9%. Six of the seven recruiting countries, including the UK, had a complete cytoreduction rate at primary laparotomy of less than 12%. Data from the SCOTROC prospective randomised chemotherapy trial also showed that cytoreduction rates in the UK were significantly lower than in other countries.[8] In addition, there is wide variation in practice in the timing of surgery. Based on existing evidence,[5,6] some centres favour the use of neoadjuvant chemotherapy over upfront surgery. It is clear that differences in surgical practice are substantial, reflecting a wide divergence in professional opinion on the value of primary surgery in the management of advanced-stage ovarian cancer. The need for carefully designed trials to address this is clear,[9] but there are major difficulties in designing such studies.

3. Supporting evidence for surgical cytoreduction

A meta-analysis by Bristow et al.[1] suggested that every 10% improvement in maximal cytoreduction resulted in an incremental improvement in overall survival of 5%. A retrospective cohort study by Aletti et al.[10] of 194 cases at the Mayo Clinic showed a significant survival advantage for women operated on by surgeons who frequently performed ultra-radical surgery compared with women operated on by surgeons who were less likely to perform ultra-radical surgery (44% compared with 17%, $P < 0.001$). These procedures were all performed within a specified time period, under the same conditions and with the same resources available. The difference in optimal cytoreduction (less than 1 cm of residual disease) in the two groups was 84.5% and 51%, respectively. When performing multivariate analysis on the subgroup of women with stage IIIC ovarian cancer, who had equally extensive carcinomatosis and good performance status, the significant results were maintained for those undergoing ultra-radical surgery, suggesting that the better survival results for this group were not confounded by the woman's performance status or the extent of the disease.

Wimberger et al.[11] performed a comparison of 761 women operated on in Germany either at centres that had demonstrated the capability of performing ultra-radical surgery (type A) or at centres that had not demonstrated such capability (type B). The women were recruited to a randomised controlled trial of cisplatin/taxol versus carboplatin/taxol. Of 136 centres, 70% were categorised as type A. The authors identified a significant improvement in survival in women managed in centres more likely to perform ultra-radical surgery, despite a greater proportion of cases with worse morbidity in this group. After adjusting for patient and tumour characteristics, the hazard ratio for overall survival at type A centres was 0.77 (95% CI 0.63–0.94, $P = 0.012$). The difference in optimal cytoreduction (less than 1 cm residual disease) between the two groups was 65.8% and 54.2%, respectively. There were no significant differences in treatment-related morbidity between the two groups. In this study, type B centres carried out total abdominal hysterectomy with bilateral salpingo-oopherectomy and omentectomy, whereas type A centres were able to carry out other necessary additional procedures, in particular pelvic and/or para-aortic lymphadenectomy and peritoneal stripping.

The results of both of these studies have their limitations owing to their retrospective design and lack of well-defined selection criteria. Women undergoing ultra-radical surgery may have been selected more carefully for surgery compared with the group not receiving this type of surgery. These limitations can be addressed only by a prospective randomised study.

4. Defining radicality of surgery

By appraising the statistics presented in the article by Vergote et al.,[5] it can be seen that standard surgery currently achieves suboptimal cytoreduction (that is, visible residual disease) in over 80% of cases. The procedures commonly performed to achieve this outcome were total abdominal hysterectomy, bilateral salpingo-oophorectomy and infra-colic omentectomy, with only a small proportion of cases receiving additional procedures.

If we class as standard surgery total abdominal hysterectomy, bilateral salpingo-oopherectomy, omentectomy and a certain percentage (cumulative) of additional procedures, greater surgery (the investigation arm) would comprise total abdominal hysterectomy, bilateral salpingo-oopherectomy, omentectomy and a higher percentage (cumulative) of additional procedures, accepting that for all recruiting surgeons their individual figures for the two groups will be different from those of other surgeons, but always higher in the investigation arm. As a result of the greater number of additional procedures performed in the investigation arm, one could expect a greater proportion of cases with less residual disease in this group and, potentially, significant benefits in outcome survival.

