

## Blue-dye Sentinel Node Mapping in Thyroid Carcinoma : Debatable Results of Feasibility

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**Key words.** Thyroid neoplasms ; sentinel node ; lymphadenectomy.

**Abstract.** The present study aims to investigate the feasibility and influence of the lymphatic mapping and sentinel node biopsy on determination of the nodal status in thyroid carcinoma using blue-dye method. Nine consecutive patients with cytological diagnosis of papillary carcinoma were included in this study. To detect the sentinel lymphnode, intra- or perinodular injection of an average quantity of 0.5 ml (range : 0.1-1.2) of *Bleu Patenté V* was performed intraoperatively in 8 cases only, as in one case a solitary cystic nodule occupied the entire lobe and thus any injection was impossible. After an average time of 16 minutes (range : 5-25) before dissection of the thyroid, no lymphnodes and no lymphatic afferent thereto visibly coloured were evidenced, except for spread of the vital dye into adjacent tissue and disrupted blood and lymphatic vessels at the injection site.

Our results evidence that : intranodular injection, does not allow proper diffusion of the dye in the adjacent parenchyma, and in nodules smaller than 1 cm it may be difficult ; and that it is hazardous in cystic nodule because of the rupture risk ; perinodular injection, at the four cardinal points, is impossible when the nodule occupies the entire lobe or the isthmus ; multinodular goiter complicates the identification by palpation of the neoplastic nodule in which the dye should be injected or, if perinodular injection is given, to detect the parenchyma surrounding the nodule.

### Introduction

As originally defined, the sentinel node is the first lymph node in the regional nodal basin that drains a primary tumour (1). The rationale of the sentinel node concept is to prevent unnecessary lymphadenectomy and morbidity connected therewith, if the lymph node removed is not metastatic, to increase sensitivity in the assessment of lymph node metastases and to reduce treatment costs (2-3). The rationale for application of sentinel node biopsy to a certain neoplasm is that the lymph node status should be an independent prognostic factor for that tumour and that it should be possible to define the lymph node staging and prognosis with greater accuracy through the immunohistochemical analysis of the lymph nodes removed (4). As concerns thyroid lymphophilic carcinomas, with the obvious exclusion of undifferentiated ones, it is pointed out that the lymph node staging at the time of the first surgery seems to affect recurrence, but not the total survival rate as concerns papillary carcinoma, though the prognostic value of the lymph node metastases involvement is widely accepted for medullary carcinoma (5). Consequently, while the importance of cervical lymphadenectomy is now recognized for medullary carcinoma, even if there is discussion as to whether it should be extended as a rule to cases where a modified neck dissection is not a matter of necessity, for the thyroid papillary carcinoma the lymphadenectomy

value is still under dispute (5-6), just as there is still discussion about thyroidectomy extension. If, in fact, the clinical-instrumental and intraoperative findings of lymph node metastases, notwithstanding their uncertain importance from a prognostic point of view, require their removal with extension of their lymph node dissection, varying from modified neck dissection (5) to berry picking (7), the choice either to neutralize possible occult metastatic nodes through a prophylactic cervical lymph node dissection, or to detect them through blind lymph node sampling (8), is no longer proposable. On the other hand, Cady himself, while excluding the assessment of nodal involvement from his scoring system (AMES : Age, Metastasis, Extrathyroidal extension, Size), recognizes and stresses, as far as survival is concerned, the usefulness of lymphadenectomy in patients with papillary carcinoma assignable to the high-risk group according to the AMES system (9).

In 1998, KELEMEN *et al.* reported the first study on the sentinel node in thyroid carcinoma using vital dye (10). In cases without preoperative or intraoperative evidence of lymph node metastases, the biopsy of the sentinel node might give a better selection of the patients to be submitted to cervical lymph node dissection in papillary high-risk and medullary carcinomas, in which the lymph node involvement in fact conditions the prognosis.

We have carried out a pilot study to assess the feasibility of intraoperative blue-dye lymphatic mapping

Table I  
Patients and Methods

n°	Age (yrs)	Sex	Size (cm)	Site	Injection	Blue dye (cc)	Time (min)*	Node dissection
1	56	m	2,5	left lobe	Intratumoral	0,8	5	central picking
2	33	f	1	right lobe	Intratumoral	0,5	16	central picking
3	35	f	0,8	left lobe	Peritumoral	1,2	25	central picking
4	44	m	2,5	isthmus	Intratumoral	0,5	17	central lymphadenectomy
5	58	m	1	left lobe	Peritumoral	0,25	25	central picking
6	31	f	1	right lobe	Peritumoral	0,1	20	central picking
7	31	m	2	right lobe	Intratumoral	0,45	13	central lymphadenectomy
8	48	f	1	left lobe	Intratumoral	0,3	10	–

\* interval of time between injection and start of thyroid dissection.

with sentinel node dissection and its usefulness in nodal staging in thyroid lymphophilic neoplasms.

