Sentinel Node in Endometrial Cancer: a brief review

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“The rooster of my tree
chases with its singing
ghosts of shadows and moon
specters and spirits”

Otilio Galíndez, Flor de mayo.

Between 2008 and 2009, the publication of the results of the ASTEC study and the trial of Panici PB et al, somewhat marked the course of trends of lymphadenectomy in early endometrial cancer. Although these studies, especially the ASTEC, had problems from the methodological point of view that made the evidence of the results still very controversial, there is a clear inclination in some researchers to deny the therapeutic value of systematic pelvic lymphadenectomy in this pathology. As well Aalders and cols, claimed it in a landmark 2007 review article, the publication of the study GOG 33 in 1987 and in 1991 divided Gynecology oncologists in three groups. A first group that supported the lymphadenectomy in all patients, based on a halstedian tradition for disease control and the remote possibility that the presence of metastatic pelvic nodes was the only finding to migrate to a stage III, and the patient receiving adjuvant treatment. The second group who with the available evidence before 2009, considered the lymphadenectomy did not offer any benefit in low-risk patients or patients with deep invasion of the myometrium and high-grade histological which, regardless of nodal status, had met the criteria to receive adjuvant radiotherapy. The third group, a sort of Solomonic third way, who supported lymphadenectomy only in those patients with significant statistical risk of lymph node disease.
Then a question arose: how to predict reliably which patients would have pelvic lymph node disease? The search for factors in the primary tumor, especially pathological, which correlate properly within a prediction model was the first attempt. The GOG 33 study results, based on the histologic grade and myometrial invasion, were able to stratify patients into risk groups for extrauterine disease, and therefore for adjuvant radiotherapy, was historically the first convincing evidence in this regard. It is necessary to remember that before the publication of this study the treatment of endometrial cancer was the intrauterine application of implants and then performing a hysterectomy with bilateral adnexectomy. In other cases, addressed initially by surgery and later adjuvant radiotherapy. With this type of treatment received radiotherapy, one way or another all patients with early endometrial cancer, which resulted in approximately 60% of the patients receiving radiant treatment without any benefit. The indiscriminate use of adjuvant radiotherapy gave way, after data from GOG 33, to a more rational way to indicate it only in patients with intermediate and high risk. Although this study was designed to make more precise criteria for adjuvant radiotherapy, its data allowed us to extrapolate in a way the same pathological factors in devising a model of prediction of lymph node disease.

In 2004 the publication of an interesting experience at the May Clinic through the use of criteria in decision making for lymphadenectomy was a relevant fact and is worthy of mention. Mariani A et al established that lymphadenectomy should be omitted, given the low risk of lymph node disease, in patients without extrauterine disease with the following criteria in the frozen cut:

1) Tumors with histological endometriod type (grade 1 or 2), with invasion less than or equal to 50% and less than or equal to 2 cm diameter tumor or
2) Tumor with endometriod type, no myometrial invasion regardless of the maximum tumor diameter.

In this subgroup of patients who met these criteria, none presented lymph node disease in the final evaluation of pieces of lymphadenectomy, and monitoring, disease-specific survival at 5 years was 100%. Likewise the omission of lymphadenectomy, based on this methodology, allowed the decrease of postoperative morbidity in obese patients and peripheral resistance to insulin, comorbidity frequently associated with endometriod types G1 and G2. However, this study's authors acknowledge that this institutional experience is probably not easy to reproduce broadly in retail experience centers.

