Controversies in the Management of Ovarian Cancer – Pros and Cons for Lymph Node Dissection in Ovarian Cancer

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Abstract. Up-front maximal surgical effort towards cytoreduction with the primary goal of maximum tumour resection is one of the cornerstones in the multimodal management of ovarian cancer. Despite the prognostic relevance of lymph node metastasis, there is a great debate about the role of pelvic and para-aortic lymph node dissection. In early-stage ovarian cancer, lymph node dissection is required to make an accurate clinical staging according to the FIGO classification and to select adequate adjuvant therapy. The effect of lymph node dissection on progression-free survival and overall survival in patients with advanced ovarian cancer is still unknown. There has only been one randomized trial which favoured systematic lymph node dissection instead of lymph node sampling due to significantly better progression-free survival, but there was no difference in overall survival. Patients with postoperative tumour residuals are unlikely to benefit from this procedure. The German AGO has now initiated the first study in advanced ovarian cancer (LION) which compares the value of systematic lymph node dissection with no lymph node resection in patients without any visible tumour residuals. Until these data are in fact available, patients with advanced ovarian cancer should be informed in detail about the pros and cons of systematic lymph node dissection.

Despite significant improvements in the treatment of patients with ovarian cancer, this tumour entity remains the leading cause of death of all gynaecological malignancies (1). Although most patients are present with bulky intraperitoneal disease in an advanced tumour stage, patients with a macroscopic completely resected tumour had a five year survival of more than 50% (2). Therefore cytoreductive surgery remains the cornerstone in the management of ovarian cancer (3-5). Ovarian cancer spreads mainly in an intraperitoneal manner but retroperitoneal metastases are also frequent in all stages of ovarian cancer. Lymph node metastasis is generally correlated with poor clinical outcome (6-10). Despite its prognostic indication, the impact on overall survival remains unclear and is controversially discussed in the current literature (9, 11, 12).

In the present article, we discuss adequate techniques and the pros and cons of lymph node dissection in the management of both early stage and advanced ovarian cancer.

Procedure

In the current literature there are different descriptions available for lymph node dissection, whereby most studies do not differentiate between lymph node sampling and systematic lymph node dissection. In general, sampling means the resection of single lymph nodes, mostly of bulky nodes, whereas systematic lymph node dissection is defined by the resection of enlarged and non-enlarged lymph nodes by the preparation of all pelvic and para-aortic lymph node regions. Systematic pelvic and paraaortal lymphadenectomy includes the removal of lymph nodes in specific areas such as: the upper para-aortic region above the inferior mesenterial artery (IMA), the lower para-aortic region between the IMA and the bifurcation aorta, the inter-aortocaval region, the right paracaval region (Figure 1), the iliaca communis region, the iliaca externa region, the fossa obturatoria region and the iliaca interna region (Figure 2).

An incision is made in the peritoneum overlying the right common iliac artery. The incision is carried up over the aorta to the level of the transversal segment of the
duodenum. Using blunt dissection, the right ureter and the ovarian vessels are identified and mobilized laterally. The ligamentum infundibulopelvicum carries the ovarian vein and artery and up to seventeen lymph vessels, and should be removed close to its origin at the vena cava. To avoid ureter fistulae, the nutritional vessels of the ureter should be preserved. Vascular abnormalities are frequent and can be observed in 13.6% of cases; anatomic variations of the veins are generally more frequent than variations of the arteries (Figures 3-5). Lymphatic drainage parallels the course of venous blood supply. However, drainage is not always as straightforward as is the blood supply. Lymph node metastases can obstruct lymph flow and can lead to retrograde metastases which appear to skip regional chains. Thus, some patients with ovarian cancer can have an isolated para-aortic lymph node spread through the lymph vessels of the infundibulopelvic ligament and show a retrograde lymphatic spread.

To perform a systematic pelvic lymph node dissection it is essential to distinguish between the different anatomic spaces around the pelvic vessels and structures. To simplify matters, it may be helpful to visualize three associated spaces: I. lateral pelvic wall. Entrance between the medial part of the psoas muscle and laterally from the external iliac artery; II. Paravesical fossa. Entrance between the posterior wall of the urinary bladder and the external pelvic vein; III. Obturator fossa. Entrance between the external iliac vein and medial umbilical artery.

The kidney vein is generally accepted to be the upper margin of the para-aortic lymph node dissection, but in some cases, higher lymph node metastasis may be observed. Generally, for the retroperitoneal access, the right colon will be mobilized and a transversal incision above the common iliac artery will be used. Then the inferior mesenteric artery can be identified.

Additionally, a supraduodenal access, medial from the gerrota fascia can be used to remove right suprarenal metastases (9, 13).

The peritoneum is not closed, and retroperitoneal drainages are not always necessary.

Systematic Lymphadenectomy in Early Ovarian Cancer

Systematic lymphadenectomy has a clear diagnostic value in early-stage ovarian cancer and is a crucial part of accurate clinical staging according to the FIGO classification (11, 14-16). In retrospective series, the rates of positive lymph nodes vary between 11% and 20% (7, 14, 16-20). In a consecutive Charité cohort of 88 patients having stage I or II, lymph node metastasis was found in 14 cases (15.9%), whereby in 14 cases pelvic (15.9%) and in 10 cases (11.4%) para-aortic metastases were documented.

An accurate staging is therefore mandatory for the indication of adequate adjuvant chemotherapy (21). According to the FIGO classification, FIGO stage IIc is defined by the presence of pelvic or para-aortic lymph node metastasis. For these patients, 6 cycles of paclitaxel and a platinum compound is considered as the gold standard of adjuvant chemotherapy.

In contrast to this, as based on large randomized studies, only three cycles or carboplatin plus paclitaxel or four cycles of carboplatin monotherapy are the best treatment options for early-stage ovarian cancer (FIGO I) (22, 23).

Nevertheless, the impact of lymph node dissection on progression-free survival and overall survival still remains unclear.

In 2006 Maggioni and co-workers published the first randomized study on the value of systematic aortic and pelvic lymphadenectomy (SL) in comparison with lymph node sampling in ovarian cancer macroscopically confined to the pelvis. Overall, 268 out of 310 patients were randomized: 138 to systematic lymphadenectomy and 130 to lymph node sampling (control group). After a median follow-up of 87.8 months, the adjusted risks for progression (hazard ratio [HR]=0.72, 95% CI=0.46-1.21, p=0.16) and death (HR=0.85, 95% CI=0.49-1.47, p=0.56) were lower, but in the SL group, were no more statistically significant than the control arm (24). Five-year progression-free survival for the control group and the SL group was 71.3 and 78.3% respectively, and 5-year overall survival was 81.3 and 84.2%, thus slightly favouring the SL group. These differences were, however, not significant.

Recently, in regard to the SEER database, Chan and co-workers reported a significant association of lymphadenectomy and overall survival in stage I ovarian cancer patients. Overall, 6,686 patients with stage I ovarian cancer were included in this analysis. The 5-year survival was significantly better in the group of patients with lymphadenectomy (92.6% compared to 87%, p<0.001) (25).

In 2008 Chan and co-workers evaluated the progress and trends in the treatment and survival of women with early-stage (I–II) epithelial ovarian cancer, again in relation to the SEER database. Of the 8,372 patients, a total of 6,152 patients (73.4%) presented with stage I and 2,220 (26.5%) with stage II disease. Over the periods 1988-1992, 1993-1997, and 1998-2001, 3-year disease-specific survivals increased from 86.1 to 87.2 to 88.8% (p=0.076) (6). At the same time, the number of patients who underwent a lymphadenectomy also increased significantly from 26.2 to 38.7 to 54.2% over the study period (p<0.001).

Many lymph node metastases are present in non-bulky nodes and have a diameter measuring uncommonly no more than 2 mm, so that palpation of lymph node metastasis is not a safe evaluation method (7, 16, 20, 24, 26). All available radiological techniques, such as ultrasound, Magnetic Resonance Imaging, Computer Tomography or Positron Emission Tomography are
Figure 1. Para-aortic region with landmarks exposed.

Figure 2. Left pelvic side wall.
Figure 3. Running right kidney artery above the vena cava.

Figure 4. Double vena cava.
also unable to detect lymph node metastasis precisely (27). In experienced tumour centres, the number of systematic lymph node dissection procedures employed is very low (11).

**Systematic Lymphadenectomy in Advanced Ovarian Cancer**

According to the FIGO classification, tumour masses larger than 2 cm, or the presence of lymph node metastasis lead to stage IIIc. But FIGO IIIc based only on lymph node involvement is associated with a better outcome than is true intraperitoneal FIGO IIIc (28, 29). The role of lymphadenectomy in advanced ovarian cancer is still under controversial debate (5, 10, 30, 31). Most of the recommendations in the older guidelines were based on non-randomized monocentric studies. For instance, Aletti and co-workers reported on a series of 219 patients with advanced ovarian cancer. A surgical lymph node assessment was performed on 93 (41%) of the patients: in 61 cases as systematic lymphadenectomy (LND) and in 32 as sampling (LNS). Overall 5-year survival was 26%. In patients with optimal cytoreduction with more systematic lymphadenectomy, the 5-year overall survival was 50% in contrast to 33% in the sampling collective, and only 29% in patients without any lymphadenectomy. In the patient cohort with residual disease, no association between the type of lymph node dissection and the clinical outcome was observed (8).

