



A narrative review of the role of anaesthesia and peri-operative medicine in improving outcomes after surgery for advanced ovarian cancer

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Contributions: (I) Conception and design: JJ Pandit; (II) Administrative support: JJ Pandit; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: None; (VI) Manuscript writing: Both authors; (VII) Final approval of manuscript: Both authors.

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Objective: The broad aim of this review is to provide a summary of the challenges facing anaesthesia for this type of surgery, the strategies used to overcome these challenges, and how effective these approaches have proved to be.

Background: Advanced ovarian cancer surgery presents anaesthetists with the challenge of managing patients with potential multiple co-morbidities undergoing major open or extended laparoscopic surgeries. The disease has overall amongst the poorest overall survival rates of all malignancies, with an estimated 5-year survival rate of <43%, and the patients being of a generally older age group present specific challenges in terms of their accumulated co-morbidities.

Methods: To inform this review, we conducted a literature search using PubMed for relevant key words, supplemented by secondary searches based on the reference lists of retrieved papers. The literature review yielded discrete themes which we were able to organise under descriptions that form the subheadings in this review: pre-operative assessment and optimisation, intra-operative considerations, and postoperative care.

Conclusions: Despite the challenging nature of the underlying disease, optimal anaesthetic strategies tailored to the needs of the patient can help in improving recovery, and therefore potentially long-term outcome, after surgery for advanced ovarian carcinoma. Specifically there is room for patient autonomy in choices exercised especially with respect to pain relief. The review acknowledges surgical advances in the near future that may influence development of anaesthetic techniques.

Keywords: Anaesthesia; peri-operative medicine; pre-operative assessment; surgical outcomes

Received: 30 March 2021; Accepted: 18 June 2021; Published: 25 June 2022.

doi: 10.21037/gpm-21-28

View this article at: <https://dx.doi.org/10.21037/gpm-21-28>

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Introduction

Ovarian cancer generally presents late, due to non-specific symptoms (1). Consequently, it has amongst the poorest overall survival rates of all gynaecological—and other—malignancies, with an estimated 5-year survival rate of 42.6% in the United Kingdom (2). Histological classification shows that malignancy arising from epithelial cells is the commonest form (90%), the remainder being germ cell, stromal or sex cord tumours (3). Surgical management forms the mainstay of both diagnosis and treatment in all tumour types (4).

Significant advances in the surgical management of advanced ovarian malignancy has meant that radical operative interventions can be offered to patients presenting at ever later stages in their disease process (5). Although this is a challenge for both surgery and anaesthesia, it also means that the benefits of even radical surgery and improvements to survival can be worthwhile.

The anaesthetist, as a member of the multi-disciplinary team, plays a pivotal role in providing care throughout the peri-operative period and in improving the long-term outcome after surgery. Additionally, due to the poor prognosis of advanced ovarian cancer, the anaesthetist may also be involved in the management of chronic pain and palliation where no operative intervention is possible. We present the following article in accordance with the Narrative Review reporting checklist (available at <https://gpm.amegroups.com/article/view/10.21037/gpm-21-28/rc>).

Methods

To inform this review, we conducted a literature search using PubMed for key words “anaesthesia”, “ovarian cancer”, “gynaecological oncology”, “laparoscopic surgery” and their combinations. We confirmed our preliminary search to papers published within the last 10 years (i.e., 2010 onwards) so as to ensure a contemporaneous literature base, whilst recognising that some principles of anaesthetic management may have been established long before then. Since this was an expert-based or narrative review, we were open to considering publications of all types (including editorials and letters as well as clinical trials) but we excluded abstracts or short symposium presentations. The primary literature search was supplemented by secondary searches led by reference lists of the retrieved papers.

From review of the retrieved papers emerged specific themes, which we organise broadly as subheadings in this

review which are: pre-operative assessment and optimisation, intra-operative considerations, and postoperative care. The broad aim of this review is to provide a summary of the challenges facing anaesthesia for this type of surgery, the strategies used to overcome these challenges, and how effective these approaches have proved to be.

