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Sentinel node mapping in papillary thyroid carcinoma using combined radiotracer and blue dye methods

Mapowanie węzłów wartowniczych w raku brodawkowatym tarczycy z zastosowaniem radioznacznika i niebieskiego barwnika

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Abstract

Introduction: In the current study, we evaluated the accuracy of sentinel node mapping in thyroid cancer patients using both radiotracer and blue dye.
Material and methods: 30 patients with a diagnosis of papillary thyroid carcinoma (PTC) were included in the study; 2–3 hours before surgery, 0.5 mCi 99m-Tc-Antimony Sulfide Colloid was injected intra-tumourally. 15 minutes post-injection, lymphoscintigraphy images of the neck were obtained. Immediately after anaesthesia induction, 0.5 mL patent blue V was also injected in the same fashion. Sentinel lymph nodes were detected intraoperatively using gamma probe and blue dye. Total thyroidectomy was performed for all patients with dissection of central neck lymph nodes as well as sampling of the lateral neck lymph nodes.
Results: At least one sentinel node could be identified during surgery in 19 patients (63.3%). The median number of sentinel nodes per patient was 1. Sentinel nodes in 12 patients were pathologically involved. No false negative case was noted. Upstaging occurred in six patients (20%).
Conclusions: Sentinel node mapping in papillary thyroid carcinoma is a feasible technique with high accuracy for the detection of lymph node involvement. This technique can guide surgeons to perform central lymph node dissection only in patients with pathologically involved sentinel nodes. Although SLN detection in the lateral neck lymph nodes increases the extension of lymphadenectomy, SLN mapping can result in upstaging in older patients (> 45 years of age) or treatment plan change in younger patients (< 45 years of age) by the detection of lateral lymph node involvement. **(Endokrynol Pol 2014; 65 (4): 281–286)**

Key words: *sentinel; thyroid cancer; lymphoscintigraphy; blue dye; radiotracer*

Streszczenie

Wstęp: W badaniu oceniono dokładność mapowania węzłów wartowniczych u chorych na raka tarczycy w przypadku jednoczesnego zastosowania radioznacznika i niebieskiego barwnika.
Materiał i metody: Do badania włączono 30 chorych z rozpoznaniem raka brodawkowego tarczycy (PTC, *papillary thyroid carcinoma*). Dwie do trzech godzin przed zabiegiem do guza wstrzykiwano koloid siarczanu antymonu znakowany 99m-Tc (0,5 mCi). Po upływie 15 minut od wstrzyknięcia radioznacznika wykonywano badanie limfoscyntygraficzne szyi. Bezpośrednio po znieczuleniu w ten sam sposób wstrzykiwano 0,5 ml błękitu patentowego V. Węzły wartownicze wykrywano śródoperacyjnie, używając sondy promieniowania gamma i błękitnego barwnika. U wszystkich pacjentów wykonano totalną tyroidektomię z wycięciem węzłów chłonnych szyjnych środkowego przedziału oraz pobraniem wycinków węzłów szyjnych bocznych.
Wyniki: U 19 chorych (63,3%) udało się zidentyfikować w trakcie zabiegu co najmniej jeden węzeł wartowniczy. Mediana liczby węzłów wartowniczych na pacjenta wynosiła 1. U 12 chorych w węzłach wartowniczych wykryto zmiany patologiczne. Nie stwierdzono ani jednego przypadku uzyskania fałszywie ujemnego wyniku. U 6 (20%) chorych zmieniono stopień zaawansowania nowotworu na wyższy.
Wnioski: Mapowanie węzłów wartowniczych w raku brodawkowatym tarczycy jest dostępną metodą cechującą się dużą dokładnością w wykrywaniu zajętych węzłów chłonnych. Ta metoda może stanowić wskazówkę dla chirurgów, aby usuwać węzły chłonne szyjne środkowego przedziału tylko u pacjentów ze zmianami w węzłach wartowniczych. Mimo, że wykrycie węzłów wartowniczych w obrębie węzłów szyjnych bocznych zwiększa zakres limfadenektomii, mapowanie węzłów wartowniczych może spowodować zmianę oceny stopnia zaawansowanie nowotworu u starszych pacjentów (> 45 lat) lub zmianę planu leczenia u młodszych pacjentów (< 45 lat) w związku z wykryciem zmian w węzłach bocznych szyi. **(Endokrynol Pol 2014; 65 (4): 281–286)**

