Langenbecks Arch Surg (2008) 393:705–708
DOI 10.1007/s00423-008-0376-5

ORIGINAL ARTICLE

99Tc Nanocolloid sentinel node procedure in thyroid carcinoma

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Received: 13 May 2008 / Accepted: 13 June 2008 / Published online: 15 July 2008

Abstract
Purpose The purposes of this study were to investigate the efficacy of radiocolloid lymphoscintigraphy and of hand-held gamma probe procedure for sentinel lymph node biopsy (SLNB) in papillary thyroid carcinoma (PTC) and to evaluate its results in clinical staging.
Materials and methods Sixty-five PTC consecutive patients entered the study. Patients underwent radiocolloid lymphoscintigraphy before surgery. Intraoperative sentinel lymph node (SLN) localization was performed using a handheld gamma probe. They were followed up at 2, 6 months, and yearly.
Results SLN metastases were diagnosed in 52%. Fifty-one patients underwent ablative 131-I therapy. The mean Tireoglobulin level in N0 vs N1 cases was 2.2 ng/ml vs 4.73 (p=0.03) and 0.68 vs 2.1 ng/ml (p=0.005) before and after 131-I therapy, respectively.
Conclusions In patients classified N0 by SLNB, ablative 131-I therapy could be avoided.

Keywords Sentinel lymph node · Thyroid cancer · Node metastases · Radiocolloid lymphoscintigraphy

Introduction

Intraoperative lymphatic mapping with sentinel lymph node (SLN) biopsy has become a revolutionary concept in the management of solid malignancies [1]. The SLN is defined as the first lymph node draining a regional lymphatic basin [1, 2]. Lymphatic mapping and SLN biopsy (SLNB) using both vital dyes and radioisotopes have been proven to be accurate in predicting the nodal status in melanoma and breast cancer [1–3]. SLNB has been developed as an alternative to elective lymph node dissection in patients with clinically node-negative disease [1–4]. Kelemen PR et al. in 1998 [5] pioneered the vital blue dye technique for SLNB in 17 thyroid cancer patients, while subsequent reports by Gallowitsch HJ et al. [6] and Rettenbacher L et al. [7] described the use of a radiotracer with intraoperative counting using a handheld gamma probe.

Since these first reports, a number of other studies have demonstrated that SLNB is indeed an accurate technique for obtaining information about cervical lymph node involvement in patients undergoing thyroidectomy [8–11].

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 [12–18]. The purposes of this study were: (a) to investigate the efficacy of radiocolloid mapping of thyroid lymphatic drainage; (b) to set up an accurate technical procedure for SLNB with the handheld gamma probe; (c) to evaluate the effectiveness of SLN procedure on postoperative clinical staging.

Material and methods

From July 2005 to March 2007, 65 patients affected by PTC entered the study. The criteria of inclusion in this study were the following: (a) the diagnosis of PTC at preoperatory FNAC, (b) the monofocality of PTC, (c) N0 at clinical and ultrasonographic examinations, (d) the absence of distant metastases, (e) no previous neck surgical treatment.

“Best of Endocrine Surgery in Europe 2008”

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Patients underwent node dissection according to the SLN procedure that was just described in our previous study [10]. Lymphoscintigraphy was performed 3 h before surgery using a single intratumoral injection of a nanocolloidal solution labeled with 99Technetium (Nanocoll, GE Healthcare), in normal saline, administered under US guidance in Nuclear Medicine Unit. Immediately after intratumoral 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 s per frame, in anterior and oblique position, followed by multiple static scintiscans until a clear visualization of sentinel node or nodes. 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 was measured by means of regions of interests (ROI). Intraoperative SLN localization was performed using a handheld gamma probe (ScintiProbe MR 100, Pol. Hi. Tech., Carsoli, Italy) with automatic peak for 99mTc-140 keV using probes of different diameter size (11 or 15 mm) and variable time count rate (1–4 s) 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 skin. Then, after a standard cervicotomy via a transversal incision, extended between the bodies of the two sternocleidomastoid muscles, the thyroid was exposed; after 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 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 to the frozen section and only when one or more lymph nodes showed thyroid cancer metastasis did the surgeon performed an enlarged node dissection of the involved compartment. The thyroid and all lymph nodes resected were stained for H and E and cytokeratin.

At the end of node dissection, the central and the lateral compartments were scanned by handheld gamma probe to verify the absence of radioactivity.