### Material and Methods

From February 2000 to February 2001, 9 patients were included in the study. They were 5 men and 4 women, with a median age of 45.1 years and with ultrasound-guided fine-needle aspiration biopsy suggestive of papillary carcinoma. Before surgery all patients gave their case history, underwent chest, thoracic outlet X-ray and oesophagogram and underwent cervical ultrasonography with fine-needle aspiration biopsy and FT3, FT4, TSH, TG, calcitonin and calcium serum levels. The patients included in the study gave their informed consent; the procedure followed was in accordance with the standards of the institutional responsible Ethical Committee. Surgery was performed under the supervision of the same senior surgeon (F.P.C.). At the time of the surgery under general anaesthesia, after transverse low-collar skin incision and thyroid gland exposition in accordance with the rules of our School and using a tuberculin syringe, a quantity of about 0.5 ml (range : 0.1-1.2) of intravascular dye Bleu Patenté V Sodique Guerbert 2.5% injectable solution (Laboratoire Guerbert, Aulnay Sous-Bois, France) was injected into the thyroid nodule, i.e. the site of the lesion, in 6 patients (cases 1, 2, 3, 4, 7,8), and in the perinodular site, at the cardinal points of the lesion, in 2 patients (cases 5, 6) (Tab. I). In a patient (case 7) with multinodular goiter intraoperative choice and localization of the nodule for injection was difficult. In one of nine cases, in which the solitary partially cystic nodule (6,5 cm in size) occupied the entire thyroid lobe, perinodular injection could not be performed and intranodular injection was contraindicated because of the risk of the rupture of the cystic nodule. We waited for an average time period of 16.3 minutes (range : 5-25 minutes) before starting dissection of the thyroid structures, to allow the dye to pass through the lymphatic channels towards the sentinel node drain-

ing the neoplastic area. As no lymph node was seen in any of the patients, we performed total thyroidectomy, after verifying malignancy by frozen section analysis on the thyroid lobe with the lesion. In 5 of the 6 low-risk patients according to AMES (9), in whom no metastases had been evidenced by biopsy of the lymph nodes which had aroused suspicion during the preoperative clinical-instrumental examination and/or during the intraoperative central and lateral compartmental exploration, and in the only one in which there was not suspicious nodes, the operation was thus concluded. In 2 equally low-risk cases but with evidence of metastases in the suspicious recurrential nodes removed, central lymphadenectomy was performed. The material removed was subjected to permanent pathological evaluation with routine hematoxylin-eosin staining.

### Results

All tumours were papillary carcinomas at definitive histology. The average size of the neoplasms was 1.4 cm (range : 0.8-2.5 cm). The localization was left lobar in 4 cases, right lobar in 3 cases and isthmic in one case. After the dye injection and after waiting for a proper period of time before starting dissection of the thyroid structures, the explorable cervical lymph node stations did not appear coloured in any of the 8 patients.

In two cases after intranodular injection, blue-stained pericapsular lymphatic vessels were seen but no sentinel node was identified : in one case lymphatics tracked superiorly beyond the superior pole and in another one into the anterior mediastinum underneath the sternum. From a technical point of view, we found that in the case of the intranodular injection indicated by KELEMEN *et al.* (10), the blue dye concentrates inside the neoplastic nodule without spreading to the rest of the parenchyma (Fig. 1). For this reason, after the intranodular injection performed in the first cases, we made the injection outside the nodule, just next to its cardinal points, in the adjoining parenchyma. Further, the intranodular



Fig. 1

Intratumoral injection does not result in staining any lymph nodes : the blue-dye remains into the neoplastic nodule.



Fig. 2

Overflowing of blue-dye

injection turned out to be complex due to the neoformations measuring less than 1 centimetre and is hazardous in cystic nodule. In the sole case in which, after intranodular injection, we found lobar diffusion of the dye, we noticed on opening the specimen that, as it was a neoplastic nodule of the maximum diameter of 0.8 cm, the injection had in fact been perinodular (case 3).