Słowa kluczowe: *węzeł wartowniczy; rak tarczycy; limfoscyntygrafia; niebieski barwnik; radioznacznik*

Introduction

Sentinel node mapping is an important technique in the lymph node staging of solid tumours. This technique relies on the orderly progression of the metastases in the lymphatic system. Lymphatic drainage of solid tumours usually drains to single or multiple lymph nodes (which are called sentinel nodes [SN]) and then

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spreads to other regional lymph nodes. The main aim of sentinel node mapping is to identify regional lymph node metastasis without performing regional lymph node dissection [1, 2].

Sentinel node mapping is currently considered as the standard of care in lymph node staging of breast cancer and melanoma [3]. It is also considered very promising in urological [4, 5], gynaecological [6], gastrointestinal [7], and many other solid tumours.

Papillary thyroid carcinoma is the most common type of differentiated thyroid cancer with a high rate of regional lymph node metastasis [8, 9]. Regional lymph node dissection is recommended for patients with macroscopic lymph node metastases in order to decrease regional recurrence [10]. On the other hand, prophylactic central and/or lateral lymph node dissection for clinically node negative patients is controversial. Central lymph node dissection can cause considerable morbidity such as permanent damage to parathyroid glands and recurrent laryngeal nerves [11–13]. Sentinel node mapping may be especially helpful in clinically node negative thyroid cancer patients to avoid unnecessary lymph node dissection in sentinel node negative patients.

Since 1998, several groups have reported their experience in sentinel node mapping of thyroid cancer with various detection and false negative rates [14–16]. In the current study, we evaluated the accuracy of sentinel node mapping for regional lymph node staging of patients with clinically node negative papillary thyroid carcinoma (PTC) by the combined radiotracer and blue dye techniques.

Material and methods

In this prospective study, from April 2010 to December 2012, 34 consecutive patients with evidence of PTC on fine needle aspiration (FNA) were included in the study. On clinical examination, all patients were clinically node negative. All patients also underwent thyroid and neck ultrasonography and no patient had evidence of lymph node enlargement. The study was approved by the local ethical committee under approval number 88830. All patients gave informed written consent before entering the study.

Two to three hours before surgery, all patients were sent to the nuclear medicine department for radiotracer injection. For each patient, 0.5 mCi (18.5 MBq)/ /0.2 mL Tc-99m Antimony Sulfide Colloid was injected intra-tumourally. Fifteen minutes post-injection, lymphoscintigraphy imaging of the neck was performed in anterior-posterior and lateral views (5 min/image, 128 × 128 matrix, low energy high resolution collimator and Tc-99m photopeak). The body contours of the patients were imaged as described by Momennezhad et al. [17, 18]. The lymphoscintigraphy images were interpreted by two nuclear medicine specialists independently, and the discordant readings were resolved by consensus.

All patients also received 0.5 mL patent blue V intratumourally immediately after anaesthesia induction. Total thyroidectomy was performed for all patients with dissection of central neck lymph nodes as well as sampling of the lateral neck lymph nodes.

The sentinel nodes were harvested during surgery by a gamma probe (EUROPROBE, France). All hot and/or blue nodes were considered as sentinel nodes and were sent separately to the pathologist. Hot nodes were defined as any node with an *ex vivo* count five times higher than the neck background which was measured on the carotid vessels. Following removal of the sentinel nodes, central lymph node (level VI) dissection was done for all patients. In addition, compartment based lymph node dissection was done for those patients found to have SLN. Finally, lymph node sampling from the other lymph node stations (at least three nodes from the lateral neck nodes) was done for all patients.

The pathological results of the SLN were compared to the other excised non-SLN to determine the false negative rate.

Results

Thirty four patients were initially included in the study. The radiotracer labelling was defective in four patients, and so they were excluded from the final report [19]. Thirty patients were available for final analyses, with an age range of 18–55 (mean age 34 ± 8 years) and F/M equal to 22/8. Mean size of the tumour was 1.5 ± 0.4 cm.

On the pre-operative lymphoscintigraphy, SLN could be identified in 20 patients (66.6%). Figures 1 and 2 show the lymphoscintigraphy images of two of our patients.

