
REVIEW ARTICLE

The Role of Surgery in the Treatment of Ovarian Cancer

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ABSTRACT

Most patients with ovarian cancer undergo surgery at some point during the course of their treatment. A primary operation may be undertaken for the purpose of confirming the diagnosis, staging, and debulking. Numerous publications have documented the importance of proper staging in ovarian cancer, which determines the treatment plan — including whether chemotherapy is indicated — and therefore impacts substantially on patient outcomes and survival. Improper staging can lead to underestimation of the extent of the disease and under-treatment. For patients with advanced disease, complete debulking surgery improves survival significantly. If patients are not suitable for primary debulking however, neoadjuvant chemotherapy should be considered. There remains uncertainty surrounding the role and effectiveness of interval debulking surgery as opposed to standard of primary debulking surgery in the course of first-line treatment of advanced ovarian carcinoma. More evidence is needed before a conclusion can be drawn about this issue. Surgery is not limited to primary treatment, but may also be indicated for patients with recurrent ovarian cancer or to provide palliative care and symptom relief for patients who are at the end stages of the disease.

Key Words: *Diagnosis; Neoplasm staging; Ovarian neoplasms*

中文摘要

手術在治療卵巢癌中的角色

譚家輝

大部份卵巢癌患者會在治療過程中接受手術治療。為要進行病情確診、分期及減瘤，患者會進行初次手術。文獻中大量記載了為卵巢癌適當分期的重要性，因為分期決定治療計劃，包括是否需要化療，繼而會大大影響治療結果及患者生存期。分期不當會低估病情及引致不恰當的治療。至於患有晚期卵巢癌的患者，完全減瘤術可以大大提高其存活期。如果患者不適合接受初次減瘤術，可考慮引導化療。對於晚期卵巢癌的一線治療應該進行間隔減瘤術還是標準的初次減瘤術，文獻對於這兩種方法的角色及效用都未有定案，因此必須要有更多實證才能下定論。事實上，手術並非只限於卵巢癌的初次治療，亦適用於一些復發性的卵巢癌患者。在已進入晚期卵巢癌的患者來說，手術也可以提供緩解治療及起症狀緩解的作用。

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INTRODUCTION

In the management of ovarian cancer, surgery plays a central role in the settings of early, advanced, and recurrent disease. Surgery is needed to establish the diagnosis, is frequently a fundamental component of the treatment plan, and may also provide palliation for patients with intractable or recurrent disease, when preserving quality of life is as important as prolonging survival.

Interestingly, in this era of evidence-based medicine, there remain several important unanswered questions in the management of ovarian cancer that have not been adequately addressed by research to date. One key example is the role and effectiveness of interval debulking surgery in the treatment of advanced ovarian carcinoma as compared to primary cytoreduction, which is the current standard of care. When interval debulking surgery is used, there is also uncertainty regarding when to undertake it following neoadjuvant chemotherapy. Hopefully, more research into these areas will resolve these issues, thereby helping to optimise future recommendations for management.

Similarly, the availability of new chemotherapies or chemotherapeutic regimens in the treatment of ovarian cancer may represent a seismic advance. Chemotherapy is the other cornerstone of ovarian cancer treatment, and can significantly improve clinical outcomes and survival, particularly in conjunction with surgery. However, while the last few decades have witnessed chemotherapeutic breakthroughs for several other types of cancer, this has not been the case for ovarian carcinoma. To this end, there has been some excitement surrounding the clinical trials of emerging targeted therapies, and the hope is that these agents will break the stalemate in chemotherapeutic options for ovarian cancer patients.

This article aimed to provide clinicians with current insight and opinion into the role of surgery in the management of ovarian cancer. This includes discussion of areas of debate and controversy, with the view to providing treating physicians and other interested stakeholders with a real-life perspective of current clinical practice in Hong Kong and elsewhere.

ROLE OF SURGERY IN THE DIAGNOSIS OF OVARIAN CANCER

Surgery plays a pivotal role in the diagnosis, staging, and treatment of ovarian cancer. In early stages of

disease, surgery is mainly indicated for diagnosis and staging, while in late-stage disease, surgery is used for diagnosis and debulking (cytoreduction). In early ovarian cancer, tumours can be small (2-3 cm in diameter) and patients are often asymptomatic, such that cystic structures may only be discovered incidentally by ultrasonography. Prior to surgery, a number of preoperative assessments can be undertaken as part of the diagnosis for ovarian cancer. They should always include imaging studies of tumour features (revealed by ultrasonography, computed tomography, magnetic resonance imaging, and occasionally positron emission tomography). Sometimes, assessment of tumour markers, most commonly cancer antigen 125 (CA-125), and establishing the patient's risk of malignancy according to the Risk Malignancy Index, may also be useful. Collectively, these initial investigations help to define whether surgery is indicated.

