

The sentinel lymph node in papillary cancer of the thyroid including histological subtype



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BACKGROUND: *The aim of this work was to reveal through sentinel node study the intraoperative presence of preoperatively undetected pathological lymph nodes.*

MATERIALS AND METHODS: *At the Surgical Science Department of "La Sapienza" University of Rome The Authors studied from January 2003 to June 2004 18 patients with papillary carcinoma of the thyroid, who presented no clinical evidence of lymph node metastasis; they performed a total thyroidectomy in all cases, removing and histologically examining all lymph nodes of the upper anterior mediastinum. Where negative they were then subjected to immunohistochemical analysis with Pan Cytokeratin.*

RESULTS: *The method was positive in 10 patients: 2 pure papillary carcinomas, 1 papillary carcinoma with poorly differentiated areas, 1 tall cell papillary carcinoma, 5 sclerosing carcinoma and 1 follicular variant papillary carcinoma; and negative in 8: 5 pure papillary carcinomas, 2 sclerosing carcinoma and 1 case of follicular variant papillary carcinoma.*

Lymph node micrometastasis was found in 2 cases through study with Pan Cytokeratin on final histological examination.

CONCLUSIONS: *Analysis of the Authors' preliminary data shows that sentinel lymph node detection has 83.3% sensitivity and 100% specificity for Upper Anterior Mediastinum lymph nodes.*

The Authors can propose two main applications: select for dissection only patients with a positive sentinel node and reduce the number of cases to be subjected to postoperative treatment with iodine ablation, in patients with "low risk" thyroid tumours and negative sentinel nodes.

KEY WORDS: Cytokeratin, Neck dissection, Sentinel lymph node, Thyroid tumours.

Introduction

Lymph nodes are the most common metastatisation sites of solid tumours. Their involvement is sometimes the first clinical sign and their surgical removal, when they are the site of neoplastic recurrence, is important in improving prognosis. However, lymphectomy for prognostic aims when the lymph nodes are not clinically involved is controversial, even when considering that papillary carcinoma of the thyroid has a high incidence of occult lymph node metastasis.

Lymph node mapping and sentinel node dissection have

been demonstrated as accurate methods in predicting lymph node involvement in mammary carcinoma and melanoma ^{1,2}.

Identification of the sentinel node in papillary carcinoma of the thyroid, introduced by Kelemen ³ in 1998, is aimed at identifying lymph node involvement without performing an in principle "unnecessary" lymphadenectomy.

The aim of our work was to reveal through sentinel node study the intraoperative presence of preoperatively undetected pathological lymph nodes, independently of their influence on prognosis.

Study of the sentinel node may permit a modulated lymph node dissection with the aim of reducing the incidence of local recurrence at the regional lymph nodes, given that lymphadenectomy in the presence of metastatic lymph nodes determines a prolongation of the disease-free time period.

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Materials and Methods

At the Department of Surgical Sciences we studied from January 2003 to June 2004 a group of patients with papillary carcinoma of the thyroid, diagnosed by pre-operative cytological examination, who presented no clinical evidence of lymph node metastasis. Preoperative evaluation included clinical history with complete physical examination, routine laboratory evaluations and cervical ultrasound determination to exclude the presence of lymph node pathologies.

A systematic surgical procedure was selected to study the sentinel node, which is the first lymph node to receive lymph fluid directly from the tumour. The thyroid lobe with pathological nodular formation was exposed, revealing the middle thyroid veins and the upper vascular pedicle.

We used a vital dye (Methylene Blue) for this study. Around 0.4 ml Methylene Blue was injected with a 26 gauge needle. Careful attention was paid to avoid contaminating surrounding tissues with the dye. After the dye's injection into the pathological node, highlighted by palpation and using intraoperative echography (nodes with <0.7 cm diameter), the node was delicately massaged for around one minute. After 10 minutes the surgical operation was performed.

