Lymphadenectomy in advanced ovarian cancer: the new evidence

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"Humans have always been creators of myths … Therefore, it can be said that from a very early age human beings have distinguished themselves by their ability to conceive ideas that go beyond their daily experience … We are creatures that look the meaning of everything."

Karen Armstrong, Short History of the Myth, 2005.

Lymphadenectomies, together with the elimination of the primary focus of disease, has historically been the dominant paradigm of surgical treatment in most solid tumors. Despite the clear tendency of advanced ovarian epithelial cancer (AOEC) to generate peritoneal implants and

lymphatic dissemination as its main routes of dissemination, the true therapeutic value of pelvic and para-aortic lymphadenectomy had not yet been established. Undoubtedly, in recent years the realization of a lymphadenectomy, with the aim of improving progression-free and/or global survival rates, was based on the doctrine of maximum cytoreduction and the surgical elimination of a potential focus of residual disease resistant to chemotherapy, commonly known as the pharmacological sancta sanctorum. Just under a dozen retrospective studies, with a very limited level of statistical evidence, were the only available argument. At the end of 2005, the value of systematic lymphadenectomy in AEOC was more a solid belief than a fairly acceptable certainty. Despite the fact that lymphadenectomy in retrospective studies showed a discreet benefit in the survival of these patients, the methodology used presented significant biases due to the expected tendency to include patients in good general conditions in the lymphadenectomy group and, due to on the contrary, a strong predisposition to omit lymphadenectomy in patients with more disseminated disease and/or associated comorbidities. Of course, the results were likely to falsely show a better prognosis in patients with lymphadenectomy. Similarly, it should be noted that in studies published before 2005, about 33% of patients undergoing lymphadenectomy left intrabdominal residual disease, something that strongly affected the final prognosis.

In 2005 Panici and collaborators[1] published a multicentre, prospective, randomized study, considered the first study with this design on lymphadenectomy at AEOC and with a good level of evidence. Unfortunately the results did not lead to a robust clinical recommendation. One of its main limitations was the design of the sample, since the researchers decided to compare patients with formal pelvic and para-aortic lymphadenectomy with those in which only an excision of the enlarged nodes was performed, instead of patients in whom lymphadenectomy was omitted. In both groups, it was established, as a precondition, to proceed to retroperitoneal lymphadenectomy when optimal cytoreduction in the visceral and peritoneal compartment was achieved. This series included a sample of 427 patients, 216 of them in the lymphadenectomy group (group A) and 211 in the group undergoing resection of the enlarged nodes (group B), with a follow-up of 68.4 months. Regarding the adjusted risk of a first relapse event, it was 25% lower in group A, which was statistically significant. Regarding the 5-year progression-free survival rate, it was 31.2% in group A vs. 21.6% in group B, a difference that reached a statistically significant difference. Progression-free survival was 29.4 months for group A and 22.4 months for group B, a difference that was also valid statistically. The risk of death for both groups was 0.97. In relation to the 5-year overall survival rate, it was 48.5% and 47%, respectively for group A and B; with a mean overall survival of 58.7 months for group A and 56.3 months in group B. Neither difference, in these two survival parameters, was statistically valid. Likewise, the operative time and the need to use transfusions were statistically significantly greater in patients of group A. In a sub-analysis based on the sample, the risk (HR) of a first event (relapse or death) was 0.69 (95% CI = 0.54 to 0.89), which could be interpreted, according to the authors as an indication of a discrete benefit of lymphadenectomy in the natural evolution of the disease. The conclusions of this series is that systematic lymphadenectomy in women diagnosed with AOEC, with optimal cytoreduction, improves progression-free survival without any benefit in overall survival.

In January 2019, Song et al[2] published the *Therapeutic value of selective lymphadenectomy in interval debulking surgery for stage IIIc and IV epithelial ovarian cancer study*, a retrospective study conducted between 1996 and 2016, whose objective was to compare the selective lymphadenectomy of the suspicious nodes and the systematic lymphadenectomy in patients with AOEC undergoing neoadjuvant chemotherapy and interval surgery with complete cytoreduction (R0). In their results, when comparing the 145 patients undergoing selective lymphadenectomy (group 1), the 118 patients undergoing systematic lymphadenectomy (group 2) and the 66 patients who were not subjected to lymphadenectomy (group 3), the average free survival time of disease was 28, 30.5 and 22 months, respectively in groups 1, 2 and 3 (Log Rank p = 0.49). In the sub-analysis of this parameter, although there was no significant statistical difference between groups 1 and 2 (Cox analysis, HR = 1.097, 95% CI 0.815 to 1.478, p = 0.541), it was determined that the omission of lymphadenectomy (group 3), was a factor that negatively affected progression-free survival (Cox analysis HR = 1.729, 95% CI 1.213 to 2.464, p = 0.002). As for the average overall survival time, there was no statistically valid difference (50, 59 and 57 months respectively for groups 1, 2, and 3, log Rank = 0,566). Likewise, in the patients of group 1 there was a lower, statistically significant incidence of lower limb lymphedema and lymphocysts than in the patients in group 2.

