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The Role of Lymphadenectomy in Ovarian Epithelial Cancer

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Abstract

High-grade serous ovarian/tubal cancer commonly spreads via the peritoneal and lymphatic routes. This chapter discusses the anatomical lymphatic drainage of the ovary and tube with reference to spread from different epithelial ovarian cancer types. The role of lymph node surgery in apparent early stage curative disease will be discussed with reference to staging and directing the need for adjuvant chemotherapy. In advanced disease, the role of lymph node sampling versus systematic dissection surgery as part of cytoreduction is assessed. The result of two randomised controlled trials (RCTs) published on the subject will be analysed along with the ongoing Lymphadenectomy in Ovarian Neoplasia (LION) study. The chapter adopts an evidence-based approach to the role of lymph node surgery in women with epithelial ovarian/tubal cancer.

Keywords: epithelial ovarian/tubal cancer, high-grade serous, para aortic lymph node, pelvic lymph node, systematic dissection sampling, FIGO staging

1. Introduction

The modern of management of women with ovarian involves complete surgical cytoreduction of all visible disease [1]. It is therefore important to understand that approximately 70% of the women will also have lymphatic spread. Even in disease, apparently confined to one or both ovaries, there is evidence of nodal metastatic spread in up to 24% of women [2].

2. The lymphatic drainage of the ovaries

An understanding of the lymphatic drainage of the ovary and fallopian tube is important in the management of women with ovarian cancer. There are three main lymphatic pathways. The principal pathway is along the ovarian vessels through the infundibulopelvic ligament to the para aortic and para caval nodes surrounding the aorta and inferior vena cava (IVC). The second pathway occurs through the broad ligaments into the pelvic nodal region. Of note, spread to contralateral pelvic nodes in women with a unilateral cancer is reported in up to 30% of women [3]. Therefore, a bilateral pelvic node dissection (PND) is recommended even with unilateral apparent stage 1 tumours.

A third lesser route is through the uterine round ligament to the inguinal nodes. In addition, women with disease involving the rectum or sigmoid colon may have tumour spread to the mesocolic lymph nodes within the sigmoid mesentery.

3. Is histopathological type important?

Over the last decade, the understanding of the pathogenesis of epithelial ovarian cancer has changed. The most common histopathological subtype, high-grade serous cancer (approximately 70–80% of cases) appears to arise in the distal fallopian tube [4]. Most of these women present with disease spread to the transperitoneal surfaces and to the lymph system. The majority of this chapter will be concerned with the role of lymphadenectomy in this group of women.

Less common types of ovarian cancer include endometrioid, clear cell, low grade serous and mucinous tumours. These appear to have separate aetiologies with a different risk of lymphatic spread. The risk of nodal metastases appears to be lower in endometrioid and mucinous cancers. For example, a meta-analysis of 278 women with apparent early mucinous cancer of the ovary who underwent a full pelvic and para aortic nodal dissection reported an incidence of involved nodes of only 1.2% [5]. Most authors no longer recommend a lymphadenectomy in early mucinous cancers.

4. What are the methods of surgical assessment?

A definition of a pelvic node dissection (PND) is widely accepted in the gynaecological oncology literature [6]. PND includes bilateral removal of nodal tissue from the distal one-half of each common iliac artery, the anterior and medial aspect of the external iliac artery and vein to the level of the deep circumflex artery, and obturator fat pad anterior to the obturator nerve. The medial aspect of the dissection is the hypogastric artery. Enlarged nodes below the obturator nerve should also be removed. The obturator nerve should be identified and guarded prior to any sharp dissection. The nodes should be swept away from the nerve with careful attention paid to the area below the nerve to avoid damage to the numerous vessels present in this area. The ideal scenario is to remove the node in a single nodal unit to reduce

the risk of nodal fracture leading to possible tumour dissemination and port site metastases. A PND may be performed either as an open procedure or as part of a laparoscopic procedure. Laparoscopic surgery lends itself to PND due to the increased magnification and illumination of the surgical field and dissected nodes can be removed through an 11/12 mm suprapubic port or removed via the vagina if a hysterectomy is performed.

Para aortic assessment/dissection has in contrast to pelvic nodes not been well quantified. Pomel et al. [7] have published a proposed classification of para aortic node assessment which ranges from radiological assessment and palpation to a full systematic dissection of all nodal tissue including the dorsal surfaces of the vessel (**Table 1**).

Open para aortic dissection (type A1 to B1) requires a generous midline abdominal incision to the xiphisternum and a self-retaining retractor to allow access to the great vessels. The right side of the colon and small bowel are mobilised by incising the peritoneum at the level of the right common iliac artery extending medially and caudally to the fourth part of the duodenum and then incising the peritoneum along the right paracolic gutter to the hepatic flexure. This allows the surgeon to perform called 'Kocher manoeuvre' mobilising the bowel off both the right renal fascia and ureter and to be retracted out of the abdomen. Following this, the surgeon should identify the left ureter lying medially underneath the inferior mesenteric vein. The node dissection should not start until all the important anatomical structures have been identified including the inferior mesenteric artery (IMA).