The sentinel node was found by identifying the blue-stained lymph vessels and following them to the first draining lymph node (which is stained an intense blue). In our preliminary study we performed a total thyroidectomy in all cases, removing and histologically examining all lymph nodes of the upper anterior mediastin. Recurring and jugular lymph nodes were removed only when they were stained with the dye. The removed lymph nodes were then dyed with Haematoxylin-Eosin and examined by optical microscope. Where negative they were then subjected to immunohistochemical analysis with Pan Cytokeratin.

Results

The study comprised 18 patients (11 F, 7 M) with papillary carcinoma of the thyroid diagnosed by pre-operative cytological examination who presented no clinical evidence of lymph node metastasis.

The method was positive in 10 patients and negative in 8 (Tab. I).

In the 10 patients in which the dye was found in the upper anterior mediastin lymph nodes (mean age 45.9, range 24 - 69), 4 were also found positive for recurrent homolateral lymph nodes and 1 also for proximal jugular lymph nodes (Tab. II). In all 10 cases, histological examination confirmed the diagnosis of neoplastic recurrence of papillary carcinoma in the removed lymph nodes. Mean tumour diameter was 1.9 cm (range 0.6 - 3.5 cm). Neoplasm involved the right lobe in 5 cases, the

TABLE I – Characteristics of patients with thyroid papillary carcinoma with lymph node of the upper anterior mediastin positive (UAM+) and negative (UAM-) for sentinel nodes with vital dye

	10 cases UAM In +	8 cases UAM In -
Age	45.9	50
Diameter	1.9	1.3
Lobe		
<i>Right</i>	5	4
<i>Left</i>	2	1
<i>Isthmus</i>		2
<i>Bilateral</i>	3	1
pT1	2	4
pT2	0	1
pT3	7	3
pT4	1	0
Multicentric	3	2
Invasion without exceeding capsule	2	2
Pre-thyroid soft tissue infiltration	7	3
Muscular infiltration	1	0
Histological vascular invasion	3	0
HISTOLOGY		
<i>Pure papillary</i>	2	5
<i>Tall cell papillary</i>	1	0
<i>Sclerosing papillary</i>	5	2
<i>Follicular variant papillary</i>	1	1
<i>Papillary with poorly differentiated areas</i>	1	0
Stage		
<i>I</i>	7	5
<i>II</i>	0	1
<i>III</i>	1	2
<i>IV</i>	2	0

left lobe in 2 cases, and both thyroid lobes in 3 cases. Results on final histological examination were: 2 cases pT1, 7 cases pT3, 1 case pT4. The neoplasm was found to be multicentric in 3 cases. In 2 cases the invasion was found not to exceed the capsule. In 7 cases infiltration was found into prethyroid soft tissues, and in 1 case muscle infiltration was revealed. Signs of histological vascular invasion were found in 3 cases.

Under the histological classification "TMN U.I.C.C. 2002 – VI Edition"⁴, we classified 7 cases as stage I, 1 as stage III and 2 cases as stage IVa.

Individual analysis of the histological subtypes revealed 2 pure papillary carcinomas (both pT3), 1 papillary carcinoma with poorly differentiated areas (pT4a), 1 tall cell papillary carcinoma (pT3), 5 sclerosing carcinoma (1 pT1, 4 pT3) and 1 follicular variant papillary carcinoma (pT1). One case had no staining of the upper anterior mediastin district but did have staining of homolateral recurrent lymph nodes at the lesion. In this case both the upper anterior mediastin lymph nodes and the recurrent lymph nodes, which were the only ones found positive, were removed. This was a stage I sclerosing papillary carcinoma with a diameter of 0.9 cm (pT1) (Tab. II).