The perinodular injection at the four cardinal points proves in fact to be impossible when the nodule is so large as to occupy the entire lobe or the isthmus. In the case of a papillary carcinoma in micro-macrofollicular multinodular goiter, problems may arise concerning the site of the perinodular injection, due both to the difficulty in locating the neoplastic nodule and to the frequent lack of adjacent non nodular parenchyma.

In the cases of perinodular injection, we noticed, in the entire lobe parenchyma, a diffusion of the dye whose concentration progressively diminished as minutes passed; we were unable to visualize both the diffusion of the dye through the lymphatic vessels and its concentration in the lymph nodes.

The injection of even minimum doses of dye, though given as slowly as possible, involves a discharge, even though minimal, from the thyroid capsule in the point of injection and from the disrupted blood and lymphatic vessels, spreading to the adjacent tissues (Fig. 2); after the injection, therefore, not infrequently, it is necessary to recognize and safeguard a blue inferior laryngeal nerve or a parathyroid gland, chromatically indistinguishable from the other cervical structures similarly coloured. This fact helps to explain the visualization of the blue-stained pericapsular lymphatics after intratumoral injection in the two described cases.

Two patients only (case n° 4 and case n° 7) had nodal metastases at hematoxylin-eosin examination. The number of metastatic lymph nodes was 4 in case n° 4 and 5 in case n° 7.

On the basis of the reported results of the first nine patients enrolled, we believed convenient to stop the study.

### Discussion

If there is no evidence of neoplastic involvement in lymph nodes, application of the sentinel node concept to high-risk papillary thyroid carcinomas and to medullary carcinomas, might assure a better selection of the patients for whom lymphadenectomy would be recommended.

In thyroid medullary carcinoma, as well as in high-risk papillary carcinoma, the location of the sentinel lymph node would also allow dissection to be orientated towards the various cervical compartments. It might be objected, against the protocol of our study, that on objective examination or preoperative instrumental investigation the lack of evidence of lymph node metastases, as indicated in other studies (10-11), is not included among the methods of selecting patients; in fact, in case of manifest lymph node metastasis, the lymph flow towards these lymph nodes may be obstructed and the lymph drain may take place through alternative ways (12). This consideration, however, would mainly justify a false negative rate ("blue" negative lymph nodes in the presence of other positive "colourless" lymph nodes) (13), but not the feasibility of the method (i.e. the percentage of cases in which sentinel lymph nodes could be detected), which on the basis of our results appears to be the principal point of discussion as to sensitivity. Regarding our patients who underwent intraoperative lymphatic mapping, only two of them had nodal metastases; these metastases were clinically suspicious in the preoperative phase and evident in the intraoperative phase.

As to the type of injection, either intra- or peritumoral, it is pointed out that in colonic cancer, breast

cancer and melanoma, the injection is performed mainly either peritumoral or at the boundaries of the biopsy (13-14), since intratumoral injection does not allow the lymphatic diffusion of the dye (13). In particular, as regards colonic carcinoma JOONSTEN *et al.* observed how the need to inject the blue-dye outside the tumour, and not inside it, helps to explain the rate of false negative sentinel lymph nodes (13). In our experience, contrary to what has been reported by KELEMEN *et al.* (10), intratumoral injection did not cause diffusion of the blue dye to the rest of the thyroid parenchyma; for this reason, after the first cases we proceeded with perinodular injection. In this way, diffusion to the extranodular lobe parenchyma took place, though it did not allow the lymphatic drainage structures to be visualized.

Concerning the use of radiopharmaceutical agents in thyroid carcinoma, preoperative lymphoscintigraphy with Tc-99m Nanocoll on a patient with clinical evidence of lymph node metastases proved to be feasible and led to diagnostic results identical to those of FDG-PET, the high cost of which are a limit to its use; a limitation of this method in thyroid carcinoma is the inability to distinguish lymph nodes in the proximity of the primary tumour (4).

