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Editorial

Early-stage epithelial ovarian cancer: is systematic lymph node staging mandatory?

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▸ See the article "The impact of lymph node dissection on survival in patients with clinical early-stage ovarian cancer" in volume 32, number 3, e40.

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The indication for lymph node dissection (LND) in ovarian cancer patients has been a major topic of debate in the last decades. The recent prospective LION trial [1], demonstrated no outcome benefit of systematic LND in advanced disease with macroscopically complete resection and clinically normal lymph node (LN), and by that ended the debate in these cases. For early disease, things appear to be more complicated and data is conflicting. Maggioni et al. [2] showed some 20 years ago in a prospective randomized trial with the primary endpoint of positive LN, that they could be identified more often by systematic LND compared to LN sampling. Unfortunately, this trial was not powered for efficacy. Several large retrospective studies have demonstrated inconsistent results regarding the therapeutic potential of systematic LND in these cases.

In the clinical world, comprehensive surgical staging, including systematic bilateral pelvic and paraaortic LND up to the left renal vein, still play a pivotal role in early stage disease (International Federation of Gynecology and Obstetrics [FIGO] stage I–IIA) due to the following reasons: occult LN metastases in apparent early stage disease range from 6% to 30% (mean incidence 15%), depending on the histological subtypes und grading [3-5]; systematic LND determines the accurate FIGO stage, and by that, the optimal adjuvant chemotherapy regimen occasionally followed by maintenance therapy; and importantly, it provides valuable prognostic information [3]. However, compared with peritoneal staging, systematic LND is a complex procedure requiring surgical expertise, and could be potentially associated with intra- and post-operative complications. Therefore, it is of utmost importance to define the role of surgical staging in the treatment of patients with early ovarian cancer.

Deng and colleagues [6] have tried to address this challenge in their retrospective cohort study titled "The impact of lymph node dissection on survival in patients with clinical early-stage ovarian cancer" published in this issue of the Journal. The authors investigated a total of 400 apparent early-stage ovarian cancer patients which were divided into 2 groups: with and without lymph node resection. The 5-year progression-free and overall survival rates were comparable between the groups, while the median operating time was markedly longer in the LND group as was the rate of lymph cysts at discharge. The strength of this analysis is the large single center design with a relatively homogeneous therapeutic strategy during the observation period. The good news is, that 5-year overall survival in patients with early-

stage disease is >90%, which is about 10% higher compared to some historical reports. This underlines that the aim in early ovarian cancer is cure and not just long-term control.

Why could the authors not show any survival impact of lymph node staging?

One issue is to do with the rate of occult LN metastases found in the cohort (3.1%, n=10)—significantly lower than previously published [3-5]. Unfortunately, histotypes are not reported as separate low- and high-grade entities. This makes it difficult to compare this data with other series. Another reason might be the inclusion of a relatively high number of patients with "low risk" histology, which will be discussed later. There were relatively few paraaortic nodes resected (median of 4), which may underpower the study when attempting to draw meaningful conclusions. The number of LNs resected serves as a surrogate marker of LN dissection quality and influences false-negative rates [7]. Furthermore, paraaortic region is the primary site of LN metastasis in ovarian cancer and may often occur as isolated metastases (in 50% to 70%) [3,5].

Another issue is to do with the different histology subtypes. Ovarian cancer is a heterogeneous disease with variable tumor biology which greatly impacts the rate of positive lymph nodes. While the rate in low- and high-grade serous carcinoma may rise above 10% [4], in other subtypes such as low grade endometrioid, and expansile mucinous ovarian cancer, these account for less than 2% [8]. Thus, the indication for LND substantially depends on different grading and histological subtypes, as well as on patients' performance status. For instance, staging LND seems to be not indicated in patients with low grade endometrioid or expansile mucinous ovarian cancer. Of note, such risk factor should be controlled for in any multivariable regression model, in order to avoid survival bias. This is not a minor issue, as several specific histological subtypes (such as mucinous and other low-grade ovarian cancer) require an expert pathologist and many times even a second pathological opinion, in order to avoid misclassification.

Finally, the standard systemic chemotherapy in patients with early-stage disease remains heterogeneous worldwide. The randomized trial, GOG 157, demonstrated no superiority for 6 versus 3 cycles of combination chemotherapy [9]. In addition, the majority of the patients in the long-term follow-up ICON 1 trial, which demonstrated a survival benefit of adjuvant chemotherapy particularly for the "high-risk" patients, received carboplatin monotherapy [10]. Therefore, it remains undefined if all patients with early ovarian cancer need a combination chemotherapy.

The authors of this editorial are in favor of the following strategy: Adjuvant carboplatin single agent chemotherapy following comprehensive surgical staging is indicated as standard therapy for early-stage epithelial ovarian cancer (FIGO I). Systematic LND remains indicated in apparent early-stage ovarian cancer patients depending on the carefully evaluated histological subtypes and where this holds a potential to impact the choice of stage-adapted systemic chemotherapy.

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