TABLE II – Characteristics of patients with thyroid papillary carcinoma with upper anterior mediastin (UAM), recurring and proximal jugular lymph node positive and negative for sentinel nodes with vital dye

	4 cases recurring ln + UAM +	1 case recurring ln + UAM –	1 case recurring ln + UAM + Proximal jugular +
Age	41.5	34	28
Diameter	1.6	0.9	1.2
Lobe	–	–	–
Right	2	1	1
Left	1	–	–
Isthmus	–	–	–
Bilateral	1	–	–
pT1	1	1	–
pT2	–	–	–
pT3	2	–	1
pT4	1	–	–
Multicentric	1	–	–
Invasion without exceeding capsule	2	1	–
Pre-thyroid soft tissue infiltration	3	–	1
Muscular infiltration	–	–	–
Histological vascular invasion	2	–	1
HISTOLOGY			
Pure papillary	–	–	–
Tall cell papillary	–	–	–
Sclerosing papillary	2	1	1
Follicular variant papillary	1	–	–
Papillary w. poorly differentiated areas	1	–	–
STAGE			
I	3	1	1
II	–	–	–
III	–	–	–
IV	1	–	–

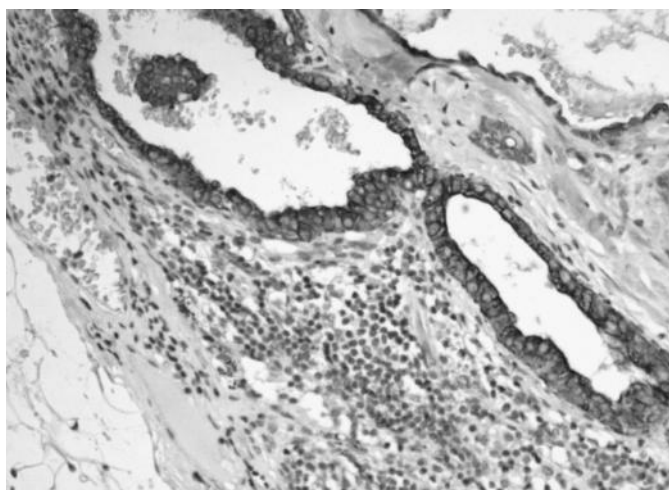


Fig. 1: Characteristic histologic features of CK+. Follicular variant papillary CK+in lymph node (original magnification x20).

In the 8 cases of papillary carcinoma for which the method gave a negative outcome, the upper anterior mediastin lymph nodes were removed anyway for decisive histological examination and subjected to study with Pan Cytokeratin following Haematoxylin-Eosin staining (Fig. 1).

Mean age was 50 (range 24-69) and mean neoplasm diameter was 1.3 cm (range 0.5-3.5 cm).

The neoplasm involved the right lobe in 4 cases, the left lobe in 1 case, the isthmus in 2 cases and both thyroid lobes in 1 case. Results on final histological examination were: 4 cases pT1, 1 case pT2, 3 cases pT3.

The neoplasm was found to be multicentric in 2 cases. In 2 cases the invasion was found not to exceed the capsule. In 3 cases infiltration was found into prethyroid tissues, and muscle infiltration in no case. No signs of histological vascular invasion were found in any case. Under the histological classification "TMN U.I.C.C. 2002 – VI Edition" (4), we classified 5 cases as stage I, 1 as stage II and 2 cases as stage III.

Individual analysis of the histological subtypes revealed 5 pure papillary carcinomas (2 pT1, 1 pT2, 2 pT3), 2 sclerosing carcinoma (1 pT1, 1 pT3) and 1 case of follicular variant papillary carcinoma (pT1). Lymph node micrometastasis was found in 2 cases through study with Pan Cytokeratin on final histological examination. These were both multicentric sclerosing papillary carcinoma, mean diameter 1 cm, one pT1 (diameter 0.8 cm) and the other pT3 (diameter 1.2 cm), with invasion of prethyroid soft tissue, both at stage I.

Comparative evaluation of the reliability of the sentinel node identification methods is given in Table III.