MORTON & OLLILA consider the blue dye as the gold standard in the technique of sentinel lymph node; the use of radiopharmaceutical agents for lymphatic mapping has some limits, such as the fact that the number of hot lymph nodes is correlated to the type of radiocolloid used, and to the interval between injection and surgery, with the consequence that not all hot lymph nodes are sentinel (15), just as the hottest ones are not always so (14, 15); in addition, the distance between lymph nodes and primary tumour is another important variable in lymphatic mapping with radiopharmaceutical agents. Also the measurement criteria defining the lymph node sentinel in terms of radioactivity are quite different (16-19). In consideration of these and various other problems, in lymphatic mapping some centres have used radiopharmaceutical agents as a complement to the blue-dye technique, in order to increase the possibility of identifying the sentinel lymph node (up to 98% of cases dealt with) (14-15). The fact is significant that in a recent study, in which blue-dye and radiopharmaceutical agents were used together, 8% of the sentinel lymph nodes, some of them metastatic, proved to be blue but not hot (15). It should be considered, however, that when the two methods are combined, the use of a gamma-probe may lead to less careful research of the coloured lymphatics, with a lesser blue lymph node identification rate, and that the sequential administration of the two agents may affect the lymph node concentration of one of them. CATARCI *et al.* underline the necessity to use the combination of preoperative lymphoscintigraphy, vital day and probe scanning in order to enhance the identifi-

cation rate of sentinel node (100% using all the three methods versus 50%, 66% and 83% using one of the methods alone for vital dye, preoperative lymphoscintigraphy and probe scanning respectively) (20). However, in the commentary on the study by CATARCI, SHAHA underlines the small number of patients treated (6 cases) and points out that often the gamma probe activity is so intense at the primary site that it may be almost impossible to distinguish the "hot" sentinel node (21). STOECKLI *et al.* point out that the combination of lymphoscintigraphy and gammaprobe accurately detect sentinel lymph nodes in the central and lateral compartment and in the mediastinum (22).

In the studies by KELEMAN *et al.* (10), JOHNSON *et al.* (23) and DIXON *et al.* (24) the dye injection is intranodular. In DIXON *et al.* series the visualization of lymphatics was possible in 78% of patients (31/40) with thyroid lesions and the sentinel node was identified in 65% (26/40). In this study of the 14 patients with papillary thyroid carcinoma, the lymphatic vessels were visualized in 12 and sentinel node was identified in 10 of these patients; the sentinel node biopsy detected 67% (6/9) of the metastatic nodal disease (24). In a recent review WISEMAN *et al.* report that the rate of sentinel node identification varies from 66% to 100% according to different authors (25). In the study by CHOW *et al.* blue-dye injection revealed sentinel lymph nodes in 10 of 15 cases (26). In the 5 patients of our series, who underwent intranodular injection, pathological examination showed that the blue-dye concentrated inside the neoplasm, without diffusion into the lobar parenchyma. This evidence can justify the failure to visualize lymphatics in our cases. On the contrary, when the injection was outside the node, we observed diffusion of the blue-dye within the entire lobe and its progressive dilution, without lymphatic channels indicating a preferential nodal drain being evidenced. Our previous report of the thyrolymphoadenography in thyroid neoplasms demonstrated a variable pathological lymphatic drainage pattern into lymph nodes located also outside the explorable cervical compartments (27): these findings help to explain the non visualization of the sentinel nodes in series with blue-stained lymphatics. In our experience, however, the detection of the pericapsular blue-stained lymphatic channels in the two described cases could be explained by a spread of the blue-dye to the adjacent tissue and vessels from the point of injection.

Our preliminary results are different from those of other studies so far reported (11, 23, 28), and this contributes to the increasing interest shown in this recent diagnostic method. Unlike other studies, ours foresees the inclusion exclusively of patients with preoperative fine-needle aspiration biopsy suggestive of papillary thyroid carcinoma, in order on the one hand to limit exposition to the anaphylactic risk correlated with the

blue-dye injection in patients with non malignant neoplasm, who therefore could not have benefitted of the possible advantages of the method, and on the other hand to assess both the feasibility and the sensitivity thereof.

As a result of the mentioned findings, we will obviously have to centre our attention principally on the identification by blue-dye injection, and then on the predictive value of the sentinel lymph node. The oncological meaning of the neoplastic involvement of sentinel lymph nodes is inevitably correlated to the still uncertain prognostic impact of lymph node metastases in thyroid differentiated carcinomas. In these tumours, the sentinel lymph node dissection technique may detect occult lymph nodes metastases, but does not assist in defining the effects of lymph node involvement and of lymphadenectomy on the prognosis.

It can be stated that the sentinel lymph node concept has proved to be valid in melanoma and breast carcinoma, while its application to gastrointestinal neoplasms is still an open question (29). In thyroid carcinoma, due to the debatable influence of occult lymph node metastases on survival, its usefulness is less definable. It will be possible to assess the sensitivity of the blue-dye method only after the feasibility study has yielded clearly positive results.

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