All patients underwent 131I Whole Body Scan (WBS), and they received 131I therapy when necessary. Patients were followed up at 2, 6 months after treatment and then on a yearly basis. Follow-up consisted of clinical examination, measurements of Thyroglobuline (Tg) and anti-Thyroglobuline antibodies, high resolution 10 MHz neck ultrasound and rhTSH 131I WBS. Statistical analysis was performed by Wilcoxon test comparing postoperative Tg values in N0 vs N1 patients. A p value <0.05 was considered statistically significant.

Results

There were 48 females and 17 males, the mean age was 43.2 years (range 20–69). The average tumor size was 1.7 cm (range 0.5–4.3 cm). The single intratumoral dose of the nanocolloidal solution labeled with 99Technetium injected under US guidance had a mean value of 5.5 MBq (range 4–7) in 0.1–0.3 ml of normal saline.

Sequential limphoscintigraphy was able to identify at least one SLN in 64 out of 65 cases (98.5%). In particular, in ten out of 64 (16%) cases, one SLN was visualized, two nodes in 13 out of 64 (20%), three nodes or more in 41 out of 64 (64%). The mean number of individualized SLNs was 3.9 (range 1–6). Using intraoperative handheld gamma probe, the surgeon was able to find at least one SLN in all cases. In particular, only one radioactive node was removed in 14 out of 65 cases (21.5%), two nodes in 14 out of 65 cases (21.5%), three nodes or more in 37 out of 65 cases (57%).

All patients underwent total thyroidectomy and node dissection on the basis of SLN procedure. According to UICC-TNM staging, 34 cases (52%) were classified T1, multifocal in seven cases, five cases (8%) T2, and 25 cases T3 (38%), multifocal in five cases. One case was classified as micro-/macro-follicular adenoma at final histology. SLN metastases were diagnosed in 34 out of 65 cases (52%): in 18 cases, the hottest SLN was positive (1st SLN), in 16 cases, the second and/or the third SLN. In 11 cases, only one SLN was involved, in 23 cases, two or more.

The average duration of follow-up was 17.5 months (range 2–31). All patients underwent 131I Whole Body Scan (WBS) at 2 months after surgery. Fifty-one patients underwent ablative 131-I therapy, in particular, 48 cases (26 cases N0 and 22 cases N1) for thyroid residual at 131-I WBS (mean 84 mCi, range 50–100) and three cases (N1) for suspected lymph node at 131-I WBS (mean 118 mCi, range 50–150).

The mean value of Thyroglobuline (Tg) in N0 vs N1 patients was 2.2 ng/ml (range 0.5–15) vs 4.73 ng/ml (range 0.5–18; $p=0.03$) and 0.68 ng/ml (range 0.5–1.0) vs 2.1 ng/ml (range 0.5–17) before and after 131-I therapy, respectively (Table 1).

Table 1 Statistical analysis by Wilcoxon test comparing thyroglobuline values in N0 vs N1 patients

Thyroglobuline measurement	N0	N1	*P* value
Before 131 I therapy	2.2	4.73	0.03
After 131I Therapy	0.68	2.1	0.005

Discussion

The thyroid gland has an extensive network of draining lymphatics, both intraglandular and extraglandular [3, 20–21]. Not surprisingly, the central neck compartment is most commonly involved with metastatic disease in patients with PTC; however lateral and mediastinal compartment disease is also common [10–21]. A number of studies have specifically examined the pattern of metastatic disease in PTC patients [12–19]. Ahuja S et al. demonstrated lymph node metastases along the jugular vein in 79% of 57 PTC patients [14]. Gimm O. et al. examined the pattern of nodal metastasis in 35 PTC patients and found node metastases in the central compartment in 83%, in the lateral compartment in 54%, and in the mediastinal compartment in 3% [16]. In 119 PTC patients, Mirallie E. et al. demonstrated central compartment metastases in 51% and lateral compartment metastases in 47% [19]. It is important to recognize that the reported incidence of regional lymphatic metastases identified in PTC patients varies according to the extent of nodal dissection carried out [3, 13, 17].

None of the commonly utilized thyroid cancer risk assessment systems, AMES [22], AGES [23], MACIS [22], GAMES [24], and TNM [25] have demonstrated that neck nodal metastases correlate with patient survival. In an extensive literature review on this topic, Grebe SK and Hay ID concluded that in PTC patients, nodal disease at presentation was not predictive of patient survival [26]. In a meta-analysis of 16 studies, Witte J et al. were unable to demonstrate any relationship between nodal metastases and survival in differentiated thyroid carcinoma (DTC) patients [27]. Mazzaferri EL et al. demonstrated that in a cohort of 1,355 DTC patients, those with cervical metastases had a higher disease recurrence rate at 30 years [28]. Similar results were obtained by Toniato A. et al. in 2008 [29].