Intra-operatively, SLN could be harvested in 19 patients (detection rate of 63.3% [95% CI: 45.1–78.4%]). Overall, 27 SLN were harvested (range 1–3, median 1 per patient). The lymphoscintigraphy images of a patient with visualised SLN but surgical detection failure were re-evaluated; the reason for the inability to harvest SLN in this patient was misinterpretation of a hot spot in the injection track line as a SLN by the nuclear physicians.

Eight (72%) of the SLN detection failures occurred in the first half of the study (the first 15 recruited patients). There were only three SLN detection failures in the remaining 15 patients who were recruited in the second half of the study.

All harvested SLNs were hot (radiotracer detection rate of 63.3%). Blue SLNs were identified in nine pa-

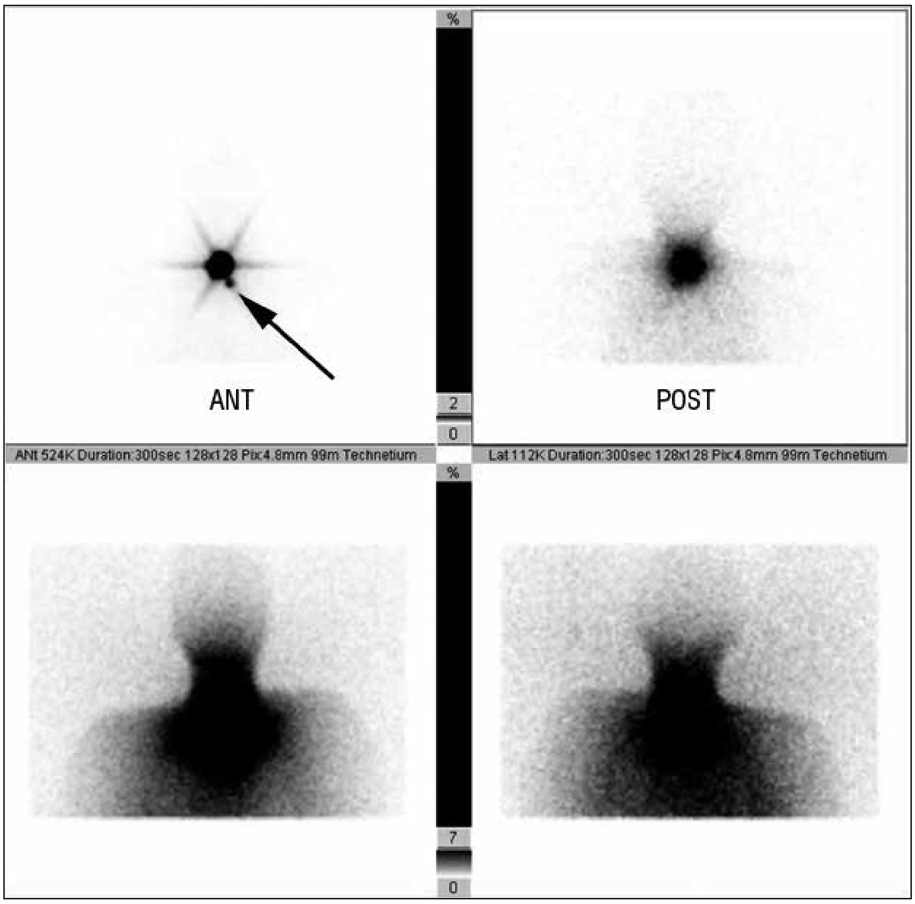

Figure 1. *Anterior (upper row, left), and posterior (upper row, right) lymphoscintigraphy images of a patient with thyroid cancer. Note sentinel lymph node distal to the injection site which is apparent on the anterior view only (arrow). Bottom row images are the corresponding scatterograms of the lymphoscintigraphy images which show the contour of the neck*

Rycina 1. *Obraz limfoscyntygrafii w projekcji przedniej (górny rząd, po lewej) i tylnej (górny rząd, po prawej) u chorego na raka tarczycy. Należy zwrócić uwagę na węzeł chłonny wartowniczy oddalony od miejsca wstrzyknięcia, widoczny tylko w projekcji przedniej (strzałka). Obrazy w dolnym rzędzie to odpowiednie skaterogramy obrazów limfoscyntyfrafii, na których widać zarys szyi*

