We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800
Open access books available

122,000
International authors and editors

135M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS BOOK CITATION INDEX INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Chapter 11

Surgical Management of Ovarian Cancer

Rasiah Bharathan

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.80891

Abstract

Advanced ovarian cancer remains a disease with a poor prognosis. Surgical therapy remains the cornerstone of treatment with essential contribution from chemotherapy. The combination therapy continues to offer the best treatment strategy. Complete cytoreductive surgery is still the most important prognostic marker. The role of primary debulking surgery in advanced ovarian cancer remains under investigation through high quality rigorous clinical trials. The current evidence regarding primary versus interval debulking surgery has drawn much criticism regarding patient recruitment and quality of surgery, both of which are key pillars in achieving complete cytoreduction. It is expected that greater centralisation and development of 'ovarian cancer surgery teams' will further enhance clinical outcomes.

Keywords: ovarian cancer, cytoreductive surgery, chemotherapy, complications, survival

1. Introduction

The surgical management of ovarian cancer has continued to evolve, particularly over the past 25 years.

The principles of cytoreductive surgery have been applied to not only the pelvic cavity but also within the abdominal and thoracic cavity. The 5 year survival for this cohort of patients has not significantly changed in the past 40 years. Presently clinical trials are examining the role of effective cytoreductive surgery (CRS) and combination chemotherapy (including anti-angiogenesis inhibitors, PARP inhibitors and immunotherapy) in optimising therapy. These are likely to yield encouraging results in the next decade or two.

Imaging, role of lymphadenectomy and the management of recurrent ovarian cancer are discussed elsewhere in this book. This chapter will describe the rationale and outcomes associated with first line (either primary or interval) surgery for ovarian, tubal or primary

peritoneal cancer. A technical description of the operative steps and intra-peritoneal chemotherapy are outside the scope of this chapter.

2. Peritoneal redistribution theory and carcinomatosis

Malignant spread of intraperitoneal tumours can occur via, local contiguous growth, non-contiguous spread along mesenteric planes, haematogenous, lymphatic or transcoelomic routes. Unlike the other routes, the transcoelomic pathway offers a rapid step change in facilitating metastasis form multiple sites from within the abdomen. The parietal peritoneum has both secretatory and absorptive functions. The omentum has an absorptive function. This has been exploited in fashioning omental flaps to minimise incidence of inguinal lymphocyst after lymphadenectomy or pelvic collection after exenteration.

The dynamics of peritoneal fluid is driven by secretion/adsorption by the peritoneum (in particular right diaphragmatic peritoneum), recesses formed by the peritoneal reflections, omental filtering, movement of diaphragm, negative pressure in the subdiaphragmatic region, motility of viscera on mesentry and the resultant fluctuation in pressure differential within the peritoneal cavity.

The 'redistribution phenomenon' was described by Sugarbaker in relation to pseudomyxoma peritonei [1]. In this process free floating malignant cells and other debris utilise the movement of peritoneal fluid (and the ascites produced) to become redistributed throughout the peritoneal cavity. This includes the lesser sac. The absorption and filtering of the peritoneal fluid by the greater and lesser omentum can result in debris and cells, including malignant cells, becoming adherent to the omentum. This may in time result in 'omental cake' noted in advanced ovarian cancer. Another major notable site of fluid absorption and disease conglomeration is the right hemidiaphragm. Gravitational distribution explains the deposits in the Pouch of Douglas, paracolic gutters and subhepatic recesses. The mobile organs such as small bowel are spared of deposits, early in the disease, whereas fixed retroperitoneal structures such as ascending/descending colon and gastric pylorus may be affected. This would necessitate resection of the organs.

3. Evolution of the concept of cytoreductive surgery

As early as in 1934, Meigs described that 'removal of as much tumour as possible' was beneficial for survival [2]. In 1968 the British gynaecological surgeon Hudson described a pioneering technique for the resection of ovarian cancer from the pelvis [3]. Although there have been modifications, the principles have remained the same and his procedure is recognised as the 'radical oophorectomy'. This was an important step in CRS. In fact it was the seminal work of Griffith's published in 1975 which demonstrated that CRS associated with smaller residual disease, can be linked to better survival in advanced ovarian cancer [4].

Benefits of CRS include removal of poorly vascularised tissues (removing the pharmacological sanctuary) and excising the chemoresistant clones. Therefore the resulting absent or minimal disease will have more favourable cell kinetics with regard to chemosensitivity [5].