The identification and the remotion of the SLN have allowed the detection of microscopic metastatic disease; through the selective lymph node dissection, the SLN procedure can avoid unnecessary nodal dissection, associated to a higher morbidity. SLN can be performed using vital dye technique [30–32], lymphoscintigraphy and gamma probe [6–8, 10], and combined technique using both vital dye and radiotracer [33].

In this study, we considered not only the safety and accuracy of the radio-guided technique in detecting the SLN, but even the follow-up of patients underwent SLN biopsy.

The SLN was individualized in 98.5% of patients at lymphoscintigraphy and in all cases with intraoperative gamma probe. According to our experience, the SLN mapping and detection with intratumoral-injected radiocolloid is an easy and accurate procedure, and it offers significant advantages over the vital dye technique, just described in our previous studies [31].

SLN metastases were diagnosed in 34 out of 65 cases (52%): the rate of nodal involvement is very high considering that all patients were defined N0 preoperatively. In 16 cases (47%), the second and/or the third SLN was positive: we underline that it is necessary to remove not only the hottest SLN but all nodes with a count higher than 10% of the hottest node.

131I WBS and Tg measurements confirmed SLN in PTC as a reliable procedure: patients defined N0 at SLN technique were all confirmed by rhTSH 131-I WBS and Tg measurement. The SLN procedure may be considered a criteria to select patients in view of the ablative 131-I therapy. In patients defined N0, at SLN technique, ablative 131-I therapy could be avoided, while in patients defined N1 at SLN biopsy, a therapeutic dose could be directly proposed.

References

1. Pasieka JL (2001) Sentinel lymph node biopsy in the management of thyroid disease. Br J Surg 88(3):321–322 doi:10.1046/j.1365-2168.2001.01694.x
2. Rubello D, Pelizzo MR, Al-Nahhas A et al (2006) The role of sentinel lymph node biopsy in patients with differentiated thyroid carcinoma. Eur J Surg Oncol 32(9):917–921 doi:10.1016/j.ejso.2006.03.018
3. Wiseman SM, Hicks WL Jr, Chu QD et al (2002) Sentinel lymph node biopsy in staging of differentiated thyroid cancer: a critical review. Surg Oncol 11(3):137–142 doi:10.1016/S0960-7404(02)00027-0
4. Delbridge L (2004) Sentinel lymph node biopsy for thyroid cancer: why bother? ANZ J Surg 74(1–2):2 doi:10.1046/j.1445-1433.2003.02939.x
5. Kelemen PR, Van Herle AJ, Giuliano AE (1998) Sentinel lymphadenectomy in thyroid malignant neoplasms. Arch Surg 133(3):288–292 doi:10.1001/archsurg.133.3.288
6. Gallowitsch HJ, Mikosch P, Kresnik E et al (1999) Lymphoscintigraphy and gamma probe –guided surgery in papillary thyroid carcinoma: the sentinel lymph node concept in thyroid carcinoma. Clin Nucl Med 24(10):744–746 doi:10.1097/00003072-199910000-00002
7. Rettenbacher L, Sungler P, Gmeiner D et al (2000) Detecting the sentinel lymph node in patients with differentiated thyroid carcinoma. Eur J Nucl Med 27(9):1399–1401 doi:10.1007/s002590000286
8. Carcoforo P, Feggi L, Trasforini G et al (2007) Use of preoperative lymphoscintigraphy and intraoperative gamma probe detection for identification of the sentinel lymph node in patients with papillary thyroid carcinoma. EJSO 33(9):1075–1080
9. Chen SL, Iddings DM, Scheri RP et al (2006) Lymphatic mapping and sentinel node analysis: current concepts and applications. CA Cancer J Clin 56(5):292–309
10. Pelizzo MR, Rubello D, Merante Boschin I et al (2007) Contribution of SLN investigation with 99m Tc-nanocolloid in clinical staging of thyroid cancer: technical feasibility. Eur J Nucl Med Mol Imaging 34(6):934–938 doi:10.1007/s00259-006-0316-y
11. Rubello D, O'Doherty MJ (2006) Sentinel lymph node biopsy in differentiated thyroid cancer: standard of care or experimental tool? Nucl Med Commun 27(11):833–835 doi:10.1097/MNM.0b013e328011022c
12. Mazzaferri EL, Kloos RT (2001) Clinical review 128: current approaches to primary therapy for papillary and follicular thyroid

