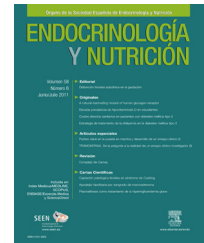




ENDOCRINOLOGÍA Y NUTRICIÓN

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EDITORIAL

Selective sentinel lymph node biopsy in papillary thyroid carcinoma[☆]

Biopsia selectiva del ganglio centinela en el carcinoma papilar de tiroides

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While significant advances have been made in the past decade in the etiopathogenesis of differentiated thyroid cancer (DTC),¹ advances in surgery have not been relevant. Thus, robot-assisted cervicoscopic techniques or procedures using approaches different from the conventional transverse cervicotomy have been developed.² The practical value of these approaches is however very limited. One of the few contributions with an impact on thyroid surgery is probably the procedure of selective sentinel lymph node biopsy (SLNB). The concept of the sentinel lymph node (SLN) refers to the first lymph node draining a tumor. SLN location and analysis indicate whether the tumor has nodal dissemination, which is essential when deciding the type of intervention to be performed.

SLNB is well standardized in some tumors, particularly melanoma³ and breast cancer,⁴ and has provided undeniable benefits in their treatment. The use of SLNB in DTC was proposed 15 years ago by Kelemen et al.⁵ Since then, its indications, benefits, and limitations have been controversial. SLNB is of particular value in papillary thyroid carcinoma (PTC) because while follicular carcinoma tends to hematogenous dissemination, PTC usually metastasizes

by the lymphatic route. In this type of tumor, the first controversial subject is the prognostic significance of nodal involvement and, thus, the value of accurate staging during surgery.^{6,7} This has led to another of the most controversial subjects of recent years, the need for prophylactic lymphadenectomy of the central compartment.^{8–10} Although it has been suggested that a prospective, randomized study on this subject is unfeasible,¹¹ SLNB may possibly contribute to clarification on this subject in the future. The purpose of this study was to review what the procedure involves, to assess its advantages and disadvantages and, finally, to establish potential lines of work which in the future will be able to answer the multiple questions still pending regarding the use of SLNB in PTC.

The first step is localization of the SLN. Two procedures are currently available for identifying the SLN. The first procedure uses a vital dye (methylene blue or some subsequent variants).⁵ This dye has a high affinity for lymphatic tissue. The dye is injected inside or around the tumor during surgery. After a few minutes, the dye drains to one or several lymph nodes which will be easily identified by the change in color. The second procedure available consists of the use as a marker of a radioactive isotope which is also injected inside or around the tumor.^{12,13} The most commonly used isotope is Tc99m, which also has a high affinity for lymph nodes. A nanocolloid is added to this isotope to achieve a molecule of an adequate size to embolize in the first lymph node and to remain there long enough to be detected. In the procedure used at our hospital, the isotope is administered the day before surgery. Under ultrasound guidance,

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4 mCi of Tc99m nanocolloid are injected in a volume of 0.1 or 0.2 mL. Intratumoral injection is preferred, but if this is not feasible (due to calcification, cystification, or size), peritumoral injection may be administered. Two hours later, scintigraphic and SPECT-CT images are taken. These images help localize the SLN on the day of surgery. During surgery, node localization using a gamma probe (Europrobe) is essential. The thyroid gland should be excised before searching for the nodes to prevent the so-called shine-through effect, i.e. that intensity of radioactivity in the tumor bed which obscures or contaminates all other areas. The probe will then precisely localize the sentinel node(s) to be excised and tested during surgery.

Various studies reported in recent years have shown the isotopic procedure to be more precise for SLN localization.^{14–16} The vital dye method is a visual technique. However, the isotopic procedure also has detractors. It is argued that it infringes the oncological criterion because the thyroid gland should be removed first, with en bloc resection being impossible. We do not share this criticism because compartment-oriented surgery is not infringed by this necessary modification. In any case, according to most reported series, the SLN is localized in 80–90% of cases using the vital dye technique^{17–19} and in 95–100% of cases with the isotopic procedure.^{16,20,21} Some authors have suggested that a combination of both procedures provides an even better yield.^{22,23}

Failure to identify the SLN is due to total or partial hematic puncture and radionuclide passage into the bloodstream, or to excess migration of the tracer causing contamination of the whole lymphatic bed of the neck, which prevents individualization of one or a group of lymph nodes. A key aspect is the number of lymph nodes to be excised, because if too many SLNs are excised, it is easier to complete the lymphadenectomy than to analyze the lymph nodes taken.

The second step is SLN analysis. Regardless of whether the dye technique or an isotopic marker is used, an intraoperative study is done using imprint cytology and frozen section analysis. A pathological examination should establish the presence or absence of lymph node metastases. The subsequent surgical approach will depend on this. One of the determinant aspects for assessing the value of SLNB is the proportion of false negatives (FNs) in the peroperative study. FNs are defined as cases where intraoperative lymph node study has been negative (no metastatic invasion was detected) but final subsequent histological study shows nodal metastasis. A high FN rate would definitely invalidate the procedure. In the meta-analysis reported by Balasubramanian and Harrison,¹⁴ this rate ranges from 8% to 15%. The main reason for FNs is the presence of micrometastases in lymph nodes. Frozen sections are not sufficiently precise, and metastases less than 2 mm in size may not be included in the section examined under the microscope. At other times, a bulky node obstructs marker progression.²⁴ Finally, tumors located at the thyroid isthmus may show bilateral drainage, which makes it difficult to interpret the result of SLNB and gives an FN in the SLN even in the presence of nodal dissemination. However, the procedure should not be contraindicated.

