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99Tc nanocolloid sentinel node procedure in papillary thyroid carcinoma: our mono-institutional experience on a large series of patients

La tecnica del linfonodo sentinella con 99Tc-nanocolloide nel carcinoma papillare della tiroide: la nostra esperienza monoistituzionale

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SUMMARY

The sentinel lymph node was defined as the first lymph node to receive drainage from a primary cancer. The aims of this study were to investigate the efficacy of radiocolloid lymphoscintigraphy and of the hand-held gamma probe procedure for sentinel lymph node biopsy in papillary thyroid carcinoma and to evaluate these results in clinical staging. A total of 99 consecutive papillary thyroid carcinoma patients entered the study. Patients underwent radiocolloid lymphoscintigraphy before surgery. Intra-operative sentinel lymph node localization was performed using a hand-held gamma probe. Patients were observed at follow-up at 2 and 6 months and, thereafter, yearly. Sequential lymphoscintigraphy was able to identify at least one sentinel lymph node in 98/99 cases (99%), using intra-operative hand-held gamma probe, the surgeon was able to detect at least one sentinel lymph node in all cases. Sentinel lymph node metastases were diagnosed in 49%. Overall, 79 patients underwent ablative ^{131}I therapy. The median value of thyroglobulin in N0 vs. N1 patients was 1 ng/ml vs. 1.9 ng/ml ($p = 0.03$) and 0.2 ng/ml vs. 1 ng/ml ($p = 0.001$) before and after ^{131}I therapy, respectively. The pre-operative lymphoscintigraphy and the intra-operative gamma probe offer significant advantages over the vital dye technique, described in our previous experience. The rate of nodal involvement (49%) is very high considering that no patients had clinically palpable nodes or suspected at echography. ^{131}I whole body scan and thyroglobulin measurements confirmed sentinel lymph node in papillary thyroid carcinoma as a reliable procedure. In patients classified N0, by sentinel lymph node biopsy, ablative ^{131}I therapy could be avoided.

KEY WORDS: Thyroid • Cancer • Node metastases • Sentinel lymph node • Radiocolloid lymphoscintigraphy

RIASSUNTO

Il linfonodo sentinella è stato definito come il primo linfonodo che riceve il drenaggio linfatico dal tumore primitivo. Gli obiettivi di questo studio sono stati indagare l'efficacia della procedura mediante linfoscintigrafia preoperatoria con radio colloide e sonda gamma manuale intraoperatoria per la ricerca del linfonodo sentinella nel carcinoma papillare della tiroide e valutare i risultati nella stadiazione clinica. Novantanove pazienti consecutivi affetti da carcinoma papillare della tiroide sono stati arruolati in questo studio. I pazienti sono stati sottoposti a linfoscintigrafia con radio colloide prima dell'intervento chirurgico. La localizzazione intraoperatoria del linfonodo sentinella è stata realizzata utilizzando una sonda gamma manuale. I pazienti sono stati seguiti nel follow-up a 2, 6 mesi e in seguito annualmente. Il linfonodo sentinella è stato individuato in 98/99 casi (99%) mediante linfoscintigrafia e in tutti i casi mediante la sonda manuale intraoperatoria. Metastasi linfonodali del linfonodo sentinella sono state individuate nel 49% dei casi. Settantanove pazienti sono stati sottoposti a terapia ablativa con ^{131}I. Il valore mediano della tireoglobulina nei pazienti N0 vs. N1 è risultato pari a 1 ng/ml vs. 1,9 ng/ml ($p = 0,003$) e 0,2 ng/ml vs. 1 ng/ml ($p = 0,001$) rispettivamente prima e dopo la terapia con ^{131}I. La ricerca del linfonodo sentinella mediante linfoscintigrafia preoperatoria e gamma camera intraoperatoria offrono significativi vantaggi rispetto alla tecnica con il colorante vitale, descritta nella nostra precedente esperienza. La percentuale di metastasi linfonodali pari a 49% è molto alta considerando che nessun paziente presentava linfonodi sospetti né clinicamente né alla ecografia preoperatoria. La scintigrafia total body con ^{131}I e i dosaggi di tireoglobulina hanno confermato l'attendibilità della procedura del linfonodo sentinella nel carcinoma papillare della tiroide. Nei pazienti definiti N0 mediante la tecnica del linfonodo sentinella la terapia con ^{131}I può essere evitata.