Laparoscopic PA node dissection is well described in the literature and can be performed either via the conventional transperitoneal route or via an extra peritoneal route. Both routes require a high degree of laparoscopic training and is considered unlikely to replicate a systematic node dissection (Pommel type A) but rather an extensive node sampling (Pommel type B1–2).

Type	
A	**Systematic para aortic node dissection**
A1	Complete (includes infrarenal and suprarenal up to coeliac trunk to midpoint of common iliac vessels)
A2	Infrarenal (as above, but does not include suprarenal dissection)
A3	Infra inferior mesenteric artery (IMA) (as above but does not include dissection above IMA)
B	**Para aortic sampling**
B1	Extensive (incudes para aortic areas, but does not allow full visualisation of structures—adventicia of vessels. Renal vessels, anterior common vertebral ligament, psoas muscle and sacrum
B2	Minimal (includes limited para aortic areas, and does not allow visualisation of structures above)
C	**Non-excisional assessment**
C1	Palpation (direct) following full exposure of PA area
C2	Palpation (indirect), transperitoneal without any exposure
C3	Radiological assessment by PET/CT or MRI

Table 1. Proposed classification of para aortic node assessment (Pomel et al. [7]).

5. What is the role of lymphadenectomy in apparent early stage ovarian cancer?

A number of women will undergo surgery for an apparently benign ovarian cyst. Postoperatively, those women with confirmed malignancy can be offered staging including lymphadenectomy. Approximately, 30% of women with ovarian cancers apparently confined to the ovaries will be upstaged following further surgery including a pelvic/para aortic node dissection/sampling (Pommel type B1) with a gynaecological oncologist [8].

It is important to understand that lymph node status is not the only factor that determines the need for adjuvant chemotherapy. Many centres offer chemotherapy to women with stage Ic or above cancers, high-grade lesions and all clear cell cancers of the ovary [9].

However, node status is important for a number of reasons: it may influence whether or not chemotherapy is given, the number of cycles or types of chemotherapy and it may result in complete cytoreduction of the cancer. Node status also partially determines the true FIGO stage and prognosis.

The ACTION trial was a randomised controlled trial (RCT) of 448 women with stage IA, IB grades 2–3, all IC, IIA and all clear cell cancer stage I–IIA and compared the administration of adjuvant chemotherapy with a control arm. The main finding showed overall survival was significantly better with the administration of chemotherapy. A subset analysis revealed that stage I patients with complete surgical staging did not benefit from chemotherapy contrast to patients that underwent incomplete staging [10]. Long-term follow-up of this study has confirmed these results [11]. It has been surmised that patients that have not being staged harbour more advanced disease, and therefore have a poorer prognosis and chemotherapy does not compensate for incomplete staging.

In older women with complex masses or those felt to have a high risk of cancer, an intraoperative frozen section histopathological analysis may be performed. A study from the Gateshead Gynaecological Oncology Centre reported a with a sensitivity of 92%, specificity of 88%, positive predictive value of 82% and negative predictive value of 95% for frozen section analysis [12]. This is equally important in determining which women should not be exposed to unnecessary surgery such as a para aortic node dissection.

Laparoscopic staging is possible, though requires a high degree of specialist training. Several centres have reported on full laparoscopic staging and have found it feasible [13, 14]. Chi et al. performed a case control study comparing staging via laparoscopy or laparotomy in 80 women [13]. They found no difference in specimen sizes and lymph nodal counts. The laparoscopic group had levels of reduced blood loss and a reduced hospital stay. A laparoscopic nodal dissection/sampling should include both the pelvic and para aortic basins to the level of the renal vessels. A case series by Nezhat et al. [15] concluded that laparoscopic staging when performed by a gynaecological oncologist did not compromise survival.

Robotically assisted laparoscopic surgery is an evolution of minimal access surgery rather than a revolution. Perceived benefits include three-dimensional vision, control of the laparoscope by the operating surgeon, more precise instrument movement and a shortened learning

curve. Perhaps, the biggest advantage is the use of instruments that fully articulate at the end in the manner of a human wrist allowing fine delicate movements. This is particularly important in the obese patient, where the increased thickness of the anterior abdominal wall produces an increased torque effect leading to decrease manoeuvrability of standard laparoscopic instruments. Robotic platforms have been used in staging apparent ovarian cancer and appear comparable to laparoscopic surgery [16–19].

Maggioni et al. [20] reported a randomised controlled trial of 268 women with apparent stage 1 or 2 ovarian epithelial cancer. The women were randomised to either a random sampling of pelvic and PA nodal basin or systematic dissection (pommel type A) of the same areas. Positive nodes were found in 9% of the control group and in 22% of the SLD group. No significant difference was recorded in 5 years year overall survival (84.2 vs. 81.3%) or progression free survival (PFS) (78.3 vs. 71.3). The SLD group had a significantly longer operating time, blood loss and blood transfusion.