As the concept of CRS became more widely embraced, the application became more aggressive. Disease on the diaphragm, large bowel, spleen or distal pancreas might have been considered unresectable are now readily resected. Patient selection for these ultraradical procedures is important. This was a concern for the doubters as it may be associated with greater risk of morbidity, delay in receiving chemotherapy as well as significant impact on the quality of life (QOL) [6–8]. Indeed it was felt that perhaps only those with smaller volume and earlier stage disease would benefit from aggressive CRS [5, 9]. However a structured approach to quality improvement through enhanced skills, team structure and commitment to CRS has been shown to improve extent of cytoreduction and hence overall median survival [10–12].

In an important meta-analysis, Bristow demonstrated that greater the volume reduction, greater the survival outcome [13]. In fact they revealed that for every 10% increase in nil residual disease, overall survival increased by 5.5% [13]. Similarly in a more recent meta-analysis of largely newer data in the platinum-taxane era, Chang et al. demonstrated that with each 10% increase in complete cytoreduction, the median overall survival improved by 2.3 months [14].

Three limitations to ultra-radical debulking surgery remain absence of grade A evidence confirming that radical surgery is more efficacious than standard surgery, morbidity/mortality associated with radical CRS and surgery in non-expert centres will only yield nil residual disease in a relatively small proportion of patients [15]. The first two arguments are unlikely to be resolved but one can certainly use big data to resolve treatment pathways for patients with advanced disease.

4. Management of early stage ovarian cancer

In early stage ovarian cancer, the disease is confined to the ovaries or the upper genital tract. Approximately 25% of ovarian cancer patients are diagnosed with stages 1 and 2. These women generally have an excellent prognosis, provided a full staging procedure has been performed. Proper staging allows identification of those who are truly early stage and those who might have more advanced disease. This will allow optimal recommendation regarding adjuvant chemotherapy for the apparent early stage patients [16]. The critical importance of proper staging is underlined by the long term (10 year) follow up data offered by the ICON 1 study [17]. In this study the 10 year survival varied between 56 and 78% depending on the completeness of staging [17].

Table 1 enumerates the steps in comprehensive surgical staging of suspected ovarian cancer. Even in unilateral ovarian cancer, the risk of contralateral lymph node metastasis only, is 3.5%; this is in addition to the 9.7% risk of metastasis on both sides and the 8.3% risk of ipsilateral metastasis [18]. Indeed the risk of para-aortic lymph node metastasis only is 7.1% and the risk

Midline laparotomy
Obtain peritoneal fluid for cytology
Careful examination of all peritoneal surfaces
Total abdominal hysterectomy and bilateral salpingo-oophorectomy
Frozen section of ovarian mass ± suspicious lesions
Infra-colic omentectomy
Appendicectomy (for mucinous tumours)
Peritoneal biopsy from diaphragmatic surface, four quadrants of the abdomen and pouch of Douglas
Pelvic and para-aortic lymphadenectomy

Table 1. Staging procedure for apparent early stage ovarian cancer.

of pelvic and para-aortic lymph node metastasis is 4.3% [18]. Therefore comprehensive staging should include bilateral pelvic and para-aortic lymphadenectomy. However, this may need to be tempered by the overall clinical status of the individual patient. The single exception to this, is early stage mucinous ovarian cancer in which the risk of lymph node metastasis is minor, that omission of lymphadenectomy can be a safe option [19]. The extent of lymphadenectomy appears to correlate with survival benefit, with better outcomes being associated with lymph node counts of greater than 10 per site [18, 20].

5. Role of primary debulking surgery and neoadjuvant chemotherapy

Abundant retrospective data supported the notion of cytoreductive surgery [11, 14, 21]. The standard treatment had been PDS followed by NACT. Where the initial PDS had not resulted in 'optimal debulking' i.e. the residual disease was >1 cm in size, a second look laparotomy for further debulking after 3 cycles of NACT had been the routine practice. Randomised studies have examined this aspect and the most recent study by Rose et al. lead to the abandonment of second look laparotomy [22]. **Table 2** lists the procedures required for the 'ultra-radical' cytoreductive surgery which is in addition to the essential staging procedure.

The EORTC group led by Vergote conducted the first randomised trial comparing PDS followed by adjuvant chemotherapy against IDS after 3 cycles of neoadjuvant chemotherapy [23]. The trial

In addition to the above, the following procedures may be required to obtain microscopic clearance of the disease.
Small bowel resection
Large bowel resection
Intestinal stoma formation
Supracolic omentectomy
Splenectomy ± distal pancreatectomy
Segmental or lobular liver resection
Cholecystectomy
Diaphragmatic peritoneal stripping ± segmental full-thickness resection of the diaphragm
Resection of suspicious or enlarged retroperitoneal lymph nodes
Resection of pleural disease ± hycardiophrenic lymph nodes

Table 2. Potential procedures in 'optimal' cytoreductive surgery.

recruited patients between 1998 and 2006. This was a time when both the surgical strategy with respect to second-look laparotomy and ultra-radical surgery as well as chemotherapy regimens was rapidly evolving.