PAROLE CHIAVE: *Tiroide • Carcinoma • Metastasi linfonodali • Linfonodo sentinella • Linfoscintigrafia con radiocolloide*

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Introduction

The sentinel lymph node (SLN) was defined as the first lymph node to receive drainage from a primary cancer [1]. Intra-operative lymphatic mapping with SLN biopsy (SLNB) has become a revolutionary concept in the management of solid malignancies [1-4]. SLNB using both vital dyes and radioisotopes has been developed as an alternative to elective lymph node dissection in patients with clinically node-negative disease [1-4]. If no metastasis is found in the SLN, there should be no metastasis in distant lymph nodes. The accuracy of this concept has been demonstrated for malignant melanoma and breast cancer.

Application of the SLN concept has also been reported in several studies in patients affected by differentiated thyroid carcinoma (DTC) [1-7]. Kelemen, et al. [8], in 1998, pioneered the vital blue dye technique for SLNB in 17 thyroid cancer patients, while subsequent reports by Gallowitsch et al. [9] and Rettenbacher et al. [10] described the use of a radiotracer with intra-operative counting using a hand-held gamma probe. In 2006, we evaluated the accuracy of SLN mapping by intra-tumoral injection of Blue Dye in a large series of patients with papillary thyroid carcinoma (PTC) and, in 2008, investigated the efficacy of the 99Tc nanocolloid SLN procedure in 65 PTC patients [4 5].

The prognostic value of lymph node metastases in papillary thyroid carcinoma (PTC) is still controversial and the clinical role of SLN in PTC is debated [11-18].

Aims of the present study were to define an accurate technical procedure for SLNB with radiocolloid lymphoscintigraphy and the hand-held gamma probe and to evaluate the effectiveness of the SLN procedure on post-operative clinical staging in a large series of patients with PTC.

Material and methods

From July 2005 to June 2009, 99 patients affected by PTC entered the study. All were pre-operatively investigated and operated upon by the same surgeon in the Department of Special Surgical Pathology, University of Padua Medical School. Inclusion criteria were: a) diagnosis of PTC at pre-operative fine-needle aspiration cytology (FNAC); b) the monofocality of PTC at clinical examination and at high resolution neck ultrasound (US); c) N0 at clinical and US examinations; d) the absence of distant metastases; e) no previous surgical treatment on the neck.

Patients underwent node dissection according to the SLN procedure as described in our previous study [10]. All cases underwent lymphoscintigraphy in the Nuclear Medicine Unit, 3 hours before the start of surgery, after a single intra-tumoral injection of a nanocolloidal solution labelled with 99 Technetium (Nanocoll, GE Healthcare), in normal saline, administered under US-guidance. Immediately after the intra-tumoral injection, a sequential scintigraphic acquisition was obtained using a single head (Siemens, Orbiter 75) or dual head gamma camera (Siemens, Ecam) coupled with a low energy high resolution collimator. Multiple lymphoscintigrams were collected, 120 sec per frame, in the anterior and oblique position, followed by multiple static scintiscans until clear visualization of sentinel node or nodes was achieved. The last image (90 min after injection) was acquired using a 57Co flat source below the patient to obtain neck and body profile. In this last image, the total counts of all nodes visualized and background activity were measured by means of regions of interests (ROI). Intra-operative SLN localization was performed using a hand-held gamma probe (ScintiProbe MR 100, Pol.Hi.Tech., Carsoli, Italy) with an automatic peak for 99mTc-140 keV using probes of different diameter size (11 or 15 mm) and variable time count rate (1-4 seconds) depending on SLN activity. The probe was placed in a sterile surgical wrap and, before surgical incision, it was slowly moved from the injection site to the two lateral cervical regions to check out any radio-seeking site that was marked on the patient's skin. Then, after a standard cervicotomy, via a transversal incision, extended between the bodies of the two sternocleidomastoid muscles, the thyroid was exposed; following thyroidectomy, using the gamma probe, the central compartment was bilaterally scanned for hot spot investigation. The hottest node and all nodes with a count rate of more than 10% of the hottest node were removed. Then, on the basis of the lymphatic map obtained by scintigraphy, the lateral compartment of the neck was scanned and all nodes with at least 10% of the hottest node were removed. Only SLNs were sent for frozen section and only when one or more lymph nodes showed thyroid cancer metastasis the surgeon enlarged node dissection to the involved compartment. The thyroid and all lymph nodes resected were stained with haematoxylin & eosin (H&E) and cytokeratin.