TABLE III – Evaluation of sentinel lymph node identification techniques

	Vital dye	Haematoxylin Eosin	Haematoxylin Eosin and CK
True positives	10	10	12
True negatives	6	6	6
False positives	0	0	0
False negatives	2	2	0
Sensitivity	83.3%		100%
Specificity	100%		100%
Positive predictive value	100%		100%
Negative predictive value	75%		100%

Discussion

In literature, lymphectomy for prognostic aims in thyroid papillary carcinomas remains controversial⁵⁻⁷. The indication and extension of lymphectomy is often correlated not only to objective evidence of lymph node metastasis but to the surgeon's therapeutic disposition. The problem's importance is highlighted by the fact that some authors have demonstrated in up to 90% of cases that clinically undamaged lymph nodes have been found

to be metastatic on subsequent histological examination. Despite this, the significance of occult metastasis is unknown⁸.

In Chow's study⁵ lymph node metastases were found in 67% of cases, confirming the opinion that papillary carcinoma of the thyroid tends to have a predilection for metastatisation through the lymphatic route.

Sentinel node dissection is considered by some authors⁹ as a useful alternative to elective lymphadenectomy, reducing unnecessary removal and thus related complications. Sentinel node dissection may be useful to the surgeon in selecting patients who need aggressive surgery or iodine ablative therapy.

The sentinel node is defined as the first lymph node in a regional lymph node area to receive fluid flow from the primary tumour.

In 1977 Kabanis⁹ proposed that the first lymph node to receive drainage from the tumour could be removed for examination, and, on the basis of its metastatic involvement, a regulated lymphectomy could be performed. In 1999, Morton¹⁰, using "Blue Dye", demonstrated the possibility of revealing fluid drainage from the melanoma.

Keleman³, in a 1998 study, was the first to demonstrate the possibility of lymphatic mapping, in 15 patients from 17 with benign and malignant thyroid tumours: tumours were associated with the sentinel node in 5 cases. Subsequently, other studies^{11,12} were conducted to evaluate the role of sentinel node study in malignant thyroid neoplasms.

Krag⁹ demonstrated the possibility of sentinel node identification using both a radioactive tracer and a vital dye (Blue Dye).

In a 1999 study, Johnson¹³ demonstrated that sentinel node study can also be applied to Hürtle cell tumours. In 2000, Dixon¹⁴ showed that sentinel node biopsy using "isosulfan blue" dye is a safe, simple procedure, as long as the parathyroid glands are identified before injection of the contrast agent. From 12 patients with thyroid carcinoma, he reports 6 true positives, 2 true negatives, 2 false negatives, and no sentinel node in 2 cases. Sentinel node study in carcinoma of the thyroid presents particular problems. In fact, the thyroid has extensive internal lymphatic connections. Many studies have demonstrated that thyroid papillary carcinoma tends to spread to the bilateral laterocervical lymph node regions¹⁵. In 1977, Cruz¹⁶ highlighted that each thyroid lobe has its own intra-glandular lymphatic system, which does not seem to be connected to the lymphatic system of the contralateral lobe. For this reason, Fukui⁶ hypothesises that injection of a contrast agent into a thyroid lobe would highlight only the lymph nodes on the same side.

In contrast, Matoba N, Kikuchi¹⁷ refer to the visualisation of lymph nodes contralateral to the pathological node after injection with Lipiodol. In Fukui's study most sentinel nodes are localised in the paratracheal region,

with only 28.8% in the proximal jugular region.

Some authors have demonstrated that immunohistochemical use may be helpful in reducing false negatives in the search for sentinel nodes, for correct neoplasm staging^{8,18,19}. Arch-Ferrer⁸ used low molecular weight cytokeratin as a tracer, much easier to use than high molecular weight cytokeratin or thyroglobulin.

In this study we used Pan Cytokeratin in the eight cases found negative, and thanks to this we found 2 micro-metastases. These were both sclerosing papillary carcinoma, mean diameter 1 cm, one pT1 and the other pT3, both at stage I. We evaluated only patients with a preoperative diagnosis of papillary carcinoma. In all cases a central lymphectomy was performed, such as to constitute the optimum condition to compare the histopathological studies.