In view of the results of this study, SLD should not be offered over more limited dissection/sampling (pommel B) in women with apparent early ovarian cancer.

6. What is the role of lymphadenectomy in advanced ovarian cancer?

The goal of surgery in advanced ovarian cancer is to remove all visible disease including a removal of all enlarged lymph nodes. This requires intraoperative assessment of the bilateral pelvic nodes and the para aortic region (pommel type C1–B1).

Given that the nodal basin is considered by some to be relatively chemotherapy insensitive, this to the question whether removal of all involved microscopically and macroscopically involved nodes has a therapeutic benefit.

Panici et al. [21] reported a randomised controlled trial of 268 women with apparent stage IIIB, IIIC/IV cancer. The women were randomised to either resection bulky of pelvic and PA nodes or systematic dissection of the same areas. Positive nodes were found in 42% of the control group and in 42% of the SLD group. No significant difference was recorded in 5 years year overall survival (47 vs. 48.4%). A significant 7-month extension in progression free survival (PFS) was demonstrated (29.4 vs. 22.4 months). The SLD group had a significantly longer operating time, blood loss and blood transfusion. Subsequently, the authors have suggested that the study may be underpowered to detect an overall survival difference.

7. Common complications

7.1. Vascular injury

Working in close proximity to the large blood vessels poses a risk of major haemorrhage. Reducing this risk involves an appropriate surgical incision with a good operative exposure involving dissection/identification of anatomical structures. This allows easier identification

of vascular anomalies and reduces the risk of collateral damage to structures such as the kidney and ureter. Initial management includes pressure to the area and appropriate communication with the rest of the team including the anaesthetist. Small vascular injuries may be oversewn using a vascular needle and small monofilament suture, ideally avoiding constricting the vessel's diameter. Larger defects require the vascular clamp and the expertise of a vascular surgeon.

7.2. Lymphocyst formation

The incidence of lymphocyst after the para aortic/pelvic dissection maybe as high as 43% [22]. The vast majority of these will resolve spontaneously and do not require any intervention. Occasionally, a larger lymphocyst may require aspiration typically by interventional radiological drainage. Occasionally, chylous ascites develop in association with an aortic node dissection especially at the level of the renal vessels. This illustrates the importance clipping large lymphatic channels especially in this region. Management of how chylous ascites includes the low-fat diet, the administration of somatosatin and occasionally total parenteral nutrition.

7.3. Other complications

Other complications associated with lymph node dissection include postoperative ileus, damage to the duodenum, damage to relevant nerves and long-term lymphoedema.

8. Ongoing research into lymphadenectomy

8.1. Early stage ovarian/tubal cancer

Serous tubal intraepithelial carcinoma (STIC) is now considered the precursor lesion for high-grade serous cancer [4]. STIC may be an incidental finding in women undergoing a salpingectomy for benign reasons and the incidence is expected to rise in women undergoing risk reducing surgery for ovarian/tubal cancer. The management of women with STIC as an incidental finding it is unclear. It is apparent, the percentage of these women will have disseminated spread of high-grade serious cancer. Based on small series, authors have suggested comprehensive surgical staging including lymphadenectomy [23, 24]. This is relatively a new condition with larger case series publication expected over the next few years.

8.2. Advanced stage cancer

Following the Panici study reporting a significant difference in PFS, the role of a full systematic node dissection is the subject of two randomised controlled trials, the Lymphadenectomy in Ovarian Neoplasia (LION) and CURACO trials [21].

The Lymphadenectomy in Ovarian Neoplasia (LION) study is an AGO randomised controlled trial including women with FIGO stage IIB–IV ovarian epithelial cancer and complete

macroscopic resection of all disease. Around 640 women were randomised to either a full systematic lymph node (SLN) or no lymph node dissection and the study results are due in late 2017. The primary end point is overall survival (OS) and secondary endpoints include progression free survival (PFS) and quality of life (QOL).

The French CURACO trial is a randomised controlled trial including women with stage III–IV epithelial ovarian cancer with complete macroscopic resection. The women are being randomised to SLN versus no node dissection. The primary end point is progression free survival.

9. Conclusion

Spread to the lymphatic system is common in epithelial ovarian cancer is common and is an early event. Para aortic and bilateral pelvic node dissection sampling (Pommel type B1) should be included in surgical staging to determine chemotherapy use and to improve prognosis in ovarian cancer apparently confined to the ovary based on the results of the ACTION trial.

In women with advanced ovarian, the retroperitoneal lymph nodes should be assessed and bulky lymph nodes removed in an attempt to achieve complete cytoreduction. Systematic lymph node (SLN) of the para aortic nodes should not be routinely performed pending the results of the LION and CURACO studies.

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