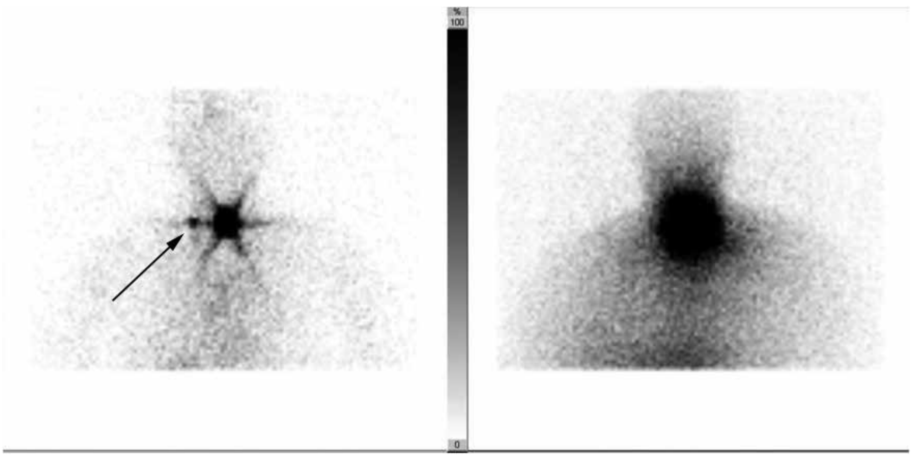

Figure 2. *Anterior (left) lymphoscintigraphy image of a patient with thyroid cancer. Note the SLN in the lateral region of the neck (arrow). The image on the right is the corresponding scatterogram*

Rycina 2. *Obraz limfoscyntygrafii w projekcji przedniej (po lewej) u chorego na raka tarczycy. Należy zwrócić uwagę na węzeł wartowniczy znajdujący się w bocznej części szyi (strzałka). Obraz po prawej stronie to odpowiedni skaterogram* tients (blue dye detection rate of 30%). The location of the harvested SLNs is shown in Figure 3.

Sentinel lymph nodes were pathologically involved in 12 patients (63.2% of patients with identified SLN). In two patients, the SLN were the only involved nodes. Six patients with SLN detection failure had pathologically involved lymph nodes (54% of patients with SLN detection failure). No false negative case was noted (100% [95% CI: 74–100%]sensitivity). Upstaging occurred in six patients (20%), details of whom can be found in Table I. In a 23-year-old patient, a lateral sentinel lymph node (station V) was pathologically involved and the staging did not change; however, due to increase of the N stage from N0 to N1b, radioiodine therapy (150 mCi) was administered to the patient.

No adverse event related to sentinel node mapping was reported in our study.

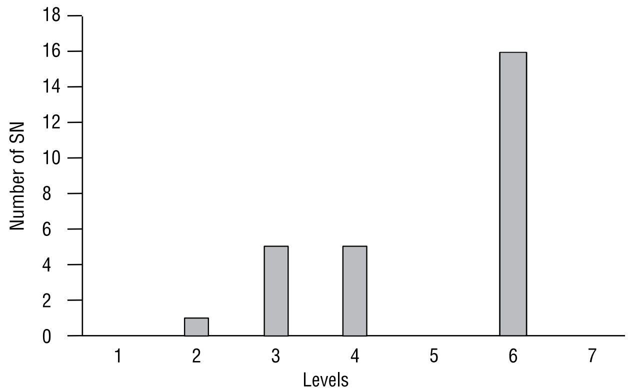

Figure 3. *Location distribution of the harvested sentinel lymph nodes during surgery*

Rycina 3. *Rozkład lokalizacji węzłów wartowniczych pobranych w trakcie zabiegu chirurgicznego*

Discussion

In the current study, we evaluated the accuracy of SLN mapping in the staging of papillary thyroid cancer using combined radiotracer and blue dye techniques. The SLN detection rate was 63.3%, which is fairly acceptable for clinical use. However, recent systematic reviews showed a pooled sentinel node detection rate of more than 90% [14, 15]. The reason of this discrepancy is most likely due to the injection technique of our study. We used an intra-tumoural injection technique which theoretically could decrease the sentinel node detection rate due to poor lymphatic drainage from the tumour parenchyma compared to the peri-tumoural area [20, 21]. Several groups have also used intra-tumoural injection of the mapping material for thyroid cancer patients with the same results as ours (about 60% SLN detection rate) [22–24], which corroborate our results. Another possible reason for the low detection rate in our study compared to the previous studies is the learning curve effect. Learning curve effect has been shown to be an important parameter in the SLN mapping success [6, 25, 26]. In our study, the majority of SLN detection failure (72%) occurred among the first 15 recruited patients, which shows a possible learning curve effect.