Histological examination requires surgical removal of the tumour. This was traditionally performed by laparotomy with a vertical incision. In the past two decades however, laparoscopy for tumour removal has grown in popularity as this approach is less invasive, associated with a smaller and more cosmetically appealing scar and faster patient recovery. Furthermore, robot-assisted laparoscopic operations have now become available, which provide surgeons with enhanced dexterity and accuracy over the procedure.

Nevertheless, there are risks and benefits associated with both laparoscopic and laparotomy approaches, which must be weighed up for each patient. In general, the selection of the surgical approach can be based on the tumour size — a very large tumour obviously cannot be removed laparoscopically. For borderline-large tumours however, the benefits of laparoscopic removal should be assessed against the potential risk of tumour rupture and spillage. Other considerations include exposure, and the risk of tumour embolisation or port-site metastases during laparoscopy.

Exposure of the upper abdomen during surgical removal of the ovarian tumour is important as it enables a thorough physical examination to be carried out. During a laparotomy, surgeons can physically examine and palpate surrounding organs and tissue, such as the peritoneal surface and diaphragm, which is not possible with laparoscopy. The lack of exposure with the laparoscopic approach may however be compensated

by high visibility of the upper abdomen provided by this technique. In which case, superior visual clarity may provide the same quality and quantity of information as that obtained from a physical examination. Using a laparoscope, only the upper part of the left hemidiaphragm remains out of sight to the surgeon, but this can also occur with laparotomy if the initial incision is not extended high enough.

There is some concern that the increase of intra-abdominal pressure with carbon dioxide required in the laparoscopic procedure may increase the risk of tumour embolisation, but there is lack of evidence to support this proposition. Similarly, port-site metastases with the laparoscopic approach are rare, particularly in patients with early-stage disease. Patients who develop port-site metastasis generally have advanced disease with the presence of ascites.^{1,2}

ROLE OF SURGERY IN STAGING OF OVARIAN CANCER

Proper and accurate staging performed via surgery is integral to management. Staging dictates the treatment plan for each patient, particularly with respect to whether adjuvant chemotherapy is indicated or not. Without precise staging of ovarian cancer, there is a very real concern that patients may be under-diagnosed and under-treated. Increasing evidence suggests that 20 to 30% of apparent early-stage ovarian cancer cases could be upgraded to more advanced disease if proper staging were to be performed. This underscores the fact that delivery of appropriate treatment in ovarian cancer may be hampered or delayed in the absence of thorough staging.

The standard staging procedure requires total abdominal hysterectomy and bilateral salpingo-oophorectomy. In addition, the staging process may also involve peritoneal lavage for cytology, omentectomy, peritoneal biopsies, bilateral pelvic / para-aortic lymphadenectomy, diaphragmatic scraping, and appendectomy for mucinous tumours.

Omentectomy

Both supracolic or infracolic omentectomy are accepted and performed in Hong Kong and elsewhere, and there is currently no evidence to suggest a difference between these two procedures in terms of outcomes. Moreover, at present, there is no evidence to support the use of omental biopsy as a replacement for omentectomy.

Lymphadenectomy

Pelvic lymphadenectomy is not considered a difficult procedure, and bilateral lymphadenectomy can be performed with few complications. Ipsilateral lymphadenectomy may not be sufficient when there is an isolated contralateral metastasis. In such cases however, care must be taken to ensure the patient has been staged correctly to avoid under-diagnosis, which may lead to withholding of adjuvant chemotherapy and thereby major consequences in terms of patient survival.

Some studies support a positive effect on survival from para-aortic lymphadenectomy, even if performed in patients with stage 1a disease.³⁻⁸ However, there is evidence against performing the procedure in patients whose disease appears confined to the ovaries, as one study showed no additional survival benefit when performed in these patients.⁹ Since para-aortic lymphadenectomy can be associated with increased morbidity, in the absence of a clear benefit, the latter study concluded that para-aortic lymphadenectomy is not recommended in some patients. The histological subtype of the tumour seems to be partly responsible for lymph node metastases. For example, serous ovarian carcinomas are much more likely to metastasise to the lymph nodes than non-serous types.^{6,10,11} Mucinous tumours seem to have the lowest risk of lymph node metastasis.⁶

A successful outcome with para-aortic lymphadenectomy relies considerably on surgical skill and should therefore be performed by surgeons who are experienced and familiar with the procedure, in order to avoid or reduce the risk of complications such as major bleeding. There is some debate, and a lack of consensus, regarding the upper boundary for para-aortic lymphadenectomy, with some surgeons advocating up to or beyond the renal vein, while others consider up to the inferior mesenteric artery to be sufficient.