Analysis of our preliminary data shows that sentinel node detection has 83.3% sensitivity and 100% specificity for Upper Anterior Mediastin lymph nodes. We also found dye in the recurring lymph nodes in 4 cases with positive upper anterior mediastin lymph nodes and also 1 case of positive proximal jugular lymph nodes. In the 8 cases found negative with vital dye, 2 cases of micro-metastasis were found on analysis with cytokeratin during the final histological examination.

Fukui⁶ found 95.5% sentinel node identification (21 of 22 cases). Other authors^{1,3} indicate lower rates. Chow⁵ found the method 90% accurate, an apparently encouraging result. However, the negative predictive index of 67% is relatively low (the sentinel node was detected in 10 of 15 cases). He highlights that the technique needs to be refined in order to improve its reliability and accuracy and to reduce false negatives, with the aim of legitimising its routine use in sentinel node detection. The negative predictive index in our study was substantially similar (75%).

In Arch-Ferrer's study⁸, the sentinel node was identified after injection of blue dye in 90% of patients with thyroid carcinoma. The author⁸ underlines that in patients with no preoperative evidence of lymphatic involvement, lymph node metastasis unsuspected with use of the standard technique was found in 53% of cases. This rose to 64% when immunohistochemistry was used. Additional lymph node metastasis was demonstrated in 10 of 12 cases with positive sentinel node, and metastasis of the lateral compartment was detected in 2 patients.

Arch-Ferrer⁸ reports 70.6% sensitivity, 100% specificity, 100% positive predictive value and 37.5% negative predictive value for the use of haematoxylin-eosin dye for sentinel node detection; all values reached 100% when immunohistochemistry for CK-7 was added. Slightly higher values were found in our study, with a sensitivity of 83.3%, 100% specificity and positive predictive value, and 75% negative predictive value. In our experience too, use of immunohistochemistry brought all the test's reliability values to 100%.

Our study showed the presence of lymph node meta-

stasis in the lateral compartment in one case, not associated with central compartment involvement, a phenomenon known as "jump lymph node metastasis". This phenomenon has been previously noted by Chow⁵, and indicates the efficacy of the sentinel node identification technique even in the present of unusual lymphatic drainage.

Some authors⁸ suggest that lymph node dissection should be performed only in patients with a positive sentinel node, and where histological examination with Haematoxylin-Eosin is negative, they recommend execution of an immunohistochemical examination for CK-7. In our study we removed lymph nodes negative to vital dye in any case and subsequently completed the histological examination with the immunohistochemical study. Arch-Ferrer⁸ found that positive sentinel nodes were no larger than negative lymph nodes: furthermore, it is interesting to note that micrometastases were present in numerous patients with both positive and negative sentinel nodes. This may mean that the metastatic area is small in both sentinel nodes and non-sentinel lymph nodes.

In conclusion, in agreement with various authors^{6,8} who underline the difficulty of correctly appreciating lymphatic state by intraoperative digital palpitation, we believe that the use of dye may be an important aid in identifying lymph nodes presumed to be metastatic. Sentinel node search is a feasible, safe method. Although some aspects of the method have yet to be finalised, we can propose two main applications. The first is to select for dissection only patients with a positive sentinel node, to reduce the extent of the operation and the number of complications. A second potential indication of sentinel node sampling is to reduce the number of cases to be subjected to postoperative treatment with iodine ablation, in patients with "low risk" thyroid tumours and negative sentinel nodes

Riassunto

SCOPO DEL LAVORO: Lo studio vuole valutare, attraverso l'analisi del linfonodo sentinella, la presenza di linfonodi patologici non evidenziati preoperatoriamente.