Discussion

Pre-operative assessment and optimisation

Pre-operative assessment is now routine practice in all patients undergoing major surgery (6,7). This affords the opportunity for thorough investigation, planning of the treatment pathway, optimisation of the pre-surgical condition and time for patient counselling and education. Wherever possible, patients should be referred to meet members of the wider multidisciplinary team, including surgeons, anaesthetists, oncologists, stoma nurses and physiotherapists, prior to surgery. While the pre-operative anaesthetic assessment clinic facilitates discussion of anaesthetic options, care should be taken that this does not result in one anaesthetist dictating the specific management for another colleague.

Specific issues to be discussed include the description of regional anaesthesia (epidural or spinal injections) that are sited before induction of general anaesthesia. These reduce post-operative opiate use and side effects, especially a reduction in nausea and vomiting, and improved return of bowel function. Their use is a particular advantage in patients with impaired lung function (e.g., asthma, chronic airways disease) as opiates can depress postoperative ventilation and hypoxic drive (8,9). The use of epidural analgesia in ovarian cancer surgery is associated in some studies with improved overall survival (10) but the evidence base has not reached a level where this should be considered mandatory. Alternative techniques such as ultrasound-guided transversus abdominus plane (TAP) blocks (11) or surgically sited wound infusion catheters should be offered to patients in whom epidural analgesia is contraindicated, or those who decline the option.

Particular symptoms of relevance to anaesthesia, common in advanced ovarian cancer, include pleural effusions and malignant ascites. Both have potential to impair peri-operative ventilation. Ascites is usually managed by pre-operative drainage (12). While pleural effusions are also managed in this way, care needs to be taken that the ‘pleural tap’ does not then pose a later risk for (tension)

pneumothorax during the positive pressure ventilation of anaesthesia. A 'blind' needle insertion and drainage of pleural effusion on the day of surgery carries a high risk of this, but this is mitigated in two ways. First, to leave a chest drain or pigtail catheter *in situ* in the pleural space; or second (now more common) to employ ultrasound-guided drainage, usually conducted by interventional radiology, which has only a very low risk of subsequent pneumothorax (13).

The employment of invasive lines (arterial and central venous) which are required for radical surgeries should also be discussed, so that the patient is aware of the magnitude of surgery and associated risks.

Attendant co-morbidities may require immediate post-operative care in the high dependency (HDU) or intensive care unit (ICU). There are no explicit rules, but the judgement is based on, amongst other things, the extent of planned surgery (including the degree of anticipated blood loss) and pre-existing co-morbidities (where severe cardiac and pulmonary disease makes HDU or ICU care more likely; and renal disease requiring early dialysis or haemofiltration is also best managed in an HDU or ICU setting) (14).

It is also now common to use pre-operative exercise testing to help assess the need for elective HDU or ICU admission (15,16). In patients who are physically able to undertake the investigation, cardiopulmonary exercise testing (CPET) aids in the objective identification of patients at high risk of perioperative morbidity. An anaerobic threshold (AT) of $<11 \text{ mL}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$ is a commonly recognised endpoint used to identify patients at high risk of complications after major surgery, although alternative endpoints within the exercise response may better indicate a patient's ability to cope with perioperative metabolic demands (17).

There has been increasing attention to the pre-operative management of anaemia, a common symptom in advanced ovarian malignancy. Anaemia is associated with adverse perioperative outcomes including the need for blood transfusion and increased length of hospital stay (LOS) (18), as well as reduced survival in patients with ovarian cancer (19). Iron deficiency, either absolute due to poor nutritional intake or blood loss; or the functional iron deficiency caused by impaired iron absorption in anaemia of chronic disease (20), is the most common cause (21). Pre-operative iron replacement has previously been advocated (22), however, recent evidence (23) has failed to show a reduction in the frequency of intraoperative blood transfusion, postoperative complications or mortality through the use of intravenous

iron replacement in anaemic patients prior to major elective abdominal surgery.

