What is the evidence for lymphadenectomy in presumed early ovarian cancer?

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Introduction

In 2017 the results of the LION phase III prospective randomised trial (LION: lymphadenectomy in ovarian neoplasms—a prospective randomized AGO study group led gynaecologic cancer intergroup trial), investigating the value of systematic lymph node dissection (LND) in advanced ovarian cancer, were published, demonstrating no progression free or overall survival benefit for systematic lymphadenectomy in advanced ($\geq$ IIB) patients with complete tumour clearance and macroscopically normally appearing lymph nodes. Primary endpoint of the study was overall survival. Secondary endpoints were morbidity and perioperative mortality. These data were a game changer in establishing the optimal management standards of advanced disease and has significant implications in national and international guidelines.

The special and novel aspect of the LION study was that all participating centres had to demonstrate for their eligibility a high standard surgical quality and expertise via the submission of operation and histopathology protocols and morbidity and mortality records. Despite the advanced tumor stage of the included patients, the reached median overall survival of the entire cohort was with 67.2 months high, whereas the 5-year survival rate was 55.9%. Nevertheless,

the study failed to demonstrate any PFS or OS survival benefit from the systematic LND despite the fact that 55.7% of the patients in the LND arm had histologically confirmed positive lymph nodes. Surgical morbidity was significantly higher in the LND arm with a relaparotomy rate of 12.4% versus 6.5% and grade III–IV infections of 25.8% versus 18.6%, whereas the perioperative mortality was with 3.1% versus 0.9% also significantly higher in the LND arm [1].

The study investigators concluded that patients with advanced ovarian cancer and macroscopically normally appearing lymph nodes do not have any survival benefit from a systematic LND, whereas they experience significantly higher surgical morbidity and mortality. For that reason, systematic LND should not be part of the debulking procedures in advanced stage IIB–IV ovarian cancer any more, in the absence of bulky nodal disease. Most patients included in the study presented with $\geq$ FIGO-stage IIIB (FIGO classification 1989) and a high-grade serous subtype.

The results of the LION study have raised doubts about the value of systematic lymphadenectomy also in early ovarian cancer. In the present article, we will discuss the evidence of systematic LND in presumed early stages ovarian cancer.

The value of LND as staging procedure in presumed epithelial early ovarian cancer

In early stages of the disease the value of lymphadenectomy is primarily to define the accurate stage that will have clinical implications on the future adjuvant management. For

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example, in patients with confirmed FIGO stage IA G1 disease adjuvant therapy can be omitted as opposed to patients with histologically proven positive nodes, that will upstage to a FIGO stage IIIA (FIGO classification 2014), and as a consequence will require postoperative systemic treatment with six cycles of paclitaxel and carboplatin. In addition to standard cytotoxic chemotherapy, these patients could be offered antiangiogenic therapy with bevacizumab as per the results of the GOG 218 study and the ICON 7/AGO OVAR 11 study and as approved by the EMA. In these studies, a significant survival advantage in progression-free survival was shown for patients receiving bevacizumab in contrast to patients who did not.

Rates of nodal involvement in presumed early ovarian cancer and associated risk factors

Grabowski et al. demonstrated that patients with presumed early ovarian cancer stage FIGO I–IIA, who had completion staging after incomplete initial surgery, appeared to have positive paraaortic nodes in 32% and pelvic nodes in 11% of the cases [2]. In a further retrospective study of Powless et al. the rate of affected lymph nodes in 190 patients with presumed early ovarian cancer was 13%, while it was significantly higher in those patients who underwent systematic pelvic and paraaortic LND (16%) compared to LN sampling alone (8%) [3]. Also in this study, as in many others previously, the risk of paraaortic lymph node involvement was with 53% higher than the pelvic lymph node involvement. A pelvic and paraaortic lymph node involvement was present in 21% of the patients. Bilateral adnexal involvement, positive peritoneal washings, presence of ascites, high-grade disease (24% in G3 versus 3% in G1 and G2) and serous histological subtype could be identified as risk factors for nodal involvement [4]. Serous tumours had a significantly higher rate of nodal involvement (28%) compared to other histological subtypes (11%). In the study of Powless, there was no LN involvement in mucinous subtypes [3].

The current body of evidence is clear that nodal involvement in low-grade mucinous ovarian cancer is negligible, and therefore, a lymph node staging does not seem to be necessary in low-grade mucinous tumours [5]. In contrast, frequency of positive nodes was found to be higher in low-grade serous ovarian cancers. A large multicentre retrospective collaborative study by Minig et al. evaluating the incidence of nodal involvement in presumed early low-grade ovarian cancers demonstrated that serous histology was associated with a 10.7% risk of positive LN, as opposed to a much lower risk of 1.5% in endometrioid subtypes [5].

Therapeutic value of systematic LND

Is there any prospective randomised evidence to suggest a possible therapeutic value of systematic LND in presumed early ovarian cancer?

The analysis of the surgical data of the EORTC trial, a study that investigated prospectively the benefit of adjuvant chemotherapy compared to follow-up alone in early ovarian cancer, demonstrated a survival advantage for patients with adequate staging comprising at least a sampling of retroperitoneal lymph nodes. Patients with incomplete staging had twice the risk of dying from their disease compared to patients who had undergone a comprehensive peritoneal and lymph node staging (HR 2.17, CI 1.25–3.76, $P = 0.005$) [6].

In the retrospective analysis of the SEER database, lymph node staging in early ovarian cancer was associated with a higher 5-year survival of 92.6% versus 87.0% in unstaged patients ($P < 0.001$). Moreover, the number of removed nodes correlated with survival. In multivariate analysis LND was shown to have an independent prognostic impact on survival [7].

However, it has to be stated critically, that both studies were retrospective without any randomisation to LND, therefore, there could be obvious bias that patients with comorbidities were more likely to be spared lymph node staging, whereas in fit patients it was performed more frequently. Therefore, the shown survival benefit may have been due to the better health status of the patients rather than the LND itself. Beyond that, it has to be kept in mind that unstaged patients with presumed early stage ovarian cancer have a high risk of occult stage III disease and hence the unstaged group has as an overall cohort a more unfavourable prognosis, since it also includes stage III patients who would have otherwise not been included in the final analysis, if known through comprehensive staging.

The only study which examined in a prospective randomised design the potential therapeutic value of systematic lymphadenectomy in presumed early ovarian cancer did not have the statistical power to detect a difference in survival due to the low number of cases. Solely a trend for an advantage in progression-free survival (5-year survival rate 78.3%) was seen in patients with complete nodal staging compared to patients with lymph node sampling alone (5 year survival rate 73.4%, $P = 0.166$) (Fig. 1) [8]. Moreover, this study demonstrated that sampling of nodes was not adequately sufficient to detect all occult lymph node disease. In the lymph node sampling group nodal involvement was found to be 9% with 5.5 removed nodes in median, as opposed to 22% in patients who underwent systematic lymphadenectomy and who had a median number of removed lymph nodes as high as 47. These data have clearly demonstrated the inadequacy
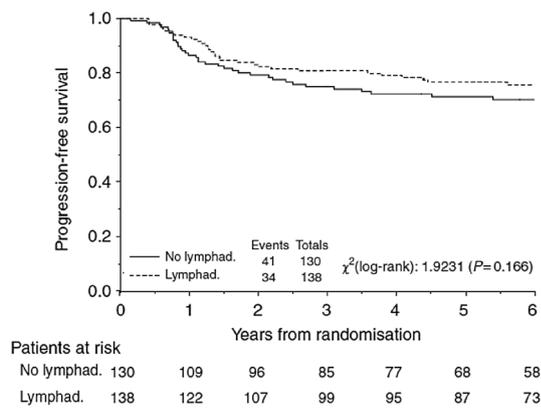
Fig. 1 Progression-free survival in patients with early ovarian cancer in relation to performance of systematic pelvic and paraaortic lymphadenectomy. 5-year progression-free survival rate was 73.4% versus 78.3% (95% CI 5.9–12.5%, not significant) in patients without lymphadenectomy compared to patients with lymphadenectomy (adapted from [8])

of LN sampling alone to detect occult microscopic nodal disease in presumed early ovarian cancer [8].

In summary, there is so far only indirect evidence for a therapeutic value of systematic LND in presumed early ovarian cancer, which can be possibly attributed to the derived staging effect.

Conclusion

The results of the LION study affect only patients with advanced, i.e. ≥ IIB epithelial ovarian cancer and should not have any implications on the management and staging procedures of early disease. Systematic paraaortic and bilateral pelvic LND remains the standard of a comprehensive surgical staging in presumed early ovarian cancer. The definition of the accurate stage has significant prognostic and therapeutic implications and is, therefore, essential part of the currently updated national German guideline recommendations. [9].

Lymph node sampling or only ipsilateral pelvic LND in cases with unilateral adnexal involvement is not sufficient to reliably detect occult nodal involvement and should, therefore, not be performed instead of systematic LND.

Outlook

Validation of molecular markers and development of imaging methods able of accurately predicting nodal status in presumed early ovarian cancer should be pursued in future studies. Sentinel node detection with indocyanine green is currently investigated and may be an option for a less invasive staging in early ovarian cancer in future [10]. Furthermore, new molecular guided imaging studies could help to determine nodal status in a non-invasive, but nevertheless reliable modus.

Compliance with ethical standards

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