REVIEW ARTICLE

ISSN 1598-1703 (Print)
ISSN 2287-6782 (Online)
Korean J Endocrine Surg 2013;13:135-143

The Korean Journal of
Endocrine Surgery

Sentinel Lymph Node Biopsy in Thyroid Cancer

Jee Soo Kim

Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

The role of sentinel lymph node biopsy (SLNB) in thyroid cancer is still debatable. The primary goals of SLNB are to facilitate accurate identification of lymph node (LN) metastasis without formal lymphadenoectomy to reduce morbidity associated with LN dissection. SLN in thyroid cancer can be identified using either vital blue dye, radioactive tracer, or a combination of these methods. Here, 26 selected studies of SLNB for thyroid cancer are analyzed and reviewed. For the vital blue dye, radioisotope, and combined methods, the overall sentinel node identification rates (SNIRs) were 84.0, 98.4 and 97.9%, the overall sensitivities were 86.1, 66.7 and 90.7% and the overall false negative rates were 11.4, 16.3, and 11.4%, respectively. The combined blue dye and radioisotope method had superior SNIRs, sensitivities, and false negative rates than the single vital blue dye technique. New tracers such as carbon nanoparticles can be used in SLNB. Lateral compartment SLNB studies employing a radioisotope technique can be useful for evaluation of the occult lateral neck LN status in patients with papillary thyroid cancer (PTC), especially in cases of central neck node metastasis. Lateral SLNB may also provide useful information for medullary thyroid cancer (MTC) treatment.

Key Words: Sentinel lymph node biopsy, Vital blue dye, Methylene blue, Isosulfan blue, Patent blue V, Radioisotope, Thyroid cancer

Received September 23, 2013,
Revised September 23, 2013,
Accepted September 23, 2013
Correspondence: **Jee Soo Kim**
Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, 50 Irwon-dong, Gangnam-gu, Seoul 135-710, Korea
Tel: +82-2-3410-6982
Fax: +82-2-3410-0253
E-mail: jskim0126@skku.edu

This review also submitted to 'Gland Surgery Journal'.

INTRODUCTION

High-resolution US has been found to accurately detect regional metastatic lymph nodes (LN) as small as 2～3 mm in the greatest dimension, nodes that were missed by palpation alone. US could detect LN metastases in the lateral neck with high sensitivity and specificity.(*1*) US, however, was unable to detect all metastatic nodes in the central compartment of the neck. The lower sensitivity of US may be due to potential limitations in the central neck, in that the presence of metastatic nodes may be masked by the thyroid gland and multifocal nodules, the surrounding structures of the central compartment, and the clavicle and sternum.(*1*) By contrast, the Sentinel Lymph Node Biopsy (SLNB) technique may more accurately detect the presence of metastatic nodes in the central neck and allow the surgeon to alter the surgical procedure in real time.

SLNB is widely investigated and performed in melanoma and breast cancer. The role of SLNB in breast cancer is clear; it decrease the need for axillary LN dissection which can cause arm edema. However, the role of SLNB in thyroid cancer which was first introduced by Kelemen et al.(*2*) in 1998 is still under investigation. The primary goals of SLNB are to enable accurate identification of lymph node metastases without the need for formal lymphadenectomy, to minimize morbidity from unnecessary surgery, and to facilitate the appropriate treatment of patients with and without nodal disease.(*3*) The presence of macroscopic LN metastases in Papillary Thyroid Cancer (PTC) at presentation, which is found in about 50% of patients, clearly increases the risk of loco-regional recurrence and warrants node dissection.(*3*) Papillary microcarcinomas have a up to

65% risk of associated metastasis.(*4*) Patients who harbor LN metastases may have shorter overall or disease-free survival and increased risk of recurrence. In patients with pathological proven cervical LN metastases (pathological N1 disease; pN1), the median risk of loco-regional LN recurrence varies markedly by clinical staging, with recurrence rates for patients who are initially clinically N0 (clinical N0 disease; cN0) of 2% (range 0%～9%) versus rates of recurrence for patients who are initially clinically N-positive (clinical N1 disease; cN1) of 22% (range 10%～42%). Furthermore, the median risk of recurrence in pN1 patients varies markedly by the number of positive nