Introduction to the teaching course in surgical oncology

Nowadays, surgery still remains the most efficient treatment, and sometimes the only one, for a great number of malignancies, some of them highly prevalent. However, the addition of neoadjuvant or adjuvant treatments to surgery such as radiotherapy or chemotherapy has been proved to continuously increase survival or diminish morbidity in some of these neoplasias. Therefore, multidisciplinary approaches are of paramount importance in the management of many cancers.

Actually, surgical oncology is not established as a discipline that needs specific competence in our country. However, the progress in the knowledge of the molecular features that determine the behaviour in different tumors will affect our making decision in the future. In addition, the increasing effectiveness of multidisciplinary approaches along with the use of sophisticated surgical techniques and strategies among others strengthen the need of specific training.

In this issue, we begin in the *Sección Docente*/Teaching Section of *Revista de Oncología* a series of topics selected by the *Sociedad Española de Oncología Quirúrgica* (SEOQ). The first of them deals with the selective biopsy of sentinel node that has recently dispelled the body of controversy maintained along decades on indications of radical lymphadenoctomy in some tumors such as melanoma.

Selective biopsy of the sentinel node: technique and present state in the different tumors

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Advances in diagnostic techniques as well as early detection programs have given rise to the fact that a large percentage of malignant tumors are diagnosed in initial stages, which makes it possible to perform less aggressive conservative local and regional treatment.

The state of the lymph nodes is one of the most important prognostic factors in oncology patients. Regional lymphadenectomy has been the only technique up to now that has made it possible to establish the prognosis and indicate, according to the result, the posterior adjuvant treatment and it is only considered therapeutic in regards to the regional control of the disease. On the other hand, this technique presents a not insignificant morbidity in regards to the patient's quality of life.

The probability of lymph node involvement is very low in tumors in initial stages. This means that the lymph nodes are free of infiltrations in most of these patients, so that complete lymphadenectomy (CLD) would not be necessary.

On the other hand, advances in the molecular biology techniques have given rise to the detection of prognostic markers inherent to the tumor that make the indication of adjuvant therapies possible.

The sentinel node (SN) is defined as the first drainage station of a primary lesion and thus that which has the greatest probability of harboring metastasis.

The concept of SN was originally described by Cabañas in 1977 in penile carcinoma[1] and is based on the hypothesis according to which lymphatic drainage of a malignant lesion is an organized process by which a tumor will first metastasize in the SN, that can be identified by lymphoscintigraphy imaging techniques. The SN technique is considered in the literature as a reliable and exact indicator of the presence of regional lymph node involvement in melanoma[2] and breast cancer[3], avoiding morbidity that can be caused by CLD, which is reserved for those cases in which the SN is histopathologically affected.

Different procedures have been used to identify the SN. Morton demonstrated that lymphatic drainage of a primary melanoma could be predicted intraoperatively[4], by perilesional injection of a vital dye and later visualization and excision of the stained nodes, using this technique as a less invasive method than the conventional lymphadenectomy.

In 1993, Krag and Alex[5] used a gamma ray detection probe after the peritumoral injection of ^{99m}Tc-sulfide colloid; in 1994, Giuliano[6] applied the intraoperative use of vital blue dye in breast cancer and Albertini[2,3], combined both methods in melanoma and breast cancer.

Exclusion criteria for selective biopsy of sentinel node (SBSN) should be established for each tumor, but in general lines, this technique is contraindicated in patients with clinical evidence of regional or distant metastasis, locally advanced or multicentric-multifocal tumors, previous treatment with radiotherapy, chemotherapy or surgery that can alter lymphatic drainage, pregnancy or breast feeding and lack of specialized equipment.

The performance of SBSN should follow a protocol defined for three technical aspects of the procedure that include Nuclear Medicine, Surgery and Pathology.

TECHNIQUES FOR THE SEARCH FOR SENTINEL NODE

There are three methods to identify the SN: isotopic technique, technique with dyes and the combination of both.

Isotopic technique

It consists in the use of labeled colloid substances with an isotopic tracer. That used most due to its low cost per Megabecquerel (MBq) is technetium (^{99m}Tc).

The technique consists in the injection of the radiopharmaceutical in the area in which the tumor is located or in the bed of the previous biopsy. After, a lymphoscintigraphic study is performed, using a low energy collimator and storing the images in 256 × 256 matrix. The examination concludes by marking the projection of the points having the greatest uptake that correspond to the SN on the skin.

At present, there is no consensus on which preparation should be used. The ideal radiopharmaceutical is that which rapidly spreads from the injection point towards the lymph node vessels, it being retained in the lymph nodes and the radiation dose received by the patient is minimal. These characteristics basically

depend on the size of the particles that should be between 50-300 nm.

Multiple radiopharmaceuticals have been used to perform lymphoscintigraphies, however the most common agents used are: ^{99m}Tc antimony trisulfide colloid (most used in Australia), human albumin colloid with particle size < 80 nm (^{99m}Tc nanocoll) and human albumin microcolloid with particle size between 200 and 1000 nm (Albu-res). The latter is used more in Europe, and the ^{99m}Tc sulfide labeled colloid (in the USA)[7].

The search for the SN in surgery is performed by using a gamma radiation detector probe. There are several models on the market, however all of them are basically made up of two elements: the detector probe and analyzer.

The detection probes can be two types: scintillation (with a sodium iodine crystal [INa] contained within a photomultiplier tube) or cadmium telluride (CdTe) semiconductors[8]. The transductor sends the signal to the analyzer that translates its detection into a digital reading and proportional acoustic signals in the zones having the greatest radiopharmaceutical concentration.

The advantages and disadvantages of the use of the isotopic technique are described in table 1.

TABLE 1. **Advantages and disadvantages of the isotopic technique**

Advantages	Disadvantages
Previous knowledge of the localization of the SN and multiple drainages	Exposure to radiation
Minimal incision for labeling on skin of the zone with greatest uptake	No consensus regarding use of different radiopharmaceuticals, doses and injection route
Distinction of the SN regarding the secondary ones based on the isotopic uptake grade	Distortion by the detection of radiation from the injection point in tumors close to the lymph node drainage area
	It should not be performed without previous lymphoscintigraphy because the SN can be undistinguishable from other hot lymph nodes detected intraoperatively

SN: sentinel node.

TABLE 2. **Advantages and disadvantages of the use of vital dyes**

Advantages	Disadvantages
Simple technique, without need for additional technical means	Learning curve
Visual control of afferent lymph node and stained SN	Major incision to locate the afferent lymph node and SN
Validation hypothesis of the SN was performed with this technique	Lack of previous knowledge of the SN site and multiple or aberrant drainages
	Probability of adverse reactions

SN: sentinel node.

Technique with dyes

It consists in the search for SN by injection of dyes in the tumor area and posterior visualization of the afferent lymph nodes and stained SN.

Several dyes have been assessed for obtaining a lymphatic map (methylene blue, Evans blue, Fluorescein, indocyamine green, indigocarmin, etc.) although they have not been approved by the Food and Drug Administration (FDA) for this indication.

In 1982, after a clinical study in 543 patients performed by Hirsh[9], the FDA approved the vital dyes for their use in the identification of lymph nodes by lymphangiography in humans. However, good results have recently been published in the identification of SN with methylene blue[10].

The vital dyes are Patent Blue V and its isomer, the isosulfan blue (2.4 disfulfonate isomer) (Lymphazurin®).

Lymphazurin at 1% is presented as a sterile aqueous solution for subcutaneous administration. After its injection, isosulfan blue is distributed selectively by the lymph node vessels and retained in the lymph nodes.

The use of dyes deserves some thoughts:

1) Mixing isosulfan blue with local anesthetics in the same syringe produces a precipitation reaction, so that the technique is not recommended.

2) The patient should be warned that the urine will present blue coloring in the following 24 hours, because part of the dose is eliminated unaltered through the urine.

3) Injection of the dye should be performed in the operating room due to the possibility of adverse reactions, that can go from mild (local inflammation, pruritus, etc.) to serious anaphylactic reactions[11].

The advantages and disadvantages of the dye technique are described in table 2.

Combined technique

It consists in the synchronic use of the isotopic technique and the technique with dyes. Both techniques are complementary and offer greater efficacy when performed together, increasing the SN detection rate and sensitivity[12].

Table 3 shows the results obtained according to the use of the three detection techniques[13].

SENTINEL NODE HISTOPATHOLOGICAL STUDY TECHNIQUES

The usual histopathological technique performed in the specimens from the lymphadenectomy consists in the dissection of the lymph nodes, included in paraffin and studied with hematoxylin-eosin staining

TABLE 3. **Results of the selective biopsy of sentinel node in breast cancer and melanoma according to the isotopic technique, with dyes and combined**

Author and reference	Technique	Histopathological study	Efficacy (%)	Accuracy (%)
Krag DN. Surg Oncol 1993; 2: 335-40	Isotopic	HE	82	100
Giuliano AE. Ann Surg 1994; 220:391-401	Dye	HE	66	96
Albertini JJ. JAMA 1996; 276: 1818-22	Combined	HE	92	100
Pipers R. J Nucl Med 1997; 38: 366-8	Isotopic	HE	92	100
Veronesi U. Lancet 1997; 349: 1864-7	Isotopic	HE	98	98
Giuliano AE. J Clin Oncol 1997; 15: 2345-50	Dye	HE+IHC	94	100
Guenther JM. Cancer J Sci Am 1997; 3: 336-40	Dye	HE	71	97
Dale PS. Amm Surg 1998; 64: 28-32	Dye	HE	66	100
Borgstein PJ. J Am Coll Surg 1998; 186: 275-83	Isotopic	HE+IHC	94	99
Barnwell JM. Ann Surg Oncol 1998; 5: 126-30	Combined	HE	90	100
O'Hea BJ. J Am Coll Surg 1998; 186: 423-7	Combined	HE	93	95
Miner TJ. Ann Surg Oncol 1998; 5: 315-21	Isotopic	HE	98	98
Cox CE. Ann Surg 1998; 227: 645-53	Combined	HE+IHC	94	98
Koller M. Eur J Surg Cancer 1998; 24: 166-8	Dye	–	98	97
Crossin JA. Am Surg 1998; 64: 666-9	Isotopic	–	84	98
Krag D. N Engl J Med 1998; 339: 941-6	Isotopic	–	93	97
Hill AD. Ann Surg 1999; 229: 528-35	Combined	HE+IHC	92	96
McMasters KM. J Clin Oncol 2000; 18: 2560-6	Dye and/or isotopic	HE+IHC	88	97
Miltemburg DM. J Surg Res 1999; 84: 138-42	Dye and/or isotopic	HE	83.6	98
Cody III HS. Ann Surg Oncol 2001; 8 (1): 13-9	Combined	–	95	–

HE: hematoxylin-eosin; IHC: immunohistochemistry.

(HE). This means that a small percentage of each lymph node is analyzed. On the other hand, a very careful study would be very expensive and difficult given the great amount of lymph nodes excised in a complete lymphadenectomy.

The hypothesis of SN as the first station in lymphatic drainage of a tumor was validated after the Turner study[14], which demonstrated that the probability of non-sentinel lymph node (NSLN) involvement is less than 0.1% if the SN is disease free.

As a consequence, the study of the SN can predict the state of the remaining lymph node area. In this way, the number of lymph nodes that are analyzed are reduced to a range of 1-3 per patient, which makes it possible to perform special histopathological techniques.

Around 30% of patients with breast cancer studied as N_0 with normal histopathological study develop recurrence of their disease within the first 10 years of follow-up.

Several retrospective studies on melanoma[15] and breast cancer[16] performing special histopathological techniques in the lymph nodes have manifested the presence of micrometastasis in between 9%-30% of the patients studied initially as N0 with the routine techniques.

Micrometastases were defined by the American Joint Committee on Cancer (AJCC) as the deposits of tumor cells in the lymph nodes with a size less than 2 mm.

There are three techniques for the detection of micrometastasis which, in growing order of sensitivity, are: *a)* seriated slices and HE staining; *b)* immunohistochemistry (IHC) for cytokeratins, and *c)* molecular biology techniques, as reverse transcriptase polymerase chain reaction (RT-PCR).

By these techniques, the lymph nodes are restaged in a higher grade in 9%-50% of the cases.

In the Consensus conferences on SN performed in Salamanca and Valencia in 2001[17] the histopathological study proposed includes:

1) Multiple sections in the totality of the lymph nodes, from a central section over its larger axis (slices every 2 mm and sections every 200 µm).
2) Studies should be performed with HE and with IHC when the HE is negative.

The significant prognosis of the micrometastasis is not known. It must be clearly established what histological characteristics (size, colony number of tumor cells, etc.) the micrometastatic invasion has and which ones are going to be those that really acquire prospective capacity for implantation. At present, several randomized clinical studies are being carried out to assess its prognostic meaning.

PRESENT STATE OF THE SELECTIVE BIOPSY OF SENTINEL NODE IN THE DIFFERENT TUMORS

Malignant melanoma

The SBSN technique has been validated as the technique of choice in patients with melanoma (MM) having intermediate risk (Breslow thickness between 0.75-4 mm) and without evidence of lymph node or distant involvement.

The SN state is considered to be an important prognostic factor in clinical N0 patients and is also an indicator to complete the lymphadenectomy and adjuvant therapy.

Recently Balch[18] published the analysis of the prognostic factors in MM after its study in the largest series in history that included 17,600 patients. The results served as a base for revision and proposal of a new MM staging.

The staging proposed by the AJCC and published this year in the sixth edition of the TNM classification of malignant tumors is based on three aspects[19]: breslow thickness, number of lymph nodes affected and size of the lymph node metastasis, and ulceration of the lesion.