MATERIALE E METODI: Presso il Dipartimento di Scienze Chirurgiche dell'Università degli Studi di Roma "La Sapienza", dal Gennaio 2003 al Giugno 2004 gli Autori hanno selezionato 18 pazienti con carcinoma papillare della tiroide, con assenza di evidenza di metastasi linfonodali preoperatorie. È stata eseguita una tiroidectomia totale in tutti i casi e sono stati asportati i linfonodi del mediastino superiore anteriore analizzati poi con esame istologico. Qualora negativi, i linfonodi sono stati sottoposti ad analisi immunoistochimica con Pan Citocheratina.

RISULTATI: Il metodo del linfonodo sentinella con colorante vitale era positivo in 10 pazienti: 2 carcinomi papil-

liferi puri, 1 papillare con aree scarsamente differenziate, 1 papillare a cellule alte, 5 carcinoma sclerosanti, 1 carcinoma papillare variante follicolare.

Micrometastasi linfonodali sono state trovate in 2 casi attraverso lo studio con Pan Citocheratina nella valutazione istologica definitiva.

CONCLUSIONI: L'analisi preliminare dei dati dimostra che lo studio del linfonodo sentinella ha l'83,3% di sensibilità ed il 100% di specificità per i linfonodi del mediastino anteriore superiore.

Gli Autori propongono due applicazioni di questa metodica: la prima è quella di sottoporre a dissezione linfonodale solamente i pazienti con linfonodo sentinella positivo, allo scopo di ridurre l'estensione dell'intervento ed il numero di complicanze operatorie. Una seconda indicazione è rivolta a limitare i casi da sottoporre a trattamento postoperatorio con iodio ablazione, nei pazienti con tumore della tiroide "a basso rischio" e con linfonodo sentinella negativi.

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Commento

Commentary

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Sul piano speculativo l'utilizzo della strategia del Nodulo sentinella (NS) al cancro papillare della tiroide, già diagnosticato prima dell'intervento, è senza dubbio interessante, anche se è un po' debole la finalità terapeutica di tipo oncologico. Infatti, una volta realizzata la tiroidectomia totale, è troppo attraente e provata nel tempo la possibilità di azzerare poi la presenza di altre eventuali cellule tiroidee ovunque si trovino con il trattamento radiometabolico dello iodio radioattivo, per trascurare questa concreta possibilità affidandosi solo al responso del NS.

Trattandosi di cancro papillare, il "picking node" dei linfonodi è una delle strategie ampiamente accettate in alternativa alla linfadenectomia radicale del collo, ormai non da tutti difesa. In tal senso la tecnica del NS potrebbe guidare ad un "picking node" mirato non soltanto dal volume dei linfonodi, ma anche dalla direzione del dosaggio linfatico dimostrato sul campo operatorio.

Qualche perplessità esiste sul metodo descritto dagli Autori perché l'uso del bleu di metilene come colorante vitale quando è ormai condiviso l'uso di coloranti ad alto peso molecolare per evidenziare le vie di deflusso linfatico (come il Patent bleu), per evitare uno spandimento anche per via venosa, come avviene certamente col bleu di metilene, e con oscuramento del campo operatorio

The sentinel node (SN) research in the global surgical technique for a preoperatively still diagnosed papillary thyroid cancer is well known, and very interesting under the specular aspect. Loss evident is its usefulness for oncologic reasons, because the possibility offered by radioiodine after a total thyroidectomy to destroy everywhere all residual thyroid cells with a correct radiometabolic treatment is too attractive to be renounceable, and confide only on such research to complete the treatment.

The picking node technique is well agreed for thyroid papillary cancer in alternative with radical neck dissection. In this sense the NS technique can be considered a more sophisticated kind of "picking node" and could be very useful to discover suspect lymph nodes not only for their volume but also for the demonstrated lymph drainage, notwithstanding the added complications of the operation.

Some wonder remains on the Author's method what is the reason to employ methylene blue as vital dye for the research, when it is nowadays well stated the more correct utilization of high molecular weight dyes like patent blue?. These last ones are electively drained from lymph vessels, and so it is avoided the venous spread typical of methylene blue that can obscure the operative field and makes more difficult the intraoperative localization of SN