Chan and co-workers have explored the SEER database concerning the impact of lymph node dissection on the clinical outcome. Of 13,918 women with stage III–IV epithelial ovarian cancer, a total of 4,260 (30.6%) underwent lymph node dissections with a median number of six resected nodes. For all patients, a more extensive lymph node dissection (0, 1, 2-5, 6-10, 11-20, and >20 nodes) was associated with an improved 5-year disease-specific survival of 26.1, 35.2, 42.6, 48.4, 47.5, and 47.8%, respectively (p<0.001). Of the stage IIIC patients with nodal metastasis, the extent of nodal resection (1, 2-5, 6-10, 11-20, and >20 nodes) was associated with improved survival of 36.9, 45.0, 47.8, 48.7, and 51.1%, respectively (p=0.023). On multivariate analysis, the extent of lymph node dissection and number of positive nodes were significant independent prognostic factors adjusting for age, year at diagnosis, stage, and grade of disease (6).

Du Bois and co-workers reported a very interesting retrospective subgroup analysis based on three large prospective randomized chemotherapy trials of the AGO (Arbeitsgemeinschaft für Gynäkologische Onkologie) study group with 3,336 patients having primary ovarian cancer.

Figure 5. Running vena renalis sinistra under the aorta abdominalis.
Overall, 1,059 (32%) had no post-operative tumour residuals. Of these patients, 757 (72%) had some extent of lymphadenectomy. The 5-year survival for patients having a lymphadenectomy was 66%, compared to 55% for patients having no lymphadenectomy ($p<0.003$) (32).

In the analyses of patients with post-operative residuals there was no significant survival advantage for patients who underwent a lymphadenectomy (32).

The first prospective randomized study has evaluated the impact of lymphadenectomy on progression-free survival and overall survival in 452 patients with advanced ovarian cancer (33). This study was restricted to patients with primary ovarian cancer (FIGO stages IIIb/c and Iva) and to these with intraperitoneal residual tumour lesions having a maximum diameter of less than 1 cm. The patients were randomized to systematic pelvic and para-aortic lymphadenectomy, or resection of bulky nodes only. Lymph nodes were considered bulky if they were 1 cm in diameter. In the lymphadenectomy arm, patients had to have resection of at least 25 pelvic nodes and more than 14 para-aortic nodes.

The median number of extirpated lymph nodes were 4 (range 0-11) in the sampling group and 51.5 (range 41-70) nodes in the systematic lymph node-dissected group.

After a median follow-up of 68.4 months, there was a 7-month benefit in progression-free survival for patients in the lymphadenectomy arm (29.4 and 22.4 months, respectively) but no benefit in terms of overall survival. However it should be noted that: i) The study took more than 12 years to complete the patient enrolment; ii) Overall, 452 patients were enrolled from 13 centres; iii) 63% of the patients had intraperitoneal residuals.

Due to the long recruitment period and the fact that a median of 2.8 patients were recruited annually, a significant selection bias cannot be excluded. For instance, in the United Kingdom, only two patients were recruited per year. Furthermore, as based on different non-randomized trials and subgroup analyses, it seems to be more likely that patients without any tumour residuals will benefit from lymph node dissection than will patients with residuals (34, 35). In this study, only 37% of all patients were without any macroscopic tumour lesions. To summarize, for this entire group, the study is completely insignificant and unable to demonstrate any potential advantage of systematic lymph node dissection.

Therefore, the German AGO study group has now initiated a large international trial in an attempt to answer the clinically relevant question of whether systematic lymph node dissection does indeed influence the overall survival in advanced ovarian cancer. In this trial, 640 patients will be recruited with the following inclusion criteria: FIGO IIB – IV, ECOG 0/1, no contraindication against lymph node dissection, no presence of visible extra-abdominal and intra-abdominal tumour residuals, and no bulky lymph nodes.

**Conclusion**

In early stage ovarian cancer, systematic lymph node dissection is required in order to perform accurate clinical staging and to select an adequate adjuvant systemic chemotherapy. Nevertheless, the effect of lymph node dissection on progression-free survival and on overall survival is still unclear.

For advanced ovarian cancer with minimal tumour residuals of up to 10 mm, it can be concluded that systematic lymph node dissection will produce a significant benefit in progression-free survival, but not in overall survival when compared to lymph node sampling only.

Today, for patients without any visible postoperative tumour residuals many guidelines recommend, that systematic lymph node dissection be performed despite the lack of evidence from randomized trials. Therefore, the conduction of prospective studies is really warranted. Until results from the prospective trial become unavailable, patients with advanced ovarian cancer should be informed in detail about the pros and cons of lymph node dissection.

**References**