In the EORTC 55971 study 670 patients were stratified and randomised to PDS or NACT followed by IDS groups. The selection criteria included PS score and 'severe disabling disease' but resectability of the disease by a surgeon was not a condition. The study design did not incorporate CT or laparoscopic scoring system in patient selection. At the time of surgery, in the PDS arm 61% of patients had tumour size >10 cm and 24.2% of the same in the NACT arm; the prevalence of these features at the time of randomisation was 39% in PDS and 42% in the NACT arms. This suggests that a significant proportion of patients appear to have rather aggressive disease. The median operation time was 165 min in PDS and 180 min in the NACT arms. The proportion of patients in whom microscopic clearance was achieved was 19.4% in PDS and 51.2% in the NACT arms. The splenectomy rates (5.8% in PDS, 4.0% NACT) and bowel resection rates (15.5% in PDS, 8.7% in NACT) in this study are far lower than those reported by other high volume centres at the same time [11]. The most frequent sites of residual disease were pelvis, diaphragm and abdominal peritoneum; most experienced teams would consider these sites technically resectable disease. In conjunction with other parameters of cytoreduction mentioned above, one would find it difficult to be certain that the benefits of upfront surgery could have been realised in these operatively unselected patients. The authors acknowledge that a drawback of NACT is fibrosis which might impede tumour resection [23].

The CHORUS group recruited patients with clinical/radiological stage III and IV disease between 2004 and 2010 [24]. Five-hundred and fifty-two women were randomised after stratification by tumour size, stage, PS score and tumour markers as well as prespecified chemotherapy regime (single agent carboplatin, carbotaxol or carboplatin with another agent). Patients received 6 cycles of chemotherapy in total with IDS performed after 3 cycles. The two groups were comparable with similar proportions diagnosed as stage IIIC or IV (89% in PDS and 87% in NACT arms). The median operation time was 120 minutes in both groups, which is a remarkable short time for debulking surgery in advanced ovarian cancer. This consistent with the rates of complete debulking achieved in arms, 17% in PDS and 39% in the NACT arms. Indeed the suboptimal debulking (residual disease >1 cm) was very high at 59% in the PDS and 27% in the NACT arms. These figures are out of kilt with data from high volume international centres. The median overall survival was similar in both groups, but lower than expected at 22.6 months for PDS and 24.2 months for NACT. Multivariate analysis did not identify a subgroup favouring one treatment over another. The size of the residual tumour was prognostic in both arms.

Overall the QOL parameters were comparable between the two groups, except at 6 months post-treatment, the NACT group had higher scores. As expected the PDS group experienced grade 3 and 4 adverse events more frequently than the NACT group with the exception of haemorrhage. Death was more frequent in the PDS (6%) compared to the NACT (<1%) group. The administration and toxicity of chemotherapy was comparable in both groups. The authors acknowledged that the older median age, significant prevalence of poorly differentiated tumour (77%) and high prevalence (19%) of poor performance (PS 2 or 3) status might have

contributed to the less than expected overall survival. Indeed only 56% of patients received combination chemotherapy in their first cycle if their PS was 2–3 but this increased to 72% if their PS was 0–1. This differential has been recognised in the design of the currently recruiting TRUST trial.

Indeed only 77% in the PDS and 79% in the NACT arms completed the allocated treatment strategy.

Both EORTC 55971 and CHORUS trials have been heavily criticised [23, 24]. Indeed one would have to question the rigour with which the peritoneal residual disease might have been assessed in these two studies. For instance the incidence of peritoneal disease within the omental bursa is in excess of 60% [25]. Adequate exploration of the omental bursa is an advanced technique requiring assessment of coeliac nodes, caudate lobe, supragastric lesser omentum and the recesses on the left lateral aspect. One cannot be certain if these steps had been implemented in the earlier RCTs. Thus leading to inaccurate estimation of residual disease. The potential issue of surgeon bias in estimating residual disease has been highlighted in a radiological referencing study [26].

Indeed three further RCTs are examining the question of primary debulking surgery versus neoadjuvant chemotherapy [27, 28]. In fact all three trials include physiological status of the patient in their inclusion criteria. This feature was lacking in the CHORUS trial; EORTC 55971 excluded patients with PS 3 or 'serious disabling disease'.