All patients underwent ^{131}I Whole Body Scan (WBS) and received ^{131}I therapy when necessary. Patients were observed at follow-up at 2 and 6 months after treatment and then on a yearly basis. Follow-up consisted of clinical examination, measurements of Thyroglobulin (Tg) and anti-Tg antibodies, high resolution 10 MHz neck US and rhTSH ^{131}I WBS. Statistical analysis was performed using Wilcoxon Test comparing post-operative Tg values in N0 vs. N1 patients. A p value < 0.05 was considered statistically significant.

Results

The study population comprised 74 females (74.7%) and 25 males (25.3%), mean age 48.4 years (range 20-76). Mean tumour size was 1.8 cm (range 0.5-4.3 cm). The single intra-tumoral dose of the nanocolloidal solution labelled with 99 Technetium injected under US guidance showed a mean value of 5.5 MBq (range 4-7) in 0.1-0.3 ml of normal saline.

Sequential lymphoscintigraphy was able to reveal at least one SLN in 98/99 cases (99%). In particular, in 17/98 (17.3%) cases, one SLN was visualized, two nodes in 32/98 (32.7%), three nodes or more in 49/98 (50%).
Using an intra-operative hand-held gamma probe, the surgeon was able to detect at least one SLN in all cases. In all patients, SLNs were always identified in the central ipsilateral compartment, in one case the 3rd SLN was in the laterocervical compartment, no metastases. Only, one radioactive node was removed in 21/99 (21.2%) cases, 2 in 33/99 (33.3%) cases, 3 in 45/99 (45.5%) cases. All patients underwent total thyroidectomy and node dissection in accordance with the SLN procedure.
According to UICC-TNM staging, 45 cases (45.9%) were classified as T1, multifocal in 10 cases (10.2%), T2 in 10 cases (10.2%) and T3 in 43 cases (43.9%), multifocal in 16 cases (16.3%). The patients with multi-focality tumour were not excluded because the multi-focality was diagnosed not pre-operatively but at the post-operative pathology report, where tumour microfoci were discovered. One case was classified as micro/macro follicular adenoma at final histology.
The SLN metastases were diagnosed in 48/98 cases (49%): in 32 cases (67%), the hottest SLN was positive (1st SLN), in 16 cases (33%), the 2nd and/or the 3rd SLN. In 23 cases (23.5%), only 1 SLN was involved, in 25 cases (25.5%), 2 or more. The mean duration of follow-up was 19.5 months (range 3-41).
All patients underwent ^{131}I WBS at 2 months after surgery. A total of 79 patients (80.6%) underwent ablative ^{131}I treatment: for thyroid residual (mean 115 mCi, range 50-100), in 74 cases (41 cases N0 and 33 cases N1), for suspected lymph node metastases (mean 118 mCi, range 50-150) in 4 cases (N1) and for both thyroid residual and suspected lymph node metastases in one case (N1).
The median value of Tg in N0 vs. N1 patients was 1 ng/ml (range < 0.1-15) vs. 1.9 ng/ml (range < 0.1-127.5) ($p = 0.03$) and 0.2 ng/ml (range < 0.1-1.2) vs. 1 ng/ml (range < 0.1-17) ($p = 0.001$) before and after ^{131}I treatment, respectively (Table I).