Another important finding of our study was considerably lower sentinel node detection rate by blue dye compared to radiotracer method (30% *vs.* 63.3%). All of the harvested sentinel nodes were hot and blue only sentinel nodes were not identified in our study. In other words, blue dye technique was not useful in our patients. A lower detection rate using the blue dye technique compared to the radiotracer has been reported in other malignancies (including thyroid cancer) too [15, 27]. Considering the adverse reactions associated with blue dyes [28] and possible staining of parathyroid glands by blue dye [22, 29], our results suggest that a radiotracer only technique would be sufficient for sentinel node mapping in thyroid cancer patients.

We had an excellent accuracy for lymph node staging in our study (no false negative result). This means that pathological examination of the harvested sentinel nodes could predict central and/or lateral lymph node stations involvement. Overall, other studies also cor-

Table I. ***Characteristics of the upstaged patients by sentinel node mapping***

Tabela I. ***Charakterystyka pacjentów, u których zmieniono stopień zaawansowania nowotworu na wyższy po mapowaniu węzłów wartowniczych***

Patient number	Age/gender	Tumour size [cm]	Number of harvested SLNs/location (level)	Location (level) of the involved SLNs	Location of the pathologically involved non-SLN	Stage shift
1	49/M	1.8	2/IV,VI	IV	IV	I to IVa
2	48/F	4.3	1/IV	IV	IV	III to IVa
3	51/F	1.5	1/IV	IV	IV	I to IVa
4	55/M	3.5	1/V	V	V	II to IVa
5	50/F	2.2	1/IV	IV	IV	II to IVa
6	48/F	2.5	2/V,VI	V	Only SLN was involved	II to IVa

roborated our results. Recent meta-analysis showed a low pooled false negative rate of 7.7% [14]. Several other studies also reported a 0% false negative rate which also corroborates our results [22, 30, 31].

The location of SLN is another important aspect of our study. 40% of the harvested SLNs in our study were located in lateral compartments (levels II, III, IV) and SLNs in the lateral compartments were the only SLNs in seven patients (23% of the patients). These results were in accordance with the previous studies too. Balasubramanian et al. reported that in 15 studies on thyroid cancer SLN mapping, 22.5% of the harvested SLNs were in the lateral locations, and 14.8% of patients had only lateral SLNs [14].

Lymphadenectomy outside the central neck compartment is not routinely performed in our centre and many centres around the world. This shows that SLN mapping could help to identify cases that require more extensive lymph node dissection and paradoxically could result in more extensive surgeries. To explore this issue more extensively, we also evaluated the possibility of upstaging by SLN mapping compared to the traditional total thyroidectomy and central lymph node dissection. As mentioned above, only central lymph node compartments are routinely removed in our centre for thyroid cancer patients and lymph node involvement in the lateral compartments would remain undetected. This may pose a potential staging problem in patients over 45 years of age, as lateral lymph node involvement in these patients can increase the stage. Our study showed that in six cases (all > 45 year old), SLN mapping upstaged the patients. This is an important finding demonstrating that SLN mapping in thyroid cancer can be much more useful in elderly patients [32]. We also had a young patient (23 years old) in whom the lateral lymph node involvement was discovered only by SLN mapping. This finding led to a treatment change using high dose radioiodine therapy and stricter TSH suppression despite no change in the staging.

Conclusion

SLN mapping in papillary thyroid carcinoma is a feasible technique with high accuracy for the detection of lymph node involvement. This technique can guide surgeons to perform central lymph node dissection only in patients with pathologically involved sentinel nodes. Although SLN detection in the lateral neck lymph nodes increases the extension of lymphadenectomy, SLN mapping can result in upstaging in older patients (> 45 years of age) or treatment plan change in younger patients (< 45 years of age) by the detection of lateral lymph node involvement.

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