Neoadjuvant chemotherapy prior to surgical intervention is increasingly used in ovarian cancer (24), and platinum-based agents such as cisplatin and carboplatin have a range of side-effects of which the anaesthetist should be aware. These include immunosuppression, and toxic effects on the pulmonary, cardiac, renal and hepatic systems, that should be detected by the electrocardiogram (ECG), baseline echocardiography and blood tests that are routine in the pre-assessment clinic.

Because of the later age group in which ovarian cancer usually presents, patients may have multiple unrelated co-morbidities and advice regarding pre-operative continuation and cessation of certain medications is important. Drugs generally continued include cardioactive, hypertensive and psychiatric medications. Drugs generally omitted include oral contraceptive agents, antiplatelets, anticoagulants and diabetic medications, each carrying specific advice as to how many doses to omit pre-operatively.

Prehabilitation aims to aid the response to surgery and postoperative recovery by improving functional and metabolic reserves prior to the surgical procedure. It forms a cornerstone of enhanced recovery programs, which are increasingly recommended in the management of gynaecological malignancy (25,26). Although it may not be feasible to allow for prolonged prehabilitation in the perioperative interval, interventions such as nutritional counselling and support, exercise prescription (27) and certain psychological interventions (e.g., counselling and stress reduction techniques) are achievable in the short term. Smoking cessation and reduction of alcohol intake should be encouraged and comorbidities such as diabetes and hypertension should be identified and treated. Enhanced recovery protocols are discussed further below.

Intra-operative considerations

The common types of surgery include salpingo-oophorectomy, hysterectomy, lymphadenectomy, peritonectomy, omentectomy and surgical debulking of the tumour. The aim is to remove the bulk of the tumour, after which platinum-based chemotherapy is usually offered (5). More recently, neoadjuvant chemotherapy has been used pre-operatively in selected patients to reduce tumour bulk (24). Additionally, hyperthermic chemotherapy may be delivered to the peritoneal cavity directly after cytoreductive surgery. Radiotherapy is rarely used in the

management of ovarian cancer, apart from the treatment of metastases. Radical surgery may also involve the need to operate on or near major arteries and veins (e.g., iliacs), bladder and ureters, and rarely, liver or spleen where there are metastases. Some surgeons favour stripping the diaphragmatic surface of any metastatic deposits, which may include entering the chest cavity.

The entire operation can now be performed laparoscopically, where access permits. Surgery duration is long: rarely less than 5 hours and often much longer. This has important implications for planning and scheduling (28) of surgical lists since undertaking more than one such case in most block-scheduling allocations of 8 or even 10 hours is difficult (29,30).

The open and laparoscopic approaches present their own respective challenges for anaesthesia. Open surgery requires particular attention to post-operative analgesia (regional anaesthesia is discussed above) and post-operative intravenous patient-controlled analgesia (opiate PCA) or patient-controlled epidural analgesia (PCEA) are commonplace. The laparoscopic approach requires attention to intra-operative patient positioning, usually in the steep head-down, Trendelenburg position. Specific concerns for the anaesthetist include impaired pulmonary function and potential for reduced ventilation (which can in turn require high inflation pressures), airway and facial oedema, increased intraocular and intracranial pressure and the risk of nerve injury (31).

A further facet of the ergonomics of the Trendelenburg position is that the gynaecologists are often standing by or close to the head of the patient, looking down into the pelvis with the laparoscope, a standing position akin to head and neck surgery. The anaesthetist therefore needs to plan the layout of the operating room and anaesthesia machine accordingly. Due to the prolonged duration of surgery, careful attention to positioning and alleviation of pressure areas is imperative. Repositioning at various intervals may be required in prolonged cases, especially in those at high risk of pressure injury, including frail or obese patients (32).

Obesity is a risk factor in ovarian malignancy (33,34) and will add to the challenges of laparoscopic surgery, pneumoperitoneum and head-down positioning (35). Obese patients are more likely to have larger tumours and disseminated disease at time of diagnosis compared to non-obese patients (36,37), making surgery and anaesthesia more high risk and technically challenging.