cancer. J Clin Endocrinol Metab 86(4):1447–1463 doi:10.1210/jc.86.4.1447
13. Noguchi M, Yamada H, Ohta N et al (1987) Regional lymph node metastases in well-differentiated thyroid carcinoma. Int Surg 72 (2):100–103
14. Ahuja S, Ernst H, Lenz K (1991) Papillary thyroid carcinoma: occurrence and types of lymph node metastases. J Endocrinol Invest 14(7):543–549
15. Shaha AR, Shah JP, Loree TR (1996) Patterns of nodal and distant metastasis based on histologic varieties in differentiated carcinoma of the thyroid. Am J Surg 172(6):692–694 doi:10.1016/S0002-9610(96)00310-8
16. Gimm O, Rath FW, Dralle H (1998) Pattern of lymph node metastases in papillary thyroid carcinoma. Br J Surg 85(2):252–254 doi:10.1046/j.1365-2168.1998.00510.x
17. Shaha AR (1998) Management of the neck in thyroid cancer. Otolaryngol Clin North Am 31(5):823–831 doi:10.1016/S0030-6665(05)70090-6
18. Machens A, Hinze R, Thomusch O et al (2002) Pattern of nodal metastasis for primary and reoperative thyroid cancer. World J Surg 26(1):22–28 doi:10.1007/s00268–001–0176–3
19. Mirallie E, Visset J, Sagan C (1999) Localization of cervical node metastasis of papillary thyroid carcinoma. World J Surg 23 (9):970–973 doi:10.1007/s002689900609
20. Robbins KT, Medina JE, Wolfe GT (1991) Standardizing neck dissection terminology. Official report of the academy's committee for head and neck surgery and oncology. Arch Otolaryngol Head Neck Surg 117:601–605
21. Robbins KT (1998) Classification of neck dissection. Current concepts and future considerations. Otolaryngol Clin North Am 31:639–655 doi:10.1016/S0030-6665(05)70077-3
22. Voutilainen PE, Siironen P, Franssila KO et al (2003) AMES, MACIS, and TNM prognostic classifications in papillary thyroid carcinoma. Anticancer Res 23(5b):4283–4288
23. Pasieka JL, Rotstein LE (1993) Consensus conference on well-differentiated thyroid cancer: a summary. Can J Surg 36(4):298–301
24. Rigual NR, Anderson GR, Loree TR et al (2005) Molecular prognosticators and genomic instability in papillary thyroid cancer. Laryngoscope 115(8):1479–1485 doi:10.1097/01.mlg.0000172045.38907.52
25. Shaha AR (2007) TNM classification of thyroid carcinoma. World J Surg 31(5):879–887 doi:10.1007/s00268–006–0864–0
26. Grebe SK, Hay ID (1996) Thyroid cancer nodal metastases: biologic significance and therapeutic considerations. Surg Oncol Clin N Am 5(1):43–63
27. Witte J, Schlotmann U, Simon D et al (1997) Significance of lymph node metastases of differentiated thyroid gland carcinomas and C-cell carcinomas for prognosis—a meta-analysis. Zentralbl Chir 122(4):259–265
28. Mazzaferri EL, Jhiang SM (1994) Long term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. Am J Med 97(5):418–428 doi:10.1016/0002–9343(94)90321–2
29. Toniato A, Boschin I, Casara D et al (2008) Papillary thyroid carcinoma: factors influencing recurrence and survival. Ann Surg Oncol 15(5):1518–1522 doi:10.1245/s10434–008–9859–4
30. Dixon E, McKinnon G, Pasieka JL (2000) Feasibility of sentinel lymph node biopsy and lymphatic mapping in nodular thyroid neoplasms. World J Surg 24(11):1396–1401 doi:10.1007/s002680010231
31. Arch-Ferrer J, Valazquez D, Fajardo R (2001) Gamboa-Domininguez A, Herrera MF. Accuracy of sentinel lymph node in papillary thyroid carcinoma. Surgery 130(6):907–913 doi:10.1067/msy.2001.118372
32. Rubello D, Nanni C, Merante Boschin I et al (2006) 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 25(4):483–486
33. Catarci M, Zaraca F, Angeloni R et al (2001) Preoperative lymphoscintigraphy and sentinel lymph node biopsy in papillary thyroid cancer. A pilot study. J Surg Oncol 77(1):21–24 doi:10.1002/jso.1058