The changes in the new version of the TNM of MM are summarized in:

1) For category T, the Breslow thickness and ulceration are used, but not the Clark level (except in T_1).
2) For category N, the number of lymph node metastases is assessed before their size. Their size is defined as macrometastasis (those clinically clear) and micrometastasis (hidden metastases).
3) Localization of the distant metastases and elevation of the serum lacto-deshydrogenase (LDH) are used for category M.
4) Ulceration is assessed in the patients with stages I, II and III.
5) A clinical TNM and pathological TNM are defined based on the information that the histopathological study supplies after the SBSN.

Breast cancer

Detection and study of the SN in breast cancer has growing importance in the treatment of the tumors in initial stages.

When the technique and its indications is perfectly established in the MM, there is no consensus on several points in breast cancer, some questions still existing:

1) Up to what tumor size can the technique be performed with guarantees of an acceptable false negative rate? (< 5%).
2) Wat is the ideal radiopharmaceutical for the performance of the technique?
3) What injection pathway provides best efficacy or detection rate?
4) What is the number of cuts and levels that should be performed in the histopathological study of the SN?
5) Do the micrometastases detected by morphological study (seriated slices with HE) have the same prognostic meaning as those that can only be detected with IHC and/or RT-PCR?

The principal guidelines for SBSN in breast cancer were gathered in the Consensus Conferences that took place in Spain in 2001[17].

The impact of the SBSN in breast cancer, after the AJCC publication of the review of the prognostic factors[20], has been manifested in the following changes published to this regards in the sixth edition of TNM[19]:

1) Micrometastasis is defined as a tumor deposit greater than 0.2 mm but not greater than 2 mm, that can have evidence of malignant activity (proliferation or stromal reaction).
2) The concept "isolated tumor cells" is defined as a group of cells not larger than 0.2 mm without histological evidence of malignant activity (proliferation or stromal reaction).
3) Micrometastases can be identified by the SBSN technique.
4) Increased lymph node sizes (N) are classified considering both the number as well as grade of the involvement of them determined by the usual study with HE or with IHC techniques.

Digestive tumors

Although some papers have been published on esophageal and gastric cancer, most of the series that have published preliminary results of the SBSN in digestive tumors refer to colorectal tumors[21].

At present, a greater number of patients and multicenter studies are necessary to draw final conclusions, however the preliminary results make it possible to state that:

1) Approximately 30% of the early digestive cancers develop systemic metastases. A subgroup of these patients could have lymph node micrometastases and thus their identification could make them benefit from adjuvant therapy.
2) Routine dissection of the lymph nodes does not give the pathologist information on which are most directly related with the tumor.
3) Most of the series have initiated the study with vital dyes.
4) The use of special histopathological techniques has shown a staging that increases between 16.6%-25%.

Gynecological tumors

Some preliminary results in uterine neck cancer have been published, however with low rate of detection and unacceptable rate of false negatives in spite of using the combined technique. However, the results obtained in vulvar cancer are encouraging, in spite of the fact that the series are still small[22].

The authors conclude that greater efficacy and sensitivity are obtained with the isotopic and combined technique, bilateral inguinal drainage is detected in a high percentage of patients and better staging is obtained with the use of special histopathological techniques.

Penile cancer

In 1977, Cabañas[1] published the first results of the SBSN in penile cancer, reaching the following conclu-

sions: *a)* in patients with negative SN, survival at 5 years was 90%; *b)* in patients with SN as the only affected lymph node, survival was 70%; *c)* in patients who had other lymph nodes affected in addition to the SN, survival was 50%, and *d)* if the involvement occurs in the iliac lymph nodes, survival decreased to 20% at 3 years. Recently, similar results have been published, although with a median follow-up of 36 months.
At present, sufficient results do not exist to adopt this technique as that of choice.

Head and neck cancer

In head and neck tumors, the revision of the different series shows greater efficacy of the three techniques, with an acceptable false negative rate.
In 2002 the first consensus conference was published on SBSN in mucosal head and neck cancer[23]. It was concluded that the grouped results of all the series that participated with a total of 316 patients verified that the SBSN has an equivalent sensitivity for staging as that of the complete lymphadenectomy in the N_0 patients.

Differentiated thyroid tumors

Finally, in regards to differentiated thyroid cancer, it stands out that:

1) The technique with dye by intratumoral injection has been the most useful for the authors with excellent results except when methylene blue was used, in which the sensitivity was low and the false negative rate unacceptable.
2) In regards to the histological type, the papillary carcinoma[24] is that which offers the best results in the SBSN.
3) More studies need to be performed for the validation of the technique.

In conclusion, SBSN should be the technique of choice for the staging of intermediate risk MM and breast cancer in initial stages, because it allows for a more careful histopathological study of the SN. Its importance for the staging of these tumors has been reflected in the new version of the TNM classification[19].
In the remaining tumors, the results are encouraging and point in the same sense, although assessment of a greater number of patients and multicenter studies are necessary.

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