Regardless of approach, general anaesthesia with tracheal intubation and mechanical ventilation is universal.

One point of debate has been whether total intravenous anaesthesia (TIVA) offers better outcomes such as smoother recovery, but also in particular some protection from cancer recurrence. This debate is based on retrospective analysis and basic science studies suggesting that propofol has specific inhibitory effects on cancer versus normal cells. However, this has not been borne out by recent prospective randomised controlled trials (38-40). With recent discoveries that volatile anaesthetics each act in their own specific way (41-43), with sevoflurane in particular being less depressive of hypoxic chemoreflexes and ventilation (44-46) and thus affording rapid recovery, there is probably no significant difference between TIVA- and volatile-based techniques.

A related debate is the use of intravenous lidocaine infusion: local anaesthetic, both as regional anaesthesia and intravenous infusion, has been suggested to reduce cancer recurrence (47,48). Again, clinical trials are not supportive (38) and this potential advantage appears to have been outweighed by the serious, life-threatening risks posed by intravenous lidocaine therapy (49).

Large fluid shifts with the potential for haemodynamic instability should be anticipated. Due to the radical nature of surgery extensive blood loss may occur. Additionally, in patients with large volume ascites, rapid drainage of ascitic fluid when opening the abdomen can result in sudden haemodynamic decompensation. The insertion of a minimum of two large bore intravenous canulae at the time of induction, along with arterial cannulation and invasive haemodynamic monitoring is recommended. Some patients may require intra-operative vasopressor support to maintain adequate perfusion, and central venous cannulation should therefore be considered. Appropriate blood products should be easily accessible, with blood loss replacement according to best practice guidelines. Blood loss may be greater in patients undergoing surgery after chemotherapy or previous interval debulking due to the presence of adhesions and fibrosis. Estimation of blood loss may be difficult due to dilution with ascites and irrigation fluid. Urinary catheterisation is necessary for both the surgery and for hourly urine output monitoring. In patients without pre-existing renal disease, urine output of $>0.5 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ is expected (50).

Arterial blood gas analysis should be performed at regular intervals for both gas exchange and glucose parameters. Metabolic derangements due to fluid shifts, blood product use and pre-existing conditions or medications are common and should be corrected.

Perioperative hyperglycaemia is an independent marker of poor surgical outcomes including delayed wound healing, surgical site infection, acute kidney injury, prolonged hospital stay and increased postoperative mortality in both diabetic and non-diabetic populations (51,52). The maintenance of intraoperative glucose levels between 6–10 mmol·L⁻¹ through the use of subcutaneous or intravenous insulin is recommended, with regular monitoring of glucose levels in order to minimize the risk of hypoglycaemia (53,54).

Patients with malignancy undergoing major surgery have an increased propensity to develop venous thrombo-embolism (55). Perioperative mechanical and chemical thromboprophylaxis according to local guidelines must be considered. Post-operatively, early ambulation should be encouraged.

Postoperative care

The requirement for post-operative HDU or ICU admission is discussed above. Regardless, as after all major surgeries, careful postoperative care is necessary. Specific attention is needed for, amongst other things: analgesia, haemodynamic stability including anaemia, renal output and fluid balance, bowel function and management of post-operative pain, nausea and vomiting.

Enhanced recovery after surgery (ERAS) is a multimodal approach to improve the functional rehabilitation of patients after surgery. Recent evidence has demonstrated the value of ERAS in patients undergoing major advanced ovarian cancer surgery (56). The PROFAST trial (57) demonstrated a reduction in the LOS without increasing complication or readmission rates.