The second aspect in search of a forecasting system was the sentinel node biopsy (SNB). The experience derived from this methodology in breast cancer, vulva and malignant melanoma between late 1980's and mid 1990's, allowed to extrapolate this possibility. However this proposal has taken to fit properly in endometrial cancer by multiple obstacles for validation as a standard methodology. First of all the anatomical features of the uterine lymphatic drainage with a double collector myometrial system, one above the isthmic which drains into pre-aorticos ganglia and another below the isthmic line, with drainage to the pelvic lymph nodes, makes more complex the ability to predict the location of Sentinel lymph node. Second, the determination of the site of
injection of the radiocolloid and coloring vital has been one of the most controversial topics. The great variation in the site and the injection technique in the initial phase of the exploration of the SNB was characterized by a kind of Tower of Babel where every series used different injection sites as the cervix, at the level of the subserous uterine and peritumoral through histeroscopic approach. Este fenómeno está claramente expresado en el metanálisis de Kang y cols\(^7\) en donde las tasa de identificación fue muy variables según el punto de inyección. Based on this trend, the Luis Razetti Oncology Institute performed the first experience in Venezuela, and one of the first in South America, with this new methodology in 2009, using the cervix as injection site\(^8\).

In the meantime began to acknowledge that the method of injection into the subserosa fundal was associated with the identification of sentinels in the para-aortic region and a low identification and sensitivity in the pelvic lymph nodes. Meanwhile the hysteroscopic injection has gradually fallen into disuse quickly in view of being the site of injection with lower rate of identification and through a methodology that requires an additional procedure. For 2008 an efficient proposal from the New York Memorial Sloan Kettering Cancer Cancer (MSKCC), hosted in 2012 by the influential National Cancer Comprehensive Network, generates a uniform methodology that comes to solve the bias of variability between the published series\(^9,10\). This algorithm based on cervical injection only with blue-dye at specific points, with detailed description of the injection technique, has made it possible to renew the interest of the SNB in endometrial cancer, whose experience begins to build up to, certainly show its results in the medium term.

On the other hand the effort of the French school expressed mainly in the SentiEndo multicenter study in early endometrial cancer whose first report was published in 2011\(^11\), and that has shown its most recent results in January 2015\(^12\). This study which used the radiocoloide and injection blue-dye at cervical level, with a technique very similar to the proposal of MSKCC, uses a strict protocol in addition to histological processing and Immunohistochemistry of the SNB\(^13\). In this study were specified strict criteria to indicate radiation therapy and/or chemotherapy adjuvant among low-risk groups, intermediate and high. It has likewise consolidated evidence of that the use of Immunohistochemistry significantly improved the sensitivity of the SNB. Of the 111 patients with one or more Sentinel nodes identified, 16 had metastases in Sentinel lymph node and 12 patients were referred to adjuvant treatment by this finding. It should be noted that in 9 of them (56.5%) this finding was exclusively by Immunohistochemistry. A finding out is that of the 11 patients with sentinel node identified there was no statistically significant difference in recurrence-free survival among patients with metastases in sentinel lymph node and those without metastasis (\(p = 0, 5\)), i.e. that the patient with metastatic sentinel lymph node who received adjuvant therapy had a similar survival to group with negative sentinel probably due to the more accurate indication of adjuvant treatment. One influential study, with a limited level of evidence, but that must be checked very carefully.

At the present time with the use of the SNB, the oncology has to overcome an evolutionary stage characterized by lymphadenectomies made in all cases, regardless of tumor size and other determinants. This resulted, for example, that in early malignant tumors of breast and vulva close
to 80% of the lymphadenectomies not identified any lymph node metastasis. Using data from the SentiEndo were lymph node metastasis were identified in only 16 of 125 patients studied, i.e. 87.2% lymphadenectomy cases would be unnecessary. In this scenario, no doubt, this procedure had been, not only unnecessary, but often followed by sequels that important and permanently impact the quality of life of the patients. Generalize is still a frequent form of mistakes and in some ways has been recognized that the routine lymphadenectomy in early lesions was a very logical proposal in the past but today, thanks to the SNB, has ceased to be. To the extent that the SNB will allow us to know the status of a lymph node basin in a certain way, determine how many sentinel metastatic nodes must be to indicate a lymphadenectomy and that this information will indicate more accurately an adjuvant treatment, an important step in the long-desired accuracy will be given. It will take that evidence that is conforming from 2012, thanks to the proposal of cervical injection and standardized the use of immunohistochemistry, show us the safest way in endometrial cancer.

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