In Hong Kong, diaphragmatic scraping is no longer routinely performed in some centres as part of staging, as the findings are rarely positive. Similarly, appendectomy is reserved for mucinous tumours and positive results are uncommon.

PRIMARY SURGERY IN ADVANCED OVARIAN CANCER

In advanced ovarian cancer, surgery is used primarily for diagnosis and cytoreductive (debulking) treatment. Primary cytoreductive surgery is considered the standard

of care for advanced ovarian carcinoma in Hong Kong and elsewhere. However, this treatment may not be initially suitable for all patients. A physical examination and other considerations help to inform whether individuals are suitable candidates. These include the patient's general status, pre-morbidities, and personal wishes. In patients who are unsuitable for, or reluctant to have surgery, biopsy (and the resulting histology) could be a guide to neoadjuvant chemotherapy as an alternative form of first treatment. For example, patients with massive ascites, large bilateral pleural effusion, extensive retroperitoneal lymphadenopathy, and disease involving the porta hepatis or with bulky intraparenchymal liver disease may be more appropriate candidates for — and gain more benefit from — neoadjuvant chemotherapy than primary debulking.

The ultimate goal of primary cytoreductive surgery is to undertake optimal (complete) debulking, which may be achieved with the help of imaging. Numerous studies have shown that complete primary debulking surgery improves survival significantly. For example, complete debulking in patients with stage 3 or 4 ovarian carcinoma was associated with a median progression-free survival of around 1.5 years.¹²⁻¹⁵ Moreover, treatment outcomes were improved, and ovarian cancer survival significantly increased, whenever residual tumour following debulking was reduced to 1 cm or less in diameter. Thus, the cut-off diameter for residual tumour after optimal debulking is generally accepted to be 1 cm or less.

Neoadjuvant Chemotherapy Versus Primary Debulking Surgery

Whether neoadjuvant chemotherapy followed by debulking surgery (so-called interval debulking surgery) is as effective as primary debulking is a controversial topic in ovarian cancer management that remains unresolved, despite numerous comparative studies to address this question. In women with advanced ovarian carcinoma (stage 3c or 4), one such study published in 2010 by Vergote et al¹⁶ compared primary debulking surgery followed by platinum-based chemotherapy with platinum-based neoadjuvant chemotherapy followed by interval debulking surgery and additional chemotherapy. The results indicated non-inferiority of neoadjuvant chemotherapy followed by debulking surgery versus primary debulking; survival rates being similar in the two groups. There was also a numerically lower liability of severe haemorrhage, infection, and venous complications in the former group. However,

several shortcomings in the design and execution of this study have been pointed out. For instance, there was significant heterogeneity in baseline patient characteristics between the two study groups, making comparisons between the two groups less meaningful. Furthermore, there was also heterogeneity among the surgeons involved in the study, in terms of their skill and experience. This may have biased the survival in favour of the neoadjuvant chemotherapy group, although the true effect of inferior surgical skill on survival in the primary debulking arm cannot be quantified. Ultimately, the imbalance in surgical skill of the surgeons treating the two groups affected the survival endpoint, and calls into question the study conclusions.

ROLE OF SURGERY FOR RECURRENT DISEASE AND PALLIATION

Evidence indicates that secondary surgical cytoreduction can be effective in the treatment of recurrent ovarian cancer. Patient selection for surgery in recurrent disease is of paramount importance in order to improve survival without jeopardising the quality of life of these patients. Patients who previously had a long disease-free interval, received complete primary debulking and had resectable recurrent disease, were regarded as most likely to benefit from secondary surgery.¹⁷⁻²¹ However, the clinical impact of secondary cytoreduction on outcomes remains unclear, as studies attempting to evaluate this have been limited by differences in the definition of optimal debulking, heterogeneity of patient populations across different studies, and a lack of information on postoperative therapy. Nevertheless, a 2004 meta-analysis of relevant studies conducted up to that point showed that secondary cytoreduction was associated with a prolonged survival benefit of 44 to 60 months, in patients who were left with no gross residual disease following the secondary procedure.²² Meanwhile, combination chemotherapy (without surgery) used as salvage therapy in recurrent ovarian cancer was reported to prolong median survival by up to 35 months.²²

Surgery can also provide palliative care for patients with recurrent or intractable disease, who may not live long. In these cases, the goal is to improve quality of life, using surgery to relieve symptoms (whenever possible).

CONCLUSION

Surgery plays an important role in the management of ovarian cancer. The goals of initial surgery are to obtain a pathological diagnosis, accurately determine

the extent of disease, and when possible, optimally cytoreduce the tumour. The selection of patients for primary optimal debulking surgery should be evidence-based and successful outcomes rely somewhat on the skill of the surgeon. Ultimately, the treatment of ovarian cancer must be individualised. At all stages of management, including formulating the treatment plan, patients' understanding of procedures must be sought and their wishes respected.

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