Since nodal metastases represent the main problem when SLNB is used, techniques other than frozen/imprint cytology,

including specific immunohistochemical stains or the use of molecular techniques for rapid diagnosis, are being tested. A method already used in other tumor types is promising in this field. This procedure is One Step Nucleotid Amplification (OSNA®, Sysmex, Kobe, Japan), a fast technique (taking approximately 30 min) based on the amplification of messenger RNA from proteins unique to the tumor (cytokeratin 19).²⁵ No reported data are available on the procedure, and subsequently a multicenter study is being conducted in Spain. An FN rate close to zero would consolidate SLNB as the procedure of choice for assessing lymph node removal in PTC.

The third step is decision taking. For practical purposes, regional nodal metastases may be detected in lymph node clusters of the central compartment (CC) or, less frequently, in the laterocervical or lateral compartment (LC) lymph nodes. In PTC, the involvement of cervical lymph nodes at the time of surgery is very high, and is even greater when micrometastases are considered.²⁶ But the use of SLNB has also allowed for establishing that nodal metastases are more common than are detected in preoperative diagnosis of disease extension, providing a greater efficacy than ultrasound for their detection. Pelizzo et al.¹⁶ found involvement in 49% of lymph nodes, and the proportion increased to 53% in the Huang et al. series.²² In our series, the proportion of patients with N1 detected using SLNB was 54%, despite the fact that preoperative staging was 12%. However, despite this high incidence of N1, there are serious doubts about the prognostic role of local lymphatic dissemination, particularly in the case of micrometastases.²⁷ The indication of prophylactic elective lymphadenectomy of CC (when no preoperative or peroperative evidence of nodal involvement exists) is therefore not completely defined.

SLNB makes it possible to know whether or not the tumor is localized in the thyroid gland, and thus to take a decision about the correct approach to lymph node territories. Once adequate scientific evidence is available, we will be able to decrease the rates of unnecessary lymph node dissection and associated comorbidities (mainly hypoparathyroidism and recurrent paresis/palsy). This will also help us to decide whether lymph node dissection should only be performed in the CC or should be extended to the LC. The literature results suggest that SLNB is able to detect involvement in both locations.²⁸ Thus patients shown to have LC involvement should undergo total dissection of both lymph node groups.

The pros and cons of SLNB in PTC: The role of SLNB in PTC is still undefined, and none of the major guidelines on tumor management published to date include it as a routine procedure.^{29,30} Although various studies analyzing its potential have been reported in recent years, it is still too early to draw final conclusions. SLNB undoubtedly has important advantages. These include reliable disease staging. SLNB has shown that cervical lymph node metastases are even more common than are found with preoperative techniques (especially neck ultrasound) and even with an intraoperative eye examination. This is a particularly important issue in metastases in the CC, the mainly affected area, in which ultrasound shows a poorer performance. Both the isotopic and colorimetric techniques have demonstrated the presence of skip metastases or adenopathies in the lateral lymph

nodes without CC involvement. This is particularly common in tumors located in the upper lobes. On the other hand, the main advantage is being able to define the indication for lymphadenectomy beyond the doubtful strategy of routine prophylactic complete excision. This would undoubtedly decrease both unnecessary lymphadenectomy and associated morbidity. It would also allow us to decide which nodal compartment should be resected.³¹ Finally, a more rational surgical approach would prevent a good number of repeat surgeries.

However, SLNB also raises some doubts.³² Beyond the much needed but so far nonexistent cost-effectiveness analysis and the debate about the most suitable procedure (vital dye or isotopic), the main disadvantage is the rate, too high for some experts, of FNs in frozen/imprint cytology. Molecular techniques may possibly solve this problem. Another reason for doubt is its actual efficacy regarding the detection of SLNs in the LC. The precision of the technique to detect N1 in this area could only be established in a prospective study where LC lymphadenectomy was performed in all cases. This would be ethically complex because no recommendation exists for such an approach and due to the high morbidity involved in the study.

Although all studies report SLN identification in more than 90% of cases, there are indications and contraindications for SLNB. A more precise definition of patients who would benefit from SLNB and those not amenable to the procedure is required. It has been suggested that SLNB is completely unnecessary in patients diagnosed with cervical nodal involvement before surgery. Some studies state that isthmus tumors should be included in SLNB protocols, although it is known that SLN detection may be more difficult. Patients with multicentric tumors should also be included, except when the number is very high. Tumors occurring in irradiated necks should undergo lymphadenectomy rather than SLNB. However, this aspect may be clarified with time. Patients with large tumors (T3 and T4) and those with tracheal invasion should be excluded from SLN protocols.

Finally, the efficacy of SLNB is markedly decreased in autoimmune thyroiditis because of the number of pathological adenopathies, but this does not contraindicate SLNB.^{33,34}

In conclusion, SLNB is a procedure which has been shown to be effective in certain tumors, such as breast cancer and melanoma. The results reported in PTC by different authors are promising. Once the initial reluctance attributed to the complex lymphatic drainage of the thyroid gland is overcome,³⁵ the selection of suitable cases and an improvement in peroperative pathological diagnosis are the most important barriers to be overcome before SLNB can become a routine procedure in the surgical management of patients with PTC.

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