Table I. Statistical analysis using Wilcoxon Test comparing thyroglobulin values in N0 vs. N1 patients.

Thyroglobulin (median)	N0	N1	P value
Before ^{131}I treatment	1	1.9	0.0035
After ^{131}I treatment	0.2	1	0.001

Discussion

Surgery is the most effective treatment for patients with PTC [19-25]. The standard therapeutic approach to DTC includes total or near total thyroidectomy together with loco-regional node dissection, ^{131}I treatment, and life-long TSH-suppressive thyroid hormone replacement [26-33]. However, it remains controversial as to whether prophylactic lymph node dissection improves prognosis and survival. The SLN procedure has achieved consensus as a staging procedure in breast cancer and melanoma patients, but few studies have evaluated the usefulness of SLN in thyroid surgery [34-36].
Through the selective lymph node dissection, the SLN procedure can avoid unnecessary node dissection, associated with higher morbidity. SLN can be performed using the vital dye technique [4 32 33], lympho-scintigraphy and gamma probe [3-5], and a combined technique using both vital dye and radiotracer [34].
In 2006, we considered 153 cases of PTC and evaluated the accuracy of SLN mapping performed by intra-tumoural injection of Blue Dye [4]. At surgery, blue positive SLNs were found in 108/153 cases (69.9%), of whom 36 (33.6%) had micro-metastases in SLN. In 4 cases, a normal parathyroid gland and, in 3 cases, fibro-adipose tissue, was stained blue and mistakenly removed as SLN (7 false positive results). On the other hand, sSLN was blue negative in 46/153 patients (30.1%), of whom 7 (15.2%) had micro-metastases in blue-negative lymph nodes. We concluded that, on the basis of our results, the blue-dye procedure for SLN detection was inappropriate as a standard of approach in PTC due to a relatively large number of false negative and false positive results.
In our previous experience, in 2008, we considered 65 cases of PTC: the SLN was detected in 98.5% of patients at lymphoscintigraphy and in all cases with intra-operative gamma probe [5]. SLN metastases were diagnosed in 34/65 cases (52%); the patients defined as N0 by the SLN technique were all confirmed by rhTSH ^{131}I WBS and Tg measurement. In this previous study, we proposed that the SLN procedure be considered a criterion to select patients in view of the ablative ^{131}I treatment. In patients defined N0, with the SLN technique, ablative ^{131}I therapy could be avoided, while in patients defined N1 at SLN biopsy, a therapeutic dose could be directly proposed.
In this study, we considered not only the safety and reliability of the radio-guided technique in detecting the SLN, but even the follow-up of the patients who underwent SLN biopsy. The SLN was detected in 98/99 cases at lymphoscintigraphy and in all cases with intra-operative gamma probe. According to our experience as far as concerns feasibility and accuracy, pre-operative lymphoscintigraphy and intra-operative gamma probe offer significant advantages over the vital dye technique, described in our previous experience: the injection of the radiopharmaceutical is performed pre-operatively, therefore avoiding disruption of the lymphatics during the initial dissection; use of the radiolabelled material offers the possibility to disclose SLN that lies outside the central compartment; there is no false positive staining of the parathyroid glands.
SLN metastases were diagnosed in 48/98 cases (49%); moreover, the rate of node involvement was very high

considering that no patients had clinically palpable nodes or suspected at echography.

In 16 cases (33%), the 2nd and/or the 3rd SLN was positive: it is worthwhile stressing that it is necessary to remove not only the hottest SLN but all nodes with a count higher than 10% of the hottest node.

^{131}I WBS and Tg measurements confirmed SLN in PTC as a reliable procedure: patients defined N0 using the SLN technique were all confirmed by ^{131}I WBS and Tg measurement. In addition to our earlier study, the 5 patients who underwent ^{131}I treatment for suspected lymph nodes metastases were defined N1 at the SLN procedure. On the basis of this large series of patients, we proposed SLN as a criteria to select patients in view of the ablative ^{131}I treatment. In patients defined N0, with the SLN technique, ablative ^{131}I treatment could be avoided, while in patients defined N1 at SLN biopsy, a therapeutic dose could be directly proposed.