The Japanese studies (JCOG0602) and the Italian (SCORPION trial) studies have published the peri-operative outcomes [27, 28]. As expected both of these studies demonstrate fewer peri-operative complications, shorter length of stay and smaller blood loss after neoadjuvant chemotherapy compared to primary debulking surgery.

The Japanese multicentre study recruited 301 between 2006 and 2011. In total, 8 cycles of carboplatin and paclitaxol were administered. Those patients with a residual tumour of >1 cm following PDS were offered IDS after 4 cycles of adjuvant chemotherapy. This is despite the publication of GOG152 by Rose et al. in 2004 demonstrating no advantage to second look laparotomy after a maximal effort at PDS [22]. Another peculiarity of this study is the interval of more than 4 years between recruitment of the last patient and submission of the manuscript.

The 'optimal debulking' rate in this study, defined as residual tumour of <1 cm, was 82% in the NACT and 37% in PDS group; when all treated patients are taken into account, including the second-look laparotomy, then the optimal debulking rate changes to 71 and 63% in the NACT and PDS arms respectively [28]. The grade 3–4 complications were less frequent after NACT compared to PDS. Resection of 'abdominal organs' and 'distant metastasis' were more common after PDS. Curiously the duration of main surgery was longer in NACT (302 versus 240 min); this may be explained by the significantly higher rates of pelvic and para-aortic lymphadenectomy in the NACT arm (pelvic LND 72.3% versus 27.2%; para-aortic LND 49.2% versus 11.6%) [28].

In the phase 3 Italian study, Fagotti and colleagues set out to investigate the best strategy for managing patients with high tumour load [27]. Patients were recruited between 2011 and 2014.

This is the first prospective randomised study seeking to verify a finding of an exploratory analysis of EORTC 55971, which stated that for a subgroup of patients with large tumour volumes, NACT lead to fewer morbidites and significantly better overall survival [29]. Therefore the selection of patients for this SCORPION trial was guided by laparoscopic predictive index (PI) [30, 31].Those patients with PI of >8 and < 12 were deemed eligible. In this study 55 were randomly assigned to each arm. None of the patients were subjected to a 'second-look' laparotomy. The cytoreductive rate to nil macroscopic disease was 45.5% in PDS arm and 57.7% in NACT arm. There was no significant difference in terms of the distribution of the residual disease between the two arms—these were military disease on small bowel serosa, hepatic hilum and nodal disease above the superior mesenteric artery. Upper abdominal procedures were carried out in 100% in the PDS and 42.3% in NACT arms. The surgical complexity score was significantly higher in the PDS arm. As a result PDS was associated with longer operating times and higher blood loss; this was accompanied by a mortality rate of 3.6% in the PDS and none in the NACT arms. Three patients in the NACT arm were not submitted for surgery due to disease progression. Many of the generic and specific parameters of QOL measures were in favour of NACT; interestingly cognitive and social functioning showed longitudinal improvement with the PDS group only. The oncological outcomes are awaited. In due course, the findings of this study may complement those of the on-going TRUST trial.

The AGO initiated multicenter international trial, TRUST study (NCT02828618), aims to address many of the short comings identified in the EORTC 55971 and the CHORUS studies. These are addressed by applying selection criteria with regards to the patients, disease and surgical team characteristics. Unlike any of the earlier RCTs in evaluating the timing of surgery in advanced epithelial ovarian cancer, involvement in the TRUST trial will entail an audit of the participating centres prior to study engagement. This ensures that the surgeon(s), surgical team and the relevant infrastructure are in place to deliver the most optimal cytoreductive surgery. The study is expected to complete recruitment in 2023. The outcomes of interest include surgical complications at 28 days, clinical outcomes at 1 year, QOL as well as oncological measures at 5 years.

6. Predictors of optimal cytoreduction

The two most important prognostic characteristics in ovarian cancer are comprehensive staging and optimal cytoreductive surgery [21]. Disease morphology (as predicted by cross sectional imaging and/or laparoscopic assessment), physiological fitness of the patient and the skill set of the surgeon or surgical team are the three key domain determining the resectability.

Since we have long abandoned the concept of second look laparotomy, it is important that where risk of residual exists, we must seek alternatives to primary debulking surgery, otherwise the patient may be dealt with a treatment strategy which is overall suboptimal. Therefore can biochemical, molecular imaging or endoscopic assessment help predict optimal surgery? This subject is a vast area and it will be briefly reviewed here in the context of cytoreductive surgery for advanced ovarian cancer.

The reader should exercise caution in interpreting results from studies for two key reasons; each study will use a different protocol for the index test of interest and secondly the assessment of residual disease is not without bias [32].