In February 2019, Philipp Harter et al[3], published in *The New England Journal of Medicine*, the expected LION study: *A Randomized Trial of Lymphadenectomy in Patients with Advanced Ovarian Neoplasms*. A multicentre, controlled and high evidence study that was designed with the intention of breaking the enigma of the true value of lymphadenectomy at AOEC. This series included 647 patients, 323 patients with pelvic and paraortic lymphadenectomy and 324 patients in the group without lymphadenectomy. Patients in stages IIB through IV (resectable metastases in pleura, liver, spleen and/or abdominal wall) were included. The randomization system was rigorously applied as follows: once the patient was included in the preselection and achieved the goal of complete cytoreduction of the intraperitoneal compartment, under stable clinical conditions, the case was distributed randomly through a telephone call. The surgeon team was informed whether or not to continue with lymphadenectomy. Likewise, during the intervention and before randomization, patients with pelvic and/or bulky para-aortic nodes were excluded. The reason for adopting this criterion was due to the fact that in previous studies, normally in the lymphadenectomy group, it was usually proceeded, breaking the research protocol, to make only a selective resection of these nodes.

The overall mean survival was 69.2 months vs 65.5 months, for the group without lymphadenectomy and with lymphadenectomy, respectively, difference without statistical validity. (HR for death in the lymphadenectomy group of 1.06; 95% CI, 0.83 to 1.34; P = 0.65). Progression-free survival was 25.5 months for both groups (HR for progression or death in the lymphadenectomy group of 1.11; 95% CI, 0.92 to 1.34; P = 0.29). Severe postoperative morbidity, expressed in the fact of a relaparotomy, was 12.4% of the lymphadenectomy group vs. 6.5% in the group without lymphadenectomy (P = 0.01). Postoperative mortality, up to 60 days, was 3.1% in the group with lymphadenectomy vs 0.9% in the group without lymphadenectomy (P = 0.049).

In the group of patients undergoing lymphadenectomy, 55.7% of them presented metastatic nodes in the definitive biopsy. When evaluating the impact of lymphadenectomy in this subgroup, with subclinical lymph node disease, no benefit in progression-free or global survival was observed. Although it is known, from the data obtained in studies with systematic lymphadenectomy in patients with AOEC, that between 44% and 53% of the patients have lymph node metastasis[2], performing a lymphadenectomy would allow the concept of complete cytoreduction to be extended by at least half of the patients. Despite the absence of survival benefit in this subgroup, it was possible to break with a widespread presumption, but without any statistical basis.

In recent years the use of methodological design elements that allow generating robust clinical evidence has been of great value. This is why this important study considered necessary, from the methodological point of view, that the group with the worst prognosis, those with residual disease after surgery and/or bulky adenopathies, were excluded before proceeding to intraoperative randomization in order to homogenize the total sample. With a final sample with all patients without residual disease and without suspected adenopathies before randomization, measuring the true value of lymphadenectomy in both groups was highly reliable. One of the weaknesses of the Panici et al. study was that in about 66% of the patients included in their study, macroscopic residual disease remained. Likewise, in order to maintain the homogeneous sample, the proportion of patients undergoing adjuvant chemotherapy, with platinum and taxane-based schemes with or without bevacizumab, was similar. Although the final group of patients included in this study, deviates significantly from the clinical reality, the results obtained allowed us to conclude that lymphadenectomy, in patients with complete cytoreduction, is not associated with a better progression-free or global survival, and on the contrary, it was correlated with a higher incidence of postoperative complications.

With these results of the LION study, the objectives in the treatment of the AOEC are better delineated. However, the importance of the LION study will not only be limited to its solid results. Thanks to its innovative design and excellent performance, it was possible to generate clinical evidence intelligently anticipating potential methodological biases, through a strict inclusion protocol and a rigorous evaluation of the surgical experience of the participating centers. In view of these data, the idea, based on high evidence studies, is reinforced that complete cytoreduction, followed by adjuvant chemotherapy with platinum and taxane-based schemes with or without bevacizumab, remains the best way to prolong survival in the treatment of advanced ovarian epithelial cancer.

Most of the time, the effort that must be made to achieve complete cytoreduction includes surgical procedures that significantly increase morbidity and postoperative mortality. With these results, the message for surgeons and training schools is very clear. First, focus on maximum cytoreduction as an essential objective, including cytoreduction of all macroscopic disease including that located in the lymph nodes, especially when optimal cytoreduction in the

intraperitoneal compartment has been achieved. That is, after the publication of the LION study, the removal of suspicious and/or enlarged nodes remains part of the cytoreductive effort, something that should be clear. Second, perhaps one of the most important conclusions of this formidable study, as Eric L Eisenhauer and Dennis S. Chi4 conclude in their editorial *Ovarian Cancer Surgery: Heed This LION's Roar*: "… eliminate procedures without any efficiency, such as elective lymphadenectomy, it is a prudent act that allows to improve the recovery time. Along the way we could also have learned how difficult it is to overcome our assumptions without a properly designed controlled trial".

Only solid and properly interpreted data can show a clearer and more efficient path. At the same time it allows us to get rid of almost legendary therapeutic assumptions, but without any scientific evidence.

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