References

1 Pasieka JL. *Sentinel lymph node biopsy in the management of thyroid disease*. Br J Surg 2001;88:321-2.

2 Pelizzo MR, Rubello D, Merante Boschin I, Piotto A, Pagetta C, Toniato A, et al. *Contribution of SLN investigation with 99m Tc-nanocolloid in clinical staging of thyroid cancer: technical feasibility*. Eur J Nucl Med Mol Imaging 2007;34:934-8.

3 Rubello D, Pelizzo MR, Al-Nahhas A, Salvatori M, O'Doherty MJ, Giuliano AE, et al. *The role of sentinel lymph node biopsy in patients with differentiated thyroid carcinoma*. Eur J Surg Oncol 2006;32:917-21.

4 Rubello D, Nanni C, Merante Boschin I, Toniato A, Piotto A, Rampin L, et al. *Sentinel lymph node (SLN) procedure with patent V blue dye in 153 patients with papillary thyroid carcinoma (PTC): is it an accurate staging method?* J Exp Clin Cancer Res 2006;25:483-6.

5 Boschin IM, Toniato A, Piotto A, Ide EC, Casara D, Guolo A, et al. *99Tc Nanocolloid sentinel node procedure in thyroid carcinoma*. Langenbecks Arch Surg 2008;393:705-8.

6 Wiseman SM, Hicks WL Jr, Chu QD, Rigual NR. *Sentinel lymph node biopsy in staging of differentiated thyroid cancer: a critical review.* Surg Oncol 2002;11:137-42.

7 Delbridge L. *Sentinel lymph node biopsy for thyroid cancer: why bother?* ANZ J Surg 2004;74:10-2.

8 Kelemen PR, Van Herle AJ, Giuliano AE. *Sentinel lymphadenectomy in thyroid malignant neoplasms.* Arch Surg 1998;133:288-92.

9 Gallowitsch HJ, Mikosch P, Kresnik E, Starlinger M, Lind P. *Lymphoscintigraphy and gamma probe-guided surgery in papillary thyroid carcinoma: the sentinel lymph node concept in thyroid carcinoma*. Clin Nucl Med 1999;24:744-6.

10 Rettenbacher L, Sungler P, Gmeiner D, Kassman H, Galvan G. *Detecting the sentinel lymph node in patients with differentiated thyroid carcinoma*. Eur J Nucl Med 2000;27:1399-401.

11 Carcoforo P, Feggi L, Trasforini G, Lanzara S, Sortini D, Zulian V, et al. *Use of preoperative lymphoscintigraphy and intraoperative gamma probe detection for identification of the sentinel lymph node in patients with papillary thyroid carcinoma*. EJSO 2007;33:1075-80.

12 Chen SL, Iddings DM, Scheri RP, Bilchik AJ. *Lymphatic mapping and sentinel node analysis: current concepts and applications.* CA Cancer J Clin 2006;56:292-309.

13 Rubello D, O'Doherty MJ. *Sentinel lymph node biopsy in differentiated thyroid cancer: standard of care or experimental tool?* Nucl Med Commun 2006;27:833-5.

14 Mazzaferri EL, Kloos RT. *Clinical review 128: current approaches to primary therapy for papillary and follicular thyroid cancer*. J Clin Endocrinol Metab 2001;86:1447-63.

15 Noguchi M, Yamada H, Ohta N, Ishida T, Tajiri K, Fujii H, et al. *Regional lymph node metastases in well-differentiated thyroid carcinoma*. Int Surg 1987;72:100-3.

16 Ahuja S, Ernst H, Lenz K. *Papillary thyroid carcinoma: occurrence and types of lymph node metastases*. J Endocrinol Invest 1991;14:543-9.

17 Shaha AR, Shah JP, Loree TR. *Patterns of nodal and distant metastasis based on histologic varieties in differentiated carcinoma of the thyroid*. Am J Surg 1996;172:692-4.