Several studies have demonstrated that preoperatively raised level of CA125 and HE4 can predict suboptimal debulking [33–35]. Indeed higher platelet count, lower lymphocyte count or higher ratio of platelet to lymphocyte count can predict suboptimal debulking in advanced ovarian cancer [36, 37].

Functional imaging such as diffusion weighted MRI and PET-CT are rapidly evolving. The key aspect for imaging should be able to identify the rate limiting steps in relation to cytoreductive surgery. Diseases on small bowel mesentry and bowel serosa are consistently the rate limiting steps in delivering microscopic clearance of the disease. At present there is significant interest in diffusion weighted MRI and a prospective imaging study is underway to delineate the role of multiplanar MRI with CT as compared with standard CT alone in guiding decision making process (ISRCTN51246892). In a recent paper, the dwMRI appears to perform very well in predicting disease map [38]. The role of CT on its own in predicting resectability provides does not provide a consistent acceptable answer particularly as the current standard of 'optimal' debulking is nil visible disease [39–41].

Laparoscopic assessment can be useful adjunct in patient selection. One must acknowledge that a laparoscopic assessment can only provide information regarding the intraperitoneal disease. Fagotti and colleagues have accomplished a body of work regarding the role of laparoscopy in advanced ovarian cancer. Studies have consistently shown that small bowel and its mesentry are common site for the residual disease [27, 31, 42]. Petrillo et al. de on laparoscopic assessment, where unresectability is indicated by a predictive score of greater than 8 [31].

It is likely that a combination of metabolic analysis and morphologic characteristics will enhance non-invasive prediction of resectability in the medium future.

7. Optimising cytoreductive surgery

In the United Kingdom, the chief medical officer, Professor Dame Sally Davies recommended that 'the Royal College of Obstetricians and Gynaecologists should make sure that subspecialist training in gynaecological oncology equips doctors to perform optimal surgery for gynaecological cancers and reduce mortality from ovarian cancer' [43].

Both modifiable (technical skills, organisation of care) and constitutional (e.g. age, biology, functional status) factors need to be addressed if we are to make incremental improvements in the outcomes for our patients.

One approach to this could frame any death from ovarian cancer as an 'error'. With such an approach one can adopt a sophisticated approach to addressing the modifiable factors [44, 45]. Vincent and colleagues articulated seven levels at which an error should be tackled. These are

institutional (and national climate), organisation & management, work environment, team, individual staff member, task and patient [45]. How this model could be used for maximising optimal cytoreductive surgery is briefly illustrated here.

The statement by the CMO above creates a national sense of the overall aim. In addition, the European Society of Gynaecological Oncology (ESGO) published a benchmark regarding ovarian cancer surgery, which adds to this impetus, about the desirable end goal [46]. This expert consensus report recommends 10 indicators relating to structural, process and outcome metrics ranging from individual performance to team decision making process within a multidisciplinary setting. Such a suite of benchmarks can set the direction of travel.

Around the globe and even within the 'developed' nations the practice of patient selection, planning and delivery of upfront surgery varies a great deal. Therefore in terms of organisation and management, centralization of care delivery will help optimise outcomes [26, 47]. With regard to team and individual factors, training should target both and the end goal should be clear to both entities, that is, microscopic clearance of the disease. The delivery of surgery could be by a sufficiently trained gynaecological oncologist with the appropriate contribution from allied surgical oncologists. ESGO have organised or sponsored numerous workshops targeting technical skills and the philosophy to support primary debulking surgery. Such a concerted effort will help to redress one of the concerns about current training. The application of the current 'gold standard' evidence from two randomised controlled trials, (though heavily criticised) will adversely impact the training of the next generation of surgeons. Further, the timing of TRUST trial outcome and retirement of those trained prior to the wide acceptance of PDS, will change the landscape of practitioners.

Indeed individual and team training can be augmented by not only skills training in workshops, but through buddy operating during the transition phase. Such an endeavour could be supported by virtual platforms to maintain skills (e.g. video based feedback on specific subtasks in cytoreductive surgery) [48, 49]. This will augment task performance.

Patient selection is discussed elsewhere in this book and will not be discussed here. The factors will include demographic, biological (including molecular characteristics of the disease) and radiomics to mention a few [50].

Another important measure in improving the outcomes as part of CRS is to enhance chemotherapy with the use of Hyperthermic Intraperitoneal Chemotherapy (HIPEC). In a recent study, addition of HIPEC to CRS appears to prolong the overall survival by almost 12 months in patients undergoing interval debulking surgery [51]. This offers an exciting complement to maximal effort CRS. These findings will require independent verification prior to widespread adaptation. This topic will not be discussed further in this chapter.