ERAS protocols in cancer surgery involve several facets. In the interval between diagnosis and surgery, the patient undergoes multidisciplinary workup including counselling and prehabilitation (discussed above). On the day of surgery, fasting times are limited, with solid food allowed up to 6 hours, and clear fluid up to 2 hours, prior to surgery. Carbohydrate loading in the form of supplemental drinks is offered and the use of bowel preparation is avoided. Intra-operatively, a standardized anaesthetic approach is employed, with focus on strategies to avoid post-operative nausea, vomiting, pain and cardiorespiratory complications. The use of tubes and catheters is limited to as short a

duration as possible. In the post-operative period, early mobilisation and resumption of oral intake is encouraged. Post-operative pain is managed using opiate-sparing strategies to limit risks such as post-operative ileus and nausea and vomiting. Successful implementation of ERAS protocols requires an engaged multidisciplinary team.

Due to the high risk of venous thrombo-embolism, mechanical and chemical thromboprophylaxis are recommended and early ambulation should be encouraged.

Atelectasis and associated pulmonary complications are common following major abdominal surgery, especially those involving high dissection in the upper abdomen. Deep breathing, coughing and mobilisation should be encouraged. Patients with coexisting cardiorespiratory disease are at increased risk of developing postoperative complications such as myocardial ischaemia, arrhythmias, pneumonia and pulmonary oedema. If diaphragmatic stripping has been undertaken, specific care should be taken to exclude signs of pneumothorax.

The development of chronic pain and altered sensation is well recognised after major gynaecological surgery. Careful management of early postoperative pain may reduce this risk. In the long term, the anaesthetist and other chronic pain physicians play a role in the management of chronic post-surgical pain.

Prior to discharge from hospital, patients should receive counselling regarding the resumption of normal activity such as work and sexual function (58,59). A low mood is common after major gynaecological surgery, both due to fatigue and hormonal changes.

Conclusions

The anaesthetist plays an important role in improving recovery, and therefore potentially long-term outcome, after surgery for advanced ovarian carcinoma (*Table 1*). The approach is not a 'one size fits all' but an opportunity to tailor technique to the patient's co-morbidities and risk factors throughout the perioperative journey. In this way patient preferences can be factored in, and patient satisfaction, especially with regard to pain relief, is a priority. Possible surgical advances that may influence future anaesthetic technique include the use of robotics (60), lasers or photodynamic therapies (61), each of which may require novel amendments to anaesthetic strategy.

Table 1 Summary of key points from this review, for each of the phases of anaesthesia/peri-operative care

Phase of anaesthesia	Key points of review
Pre-operative assessment and optimisation	<ul style="list-style-type: none"> • Multidisciplinary involvement before surgery • Discuss options for analgesia • Optimise any co-morbidities • Screen for pleural effusion and ascites • Manage anaemia if present • Discuss risks (including need for invasive lines, HDU, ICU) • Consider prehabilitation
Intra-operative considerations	<ul style="list-style-type: none"> • Plan and schedule theatre lists to take account of operation time • Lung ventilation strategies for laparoscopic surgery • Consider TIVA • Consider intravenous lidocaine if no other blocks, epidural or infiltration employed • Careful monitoring of blood indices during prolonged surgery
Postoperative care	<ul style="list-style-type: none"> • Elective HDU or ICU admission for some patients, sometimes requiring prolonged lung ventilation • ERAS pathway for some patients • Continued analgesia, anti-thromboembolic and physiotherapy care • Psychological counselling may be needed

HDU, high dependency unit; ICU, intensive care unit; TIVA, total intravenous anaesthesia; ERAS, enhanced recovery after surgery.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor (Hooman Soleymani Majd) for the series “Evolutions in the Management of Advanced Ovarian Cancer” published in *Gynecology and Pelvic Medicine*. The article has undergone external peer review.

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at <https://gpm.amegroups.com/article/view/10.21037/gpm-21-28/rc>

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at <https://gpm.amegroups.com/article/view/10.21037/gpm-21-28/coif>). The series “Evolutions in the Management of Advanced Ovarian Cancer” was commissioned by the editorial office without any funding or sponsorship. The authors have no

other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/gpm-21-28

Cite this article as: Manicom A, Pandit JJ. A narrative review of the role of anaesthesia and peri-operative medicine in improving outcomes after surgery for advanced ovarian cancer. *Gynecol Pelvic Med* 2022;5:16.