18 Gimm O, Rath FW, Dralle H. *Pattern of lymph node metastases in papillary thyroid carcinoma*. Br J Surg 1998;85:252-4.

19 Shaha AR. *Management of the neck in thyroid cancer.* Otolaryngol Clin North Am 1998;31:823-31.

20 Machens A, Hinze R, Thomusch O, Dralle H. *Pattern of nodal metastasis for primary and reoperative thyroid cancer*. World J Surg 2002;26:22-8.

21 Mirallie E, Visset J, Sagan C, Hamy A, Le Bodic MF, Paineau J. *Localization of cervical node metastasis of papillary thyroid carcinoma.* World J Surg 1999;23:970-3.

22 Robbins KT, Medina JE, Wolfe GT, Levine PA, Sessions RB, Pruet CW. *Standardizing neck dissection terminology. Official Report of the Academy's Committee for Head and Neck Surgery and Oncology.* Arch Otolaryngol Head Neck Surg 1991;117:601-5.

23 Robbins KT. *Classification of neck dissection. Current concepts and future considerations*. Otolaryngol Clin North Am 1998;31:639-55.

24 Voutilainen PE, Siironen P, Franssila KO, Sivula A, Haapiainen RK, Haglund CH. *AMES, MACIS, and TNM prognostic classifications in papillary thyroid carcinoma*. Anticancer Res 2003;23:4283-8.

25 Pasieka JL, Rotstein LE. *Consensus conference on well-differentiated thyroid cancer: a summary*. Can J Surg 1993;36:298-301.

26 Rigual NR, Anderson GR, Loree TR, Wiseman S, Alrawi S, Stoler DL. *Molecular prognosticators and genomic instability in papillary thyroid cancer*. Laryngoscope 2005;115:1479-85.

[27] Shaha AR. *TNM classification of thyroid carcinoma*. World J Surg 2007;31:879-87.

[28] Grebe SK, Hay ID. *Thyroid cancer nodal metastases: biologic significance and therapeutic considerations.* Surg Oncol Clin N Am 1996;5:43-63.

[29] Witte J, Schlotmann U, Simon D, Dotzenrath C, Ohmann C, Goretzki PE. *Significance of lymph node metastases of differentiated thyroid gland carcinomas and C-cell carcinomas for prognosis -- a meta-analysis*. Zentralbl Chir 1997;122:259-65.

[30] Mazzaferri EL, Jhiang SM. *Long term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer.* Am J Med 1994;97:418-28.

[31] Toniato A, Boschin I, Casara D, Mazzarotto R, Rubello D, Pelizzo M. *Papillary thyroid carcinoma: factors influencing recurrence and survival*. Ann Surg Oncol 2008;15:1518-22.

[32] Dixon E, McKinnon G, Pasieka JL. *Feasibility of sentinel lymph node biopsy and lymphatic mapping in nodular thyroid neoplasms.* World J Surg 2000;24:1396-401.

[33] Arch-Ferrer J, Valazquez D, Fajardo R, Gamboa-Dominguez A, Herrera MF. *Accuracy of sentinel lymph node in papillary thyroid carcinoma*. Surgery 2001;130:907-13.

[34] Lee SK, Choi JH, Lim HI, Kim WW, Kim SM, Choe JH, et al. *Sentinel lymph node biopsy in papillary thyroid cancer: comparison study of blue dye method and combined radioisotope and blue dye method in papillary thyroid cancer*. Eur J Surg Oncol 2009;35:974-9.

[35] Catarci M, Zaraca F, Angeloni R, Mancini B, de Filippo MG, Massa R, et al. *Preoperative lymphoscintigraphy and sentinel lymph node biopsy in papillary thyroid cancer. A pilot study*. J Surg Oncol 2001;77:21-4.

[36] Roh JL, Park CI. *Sentinel lymph node biopsy as guidance for central neck dissection in patients with papillary thyroid carcinoma*. Cancer 2008;113:1527-31.

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