8. Conclusions

At present the grade A evidence reveals no significant difference in the 5 year survival amongst patients receiving either primary or interval debulking surgery for ovarian cancer. It

must be borne in mind that the evidence base is not without significant criticism. It is likely that on-going surgical and medical trials in ovarian cancer will alter our management of this heterogeneous entity. Clinicians will appreciate that given the morbidity of cytoreductive surgery, development of this service requires appropriate governance structure.

How to optimise surgery: will involve better characterisation of the disease through molecular stratification, better selection of patients in terms of physiological fitness (so reduce complications), continued training of surgeons & teams, centralization of service for those who would be best suited for maximal effort surgery.

Conflict of interest

The author has no conflicts of interest to declare.

Author details

Rasiah Bharathan

Address all correspondence to: rasiah.bharathan@nhs.net

Department of Gynaecological Oncology, University Hospitals of Leicester NHS Trust, Leicester, United Kingdom

References

[1] Sugarbaker PH. Peritonectomy procedures. Annals of Surgery. 1995;**221**(1):29-42

[2] Meigs JV. Tumors of the Female Pelvic Organs. New York: The Macmillan Company; 1934

[3] Hudson CN. A radical operation for fixed ovarian tumours. The Journal of Obstetrics and Gynaecology of the British Commonwealth. 1968;**75**(11):1155-1160

[4] Griffiths CT. Surgical resection of tumor bulk in the primary treatment of ovarian carcinoma. National Cancer Institute Monograph. 1975;**42**:101-104

[5] Covens AL. A critique of surgical cytoreduction in advanced ovarian cancer. Gynecologic Oncology. 2000;**78**(3 Pt 1):269-274

[6] Wright JD, Lewin SN, Deutsch I, Burke WM, Sun X, Neugut AI, et al. Defining the limits of radical cytoreductive surgery for ovarian cancer. Gynecologic Oncology. 2011;**123**(3): 467-473

[7] Wright JD, Herzog TJ, Neugut AI, Burke WM, Lu Y-S, Lewin SN, et al. Effect of radical cytoreductive surgery on omission and delay of chemotherapy for advanced-stage ovarian cancer. Obstetrics and Gynecology. 2012;**120**(4):871-881

[8] Wright JD, Ananth CV, Tsui J, Glied SA, Burke WM, Lu Y-S, et al. Comparative effectiveness of upfront treatment strategies in elderly women with ovarian cancer. Cancer. 2014; **120**(8):1246-1254

[9] 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. Journal of Clinical Oncology. 2005;**23**(34): 8802-8811

[10] Harter P, Muallem ZM, Buhrmann C, Lorenz D, Kaub C, Hils R, et al. Impact of a structured quality management program on surgical outcome in primary advanced ovarian cancer. Gynecologic Oncology. 2011;**121**(3):615-619

[11] 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. Gynecologic Oncology. 2009;**114**(1):26-31

[12] Aletti GD, Cliby WA. Time for centralizing patients with ovarian cancer: What are we waiting for? Gynecologic Oncology. United States. 2016;**142**:209-210

[13] 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. Journal of Clinical Oncology. 2002;**20**(5):1248-1259

[14] Chang S-J, Hodeib M, Chang J, Bristow RE. Survival impact of complete cytoreduction to no gross residual disease for advanced-stage ovarian cancer: A meta-analysis. Gynecologic Oncology. 2013;**130**(3):493-498

[15] Chang SJ, Bristow RE, Chi DS, Cliby WA. Role of aggressive surgical cytoreduction in advanced ovarian cancer. Journal of Gynecologic Oncology. 2015;**26**(4):336-342

[16] Lawrie TA, Winter-Roach BA, Heus P, Kitchener HC. Adjuvant (post-surgery) chemotherapy for early stage epithelial ovarian cancer. Cochrane Database of Systematic Reviews. 2015;**12**:CD004706

[17] Trimbos B, Timmers P, Pecorelli S, Coens C, Ven K, van der Burg M, et al. Surgical staging and treatment of early ovarian cancer: Long-term analysis from a randomized trial. Journal of the National Cancer Institute. 2010;**102**(13):982-987

[18] Kleppe M, Wang T, Van Gorp T, Slangen BFM, Kruse AJ, Kruitwagen RFPM. Lymph node metastasis in stages I and II ovarian cancer: A review. Gynecologic Oncology. 2011;**123**(3): 610-614

[19] Powless CA, Aletti GD, Bakkum-Gamez JN, Cliby WA. Risk factors for lymph node metastasis in apparent early-stage epithelial ovarian cancer: Implications for surgical staging. Gynecologic Oncology. 2011;**122**(3):536-540

