Lymphadenectomy in endometrial cancer and the ASTEC study: the unsuccessful evidence

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"When looking for the circumference of its sphericity, it will tell that is raised to its infinite, because what is indeterminate lacks of dimension, as it was the beginning of creation."


Lymphadenectomy in endometrial cancer emerges as a real necessity from the 1988 FIGO classification and became even more imperative after the 2009 amendment, when the category IIIC stage was subdivided IIIC1 stage for those patients with positive pelvic lymph nodes, and IIIC2 stage for those patients with metastases in the para-aortic nodes. Despite the need to rule out the presence of nodal disease, lymphadenectomy in this pathology has always presented a series of obstacles that have limited its acceptance and more widespread use. Although endometrial cancer is presented as a disease limited to the uterus in 75% of cases, is frequently the relationship of this condition with associated diseases such as morbid obesity, hypertension and diabetes mellitus, which are not formal contraindications to perform a lymphadenectomy, make more laborious, not without complications, perceiving certain tendency to stop performing it, especially in non-specialist centers. The results of the largest multicenter study on this topic in the ASTEC (A Study in the Treatment of Endometrial Cancer) published in 2009 showed that there is no evidence that supports that the pelvic lymphadenectomy has proven therapeutic value (1). After reading it, highlights, besides the results, the eloquent final paragraph that reads as follows:

“In conclusion, this large randomised trial suggest that unless surgical staging will directly affect adjuvant therapy, routine systematic pelvic lymphadenectomy cannot be recommended in women undergoing primary surgery for stage I endometrial cancer outside of clinical trials”.

In this paragraph, is eying almost premonitory what happened later. The largest clinical study designed to test the true value of pelvic lymphadenectomy in patients with stage I endometrial cancer, regardless of the use of radiation therapy, which included 1408 patients treated in the UK, South Africa, Poland and New Zealand, with a sleek design and a formidable financial, capsized shortly after its publication, as happened to the Titanic. The relentless criticism of the multiple faults as was the lack of adherence to the protocol established for each arm, low number of nodes removed and even criticism from ethically, made that this promising and awaited study were virtually dismissed, if not ignored. The great ASTEC study failed to show convincingly that lymphadenectomy did not benefit the
patient survival, but more worryingly, due to defects in its performance was also unable to prove anything. Without detracting from the effort made by the authors, the ASTEC vanished as evidence simply because what reported was based on "soft data". At the mention of the same in the discussion of the NCCN guidelines 2013 claim verbatim as follows (2):

"Recent data have questioned the role of routine pelvic lymphadenectomy in early-stage endometrial carcinoma, however, these findings remain a point of contention and are not currently reflected in North American practice. Two randomized clinical trials from Europe report that lymph node dissection did not improve the outcome of endometrial cancer patients; however, lymphadenectomy did identify those with nodal disease. To avoid over interpretation of these results it is important to address the limitation of these randomized studies including selection of patients, extent of lymph node dissection, and standardization of post-operative therapy. The other concerns regarding these trials include the lack of central pathology review subspecialty of surgeons, and adequacy of statistical power".

To date it is unknown whether there is any ongoing study of the dimensions of ASTEC to re-address this dilemma. Systematic lymphadenectomy in early stages, like all surgery indiscriminately applied, is most often an unnecessary procedure with a complication rate that could eventually affect the postoperative course of the patient and her quality of life. The use of sentinel node biopsy, which aims to proper selection of patients to undergo a lymphadenectomy in endometrial cancer studies unfortunately have not given a satisfactory answer, because the results are still controversial, among other reasons because of its poor reproducibility and lack of standardization of the methods, particularly with regard to the site of the vital dye injection and radiotracer. The answer could also be in the detailed assessment of existing data, an affordable, reliable and cheaper tool than embarking on a costly multicenter, randomized design. This would probably have been understood at Memorial Sloan Kettering Cancer Center (MSKCC) in New York with his recent publication in The Lancet Oncology: Classification and regression trees (CART) analysis of endometrial carcinoma: seeing the forest for the trees (5). In the univariate analysis the total number of nodes removed (pelvic and para-aortic) was associated with better overall survival (P <0.001). But analyzing the impact of para-aortic lymphadenectomy alone in overall survival, a statistically significant difference was not recorded in comparison with those patients which underwent only pelvic lymphadenectomy. Within the limitations of this study, the authors recognize a low rate of para-aortic lymph nodes dissected (average of 5 nodes) compared to the iconic SEPAL a japanese retrospective study that demonstrated significant overall survival benefit of lymphadenectomy and reported a mean of 59 and 23, pelvic node resected and para-aortic, respectively. Finally, it is prudent to recognize that pelvic lymphadenectomy in endometrial cancer treatment is kept as part of the standard treatment although the
benefit in terms of survival has not been demonstrated and presenting a higher rate of complications, becoming perhaps one of the toughest strongholds Halsted mechanistic paradigm. Paradigm deeply rooted and that shall be only overcome by strong evidence that will soon follow. Meanwhile, invitation underlying the MSKCC study is to stay focused, not only on the details, but to assess the evidence that we have in panoramic view, as it says in its title: seeing the forest for the trees.

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Referencias:

2) www.nccn.org