5. The definitive trial

A trial of chemotherapy and surgery versus chemotherapy alone should determine the true value and place of surgery in the management of advanced disease. However, such a study raises ethical concerns as one group would not receive an intervention that has been shown from repeated retrospective and prospective studies to potentially have an impact on survival outcome. The randomised controlled trial by van der Burg et al.[6] determined that a maximal attempt at cytoreduction performed as an interval debulking procedure improved survival outcome, but it is possible that the weight of evidence is affected by publication bias and suboptimal methodology.

It is unclear whether optimal surgery in such a study should include procedures such as supracolic omentectomy, bowel surgery, peritoneal stripping, splenectomy with excision of tail of pancreas, diaphragmatic resection and liver resection in addition to total abdominal hysterectomy, bilateral salpingo-oopherectomy and infra-colic omentectomy.[12] Some may also consider carrying out systematic pelvic/para-aortic lymphadenectomy in these women; although a randomised controlled trial of this additional procedure showed an improvement in disease-free survival, there was no benefit in overall survival.[13]

Surgeons would need to be in equipoise to agree to randomise women to each treatment. In addition, there are significant issues regarding the expertise needed to carry out proposed radical and ultra-radical surgery, with potentially major variations in surgical morbidity between one surgeon/centre and another.

There are other challenges with such a study. There is no clear evidence on the accuracy of determining disease before surgery and therefore eligibility for recruitment. It is also unclear whether randomisation should be performed preoperatively based on the preoperative investigations or intraoperatively based on the surgical findings.

In addition, there is uncertainty whether all women with stage IIIC ovarian cancer have the same prognosis or if there are different degrees of abdominoperitoneal spread which impact on survival.[14] Optimal cytoreduction needs to be defined clearly. The Gynaecological Cancer Inter-Group is proposing to redefine optimal cytoreduction as no visible disease. If this is the way forward, the current definition of less than 1 cm residual disease would then be classed as 'suboptimal cytoreduction' or kept as a separate category. The extent of residual disease also needs to be measured, and whether this is performed by the operating surgeon, radiologically or both[15] remains debatable. If, after completion of the study, it is seen that the complete cytoreduction rate in the surgical group was less than 10% overall, it will be difficult to make any meaningful conclusions on the true value of surgery, and it is unlikely that these results would be sufficiently credible to convince the surgical community to change their practice.

Of the ethical issues, proponents of surgery will argue that it would be unethical to perform a randomised controlled trial to 'show that parachutes save lives'. They might agree, however, that a randomised controlled trial would be useful if it was to show that 'one parachute was better than another'. Comparing one form of surgery with another form of surgery might therefore meet the requirement of clinical equipoise and was the principle behind the study by Vergote et al.[5] Comparing standard surgery with lesser surgery would incur the same difficulties as a study of 'no surgery', but it might be possible and appropriate to conduct a study of standard surgery versus greater surgery. This would require clear definition of these terms.[16]

6. Additional surgical factors

Additional training may be necessary to perform these radical/ultra-radical procedures. Chi et al.[17] showed that the acquisition of these skills required a paradigm shift in the surgeon's approach to surgery and that the additional procedures could be learned over a relatively short period, resulting in dramatic increases in optimal/complete cytoreduction rates with no significant increases in perioperative morbidity. Similarly, Naik et al.[18] achieved optimal cytoreduction rates of up to 88% at primary laparotomy in advanced-stage ovarian cancer by gynaecological oncologists working as a team, without any increase in morbidity.

A case series of radical/ultra-radical procedures shows that there are also additional demands on surgical time and perioperative support,[19] which have to be considered against the potential benefits in survival. Cost-effectiveness would need to be an important secondary outcome measure of any proposed trial, in addition to quality of life assessments and patient-reported outcome measures. These important parameters unfortunately have been rarely considered in publications and their importance cannot be overestimated.