[20] Chan JK, Munro EG, Cheung MK, Husain A, Teng NN, Berek JS, et al. Association of lymphadenectomy and survival in stage I ovarian cancer patients. Obstetrics and Gynecology. 2007;**109**(1):12-19

[21] Bristow RE, Nugent AC, Zahurak ML, Khouzhami V, Fox HE. Impact of surgeon specialty on ovarian-conserving surgery in young females with an adnexal mass. The Journal of Adolescent Health. 2006;**39**(3):411-416

[22] Rose PG, Nerenstone S, Brady MF, Clarke-Pearson D, Olt G, Rubin SC, et al. Secondary surgical cytoreduction for advanced ovarian carcinoma. The New England Journal of Medicine. 2004;**351**(24):2489-2497

[23] Vergote I, Trope CG, Amant F, Kristensen GB, Ehlen T, Johnson N, et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. The New England Journal of Medicine. 2010;**363**(10):943-953

[24] Kehoe S, Hook J, Nankivell M, Jayson GC, Kitchener H, Lopes T, et al. Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): An open-label, randomised, controlled, non-inferiority trial. Lancet (London, England). 2015;**386**(9990):249-257

[25] Raspagliesi F, Ditto A, Martinelli F, Haeusler E, Lorusso D. Advanced ovarian cancer: Omental bursa, lesser omentum, celiac, portal and triad nodes spread as cause of inaccurate evaluation of residual tumor. Gynecologic Oncology. 2013;**129**(1):92-96

[26] Sinno AK, Li X, Thompson RE, Tanner EJ 3rd, Levinson KL, Stone RL, et al. Trends and factors associated with radical cytoreductive surgery in the United States: A case for centralized care. Gynecologic Oncology. 2017;**145**(3):493-499

[27] Fagotti A, Ferrandina G, Vizzielli G, Fanfani F, Gallotta V, Chiantera V, et al. Phase III randomised clinical trial comparing primary surgery versus neoadjuvant chemotherapy in advanced epithelial ovarian cancer with high tumour load (SCORPION trial): Final analysis of peri-operative outcome. European Journal of Cancer. 2016;**59**:22-33

[28] Onda T, Satoh T, Saito T, Kasamatsu T, Nakanishi T, Nakamura K, et al. Comparison of treatment invasiveness between upfront debulking surgery versus interval debulking surgery following neoadjuvant chemotherapy for stage III/IV ovarian, tubal, and peritoneal cancers in a phase III randomised trial: Japan clinical oncology gr. European Journal of Cancer. 2016;**64**:22-31

[29] van Meurs HS, Tajik P, Hof MHP, Vergote I, Kenter GG, Mol BWJ, et al. Which patients benefit most from primary surgery or neoadjuvant chemotherapy in stage IIIC or IV ovarian cancer? An exploratory analysis of the European Organisation for Research and Treatment of Cancer 55971 randomised trial. European Journal of Cancer. 2013;**49**(15):3191-3201

[30] Fagotti A, Vizzielli G, De Iaco P, Surico D, Buda A, Mandato VD, et al. A multicentric trial (Olympia-MITO 13) on the accuracy of laparoscopy to assess peritoneal spread in ovarian cancer. American Journal of Obstetrics and Gynecology. 2013;**209**(5):462.e1-462.e11

[31] Petrillo M, Vizzielli G, Fanfani F, Gallotta V, Cosentino F, Chiantera V, et al. Definition of a dynamic laparoscopic model for the prediction of incomplete cytoreduction in advanced epithelial ovarian cancer: Proof of a concept. Gynecologic Oncology. 2015;**139**(1):5-9

[32] Chi DS, Barlin JN, Ramirez PT, Levenback CF, Mironov S, Sarasohn DM, et al. Follow-up study of the correlation between postoperative computed tomographic scan and primary surgeon assessment in patients with advanced ovarian, tubal, or peritoneal carcinoma reported to have undergone primary surgical cytoreduction to residual disea. International Journal of Gynecological Cancer. 2010;**20**(3):353-357

[33] Kang S, Kim T-J, Nam B-H, Seo S-S, Kim B-G, Bae D-S, et al. Preoperative serum CA-125 levels and risk of suboptimal cytoreduction in ovarian cancer: A meta-analysis. Journal of Surgical Oncology. 2010;**101**(1):13-17