7. Concluding points

A randomised controlled trial of chemotherapy and surgery versus chemotherapy alone in the management of women with recurrent ovarian cancer will be starting shortly in the UK. The DESKTOP III study, developed by the Arbeitsgemeinschaft Gynaekologische Onkologie Ovarian Cancer Study Group in Germany, will determine whether there is a survival advantage to the addition of surgery over and above the use of chemotherapy alone in the treatment of recurrent disease. If this study is able to show a survival advantage of surgery in the recurrent setting, where surgery is currently not considered part of standard treatment, it may have some implications for the value of primary surgery in women with advanced-stage ovarian cancer at primary presentation.

However, until the definitive randomised controlled trial is performed, opinions will remain divided. The study by Vergote et al.[5] demonstrated that robust surgical studies can be completed through collaborative networks. The surgical community should be striving to deliver optimal care from continual thoughtful evaluation of their individual practices. Further randomised controlled trials are the only way forward to define the true role of optimal cytoreductive surgery; this should be the ambition of the gynaecological oncology community.

8. Opinion

The list of unanswered questions on the role and true value of optimum surgery in the management of advanced-stage ovarian cancer will be determined only by randomised controlled trials that are designed in a pragmatic fashion. Both proponents and opponents of surgery will need to agree on design and patient selection for these trials. Until then, women will need to be selected to determine whether they are best suited to be managed by primary surgery or by neoadjuvant chemotherapy. Irrespective of when the surgical procedure is performed, a maximal attempt at complete/optimal cytoreduction should be made. The skills to perform these procedures can be acquired with collaborative working, training and support. Gynaecological oncologists in the UK should be encouraged to design randomised controlled trials to address some of the uncertainties discussed and aim to support recruitment to suitable international studies such as the DESKTOP III study.[20] Changing surgical practice will also have important implications for training and the use of available resources.

References

1. Bristow RE, Tomacruz RS, Armstrong DK, Trimble EL, Montz FJ. Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. *J Clin Oncol* 2002;20:1248–59.
2. Hunter RW, Alexander ND, Soutter WP. Meta-analysis of surgery in advanced ovarian carcinoma: is maximal cytoreductive surgery an independent determinant of prognosis? *Am J Obstet Gynecol* 1992;166:504–11.
3. Hoskins WJ, Bundy BN, Thigpen JT, Omura GA. The influence of cytoreductive surgery on recurence-free interval and survival in small-volume stage III epithelial ovarian cancer: A Gynecologic Oncology Group Study. *Gynecol Oncol* 1992;47:159–66.
4. Eisenkop SM, Spirtos NM. What are the current surgical objectives, strategies and technical capabilities of gynaecologic oncologists treating advanced epithelial ovarian cancer? Gynecol *Oncol* 2001;82:489–97.
5. Vergote I, Tropé CG, Amant F, Kristensen GB, Ehlen T, Johnson N, et al.; European Organization for Research and Treatment of Cancer¬–Gynaecological Cancer Group; NCIC Clinical Trials Group. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. *N Engl J Med* 2010;363:943–53.
6. van der Burg ME, van Lent M, Buyse M, Kobierska A, Colombo N, Favalli G, et al. The effect of debulking surgery after induction chemotherapy on the prognosis in advanced epithelial ovarian cancer: Gynecologic Cancer Cooperative Group of the European Organization for Research and Treatment of Cancer. *N Engl J Med* 1995;332:629–34.
7. Rose PG, Nerenstone S, Brady MF, Clarke-Pearson D, Olt G, Rubin SC, et al.; Gynecologic Oncology Group. Secondary surgical cytoreduction for advanced ovarian carcinoma. *N Engl J Med* 2004;351:2489–97.
8. Crawford SC, Vasey PA, Paul J, Hay A, Davis JA, Kaye SB. Does aggressive surgery only benefit patients with less advanced ovarian cancer? Results from an international comparison within the SCOTROC-1 Trial. *J Clin Oncol* 2005;23:8802–11.
9. Markman M. Concept of optimal surgical cytoreduction in advanced ovarian cancer: a brief critique and a call for action. *J Clin Oncol* 2007;25:4168–70.
10. Aletti GD, Dowdy SC, Gostout BS, Jones MB, Stanhope CR, Wilson TO, et al. Aggressive surgical effort and improved survival in advanced-stage ovarian cancer. *Obstet Gynecol* 2006;107:77–85.
11. Wimberger P, Lehmann N, Kimmig R, Burges A, Meier W, Du Bois A; Arbeitsgemeinschaft Gynaekologische Onkologie Ovarian Cancer Study Group. Prognostic factors for complete debulking in advanced ovarian cancer and its impact on survival. An exploratory analysis of a prospectively randomized phase III study of the Arbeitsgemeinschaft Gynaekologische Onkologie Ovarian Cancer Study Group (AGO-OVAR). *Gynecol Oncol* 2007;106:69–74.

12. Eisenkop SM, Spirtos NM. Procedures required to accomplish complete cytoreduction of ovarian cancer: is there a correlation with "biological aggressiveness" and survival? *Gynecol Oncol* 2001;82:435–41.
13. Panici PB, Maggioni A, Hacker N, Landoni F, Ackermann S, Campagnutta E, et al. Systematic aortic and pelvic lymphadenectomy versus resection of bulky nodes only in optimally debulked advanced ovarian cancer: a randomized clinical trial. *J Natl Cancer Inst* 2005;97:560–6.
14. Eisenkop SM, Spirtos NM, Friedman RL, Lin WC, Pisani AL, Perticucci S. Relative influences of tumour volume before surgery and the cytoreductive outcome on survival for patients with advanced ovarian cancer: a prospective study. *Gynecol Oncol* 2003;90:390–6.
15. Chi DS, Ramirez PT, Teitcher JB, Mironov S, Sarasohn DM, Iyer RB, et al. Prospective study of the correlation between postoperative computed tomography scan and primary surgeon assessment in patients with advanced ovarian, tubal, and peritoneal carcinoma reported to have undergone primary surgical cytoreduction to residual disease 1 cm or less. *J Clin Oncol* 2007;25:4946–51.
16. Pomel C, Dauplat J. [Management of malignant epithelial tumors of the ovary]. *J Chir (Paris)* 2004;141:277–84. Article in French.
17. Chi DS, Eisenhauer EL, Zivanovic O, Sonoda Y, Abu-Rustum NR, Levine DA, et al. Improved progression-free and overall survival in advanced ovarian cancer as a result of a change in surgical paradigm. *Gynecol Oncol* 2009;114:26–31.
18. Naik R, Galaal K, Alagoda B, Katory M, Mercer-Jones M, Farrel R. Surgical training in gastrointestinal procedures within a UK gynaecological oncology subspecialty programme. *BJOG* 2010;117:26–31.
19. Bristow RE, Palis BE, Chi DS, Cliby WA. The National Cancer Database report on advanced-stage epithelial ovarian cancer: impact of hospital surgical case volume on overall survival and surgical treatment paradigm. *Gynecol Oncol* 2010;118:262–7.
20. [http://www.clinicaltrials.gov/ct2/show/NCT01166737?term=DESKTOP+III&rank=1].

This Scientific Impact Paper was produced on behalf of the Royal College of Obstetricians and Gynaecologists by:
Mr R Naik FRCOG, Newcastle-upon-Tyne, Mr GAJ McIndoe MRCOG, London, Mr TAJ Mould FRCOG, London and Mrs SS Sundar MRCOG, Birmingham

and peer reviewed by: Mr DPJ Barton MRCOG, London; Dr A Clamp, Department of Medical Oncology, The Christie NHS Trust, Manchester; Mr JJO Herod MRCOG, Liverpool; Professor DM Luesley FRCOG, Birmingham; Dr NA Siddiqui FRCOG, Glasgow; Dr K Reynolds, Barts and the London NHS Trust; British Gynaecological Cancer Society; RCOG Consumers' Forum.

Conflicts of interest: none declared.

The Scientific Advisory Committee lead reviewers were:
Dr S Ghaem-Maghami MRCOG, London and Dr PL Martin-Hirsch FRCOG, Preston.

The final version is the responsibility of the Scientific Advisory Committee of the RCOG.

The review process will commence in 2014, unless otherwise indicated.