[34] Pelissier A, Roulot A, Guery B, Bonneau C, Bellet D, Rouzier R. Serum CA125 and HE4 levels as predictors for optimal interval surgery and platinum sensitivity after neoadjuvant platinum-based chemotherapy in patients with advanced epithelial ovarian cancer. Journal of Ovarian Research. 2016;**9**(1):61

[35] Plotti F, Scaletta G, Capriglione S, Montera R, Luvero D, Lopez S, et al. The role of HE4, a novel biomarker, in predicting optimal cytoreduction after neoadjuvant chemotherapy in advanced ovarian cancer. International Journal of Gynecological Cancer. 2017;**27**(4): 696-702

[36] Raungkaewmanee S, Tangjitgamol S, Manusirivithaya S, Srijaipracharoen S, Thavaramara T. Platelet to lymphocyte ratio as a prognostic factor for epithelial ovarian cancer. Journal of Gynecologic Oncology. 2012;**23**(4):265-273

[37] Arab M, Jamdar F, Sadat Hosseini M, Ghodssi-Ghasemabadi R, Farzaneh F, Ashrafganjoei T. Model for prediction of optimal debulking of epithelial ovarian cancer. Asian Pacific Journal of Cancer Prevention. 2018;**19**(5):1319-1324

[38] Michielsen K, Dresen R, Vanslembrouck R, De Keyzer F, Amant F, Mussen E, et al. Diagnostic value of whole body diffusion-weighted MRI compared to computed tomography for pre-operative assessment of patients suspected for ovarian cancer. European Journal of Cancer. 2017;**83**:88-98

[39] Borley J, Wilhelm-Benartzi C, Yazbek J, Williamson R, Bharwani N, Stewart V, et al. Radiological predictors of cytoreductive outcomes in patients with advanced ovarian cancer. BJOG: An International Journal of Obstetrics and Gynaecology. 2015;**122**(6):843-849

[40] Mac Kintosh ML, Rahim R, Rajashanker B, Swindell R, Kirmani BH, Hunt J, et al. CT scan does not predict optimal debulking in stage III-IV epithelial ovarian cancer: A multicentre validation study. Journal of Obstetrics and Gynaecology. 2014;**34**(5):424-428

[41] Nasser S, Kyrgiou M, Krell J, Haidopoulos D, Bristow R, Fotopoulou C. A review of thoracic and mediastinal cytoreductive techniques in advanced ovarian cancer: Extending the boundaries. Annals of Surgical Oncology. 2017;**24**(12):3700-3705

[42] Heitz F, Harter P, Alesina PF, Walz MK, Lorenz D, Groeben H, et al. Pattern of and reason for postoperative residual disease in patients with advanced ovarian cancer following upfront radical debulking surgery. Gynecologic Oncology. 2016;**141**(2):264-270

[43] Davies S. Department of H. Chief Medical Officer. Annual Report 2014: Women's Health. [Internet]. 2014 [cited 2018 Aug 7]. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/595439/CMO_annual_report_2014.pdf

[44] Vincent C, Taylor-Adams S, Stanhope N. Framework for analysing risk and safety in clinical medicine. BMJ. 1998;**316**(7138):1154-1157

[45] Vincent C. Understanding and responding to adverse events. The New England Journal of Medicine. 2003;**348**(11):1051-1056

[46] Querleu D, Planchamp F, Chiva L, Fotopoulou C, Barton D, Cibula D, et al. European society of gynaecologic oncology quality indicators for advanced ovarian cancer surgery. International Journal of Gynecological Cancer. 2016;**26**(7):1354-1363

[47] Cowan RA, O'Cearbhaill RE, Gardner GJ, Levine DA, Roche KL, Sonoda Y, et al. Is it time to centralize ovarian cancer care in the United States? Annals of Surgical Oncology. 2016; **23**(3):989-993

[48] Moore AM, Carter NH, Wagner JP, Filipi CJ, Chen DC. Web-based video assessments of operative performance for remote telementoring. Surgical Technology International. 2017; **30**:25-30

[49] Moore MD, Abelson JS, O'Mahoney P, Bagautdinov I, Yeo H, Watkins AC. Using GoPro to give video-assisted operative feedback for surgery residents: A feasibility and utility assessment. Journal of Surgical Education. 2018;**75**(2):497-502

[50] Keek SA, Leijenaar RT, Jochems A, Woodruff HC. A review on radiomics and the future of theranostics for patient selection in precision medicine. The British Journal of Radiology. 2018; 20170926

[51] van Driel WJ, Koole SN, Sikorska K, Schagen van Leeuwen JH, Schreuder HWR, Hermans RHM, et al. Hyperthermic intraperitoneal chemotherapy in ovarian cancer. The New England Journal of Medicine. 2018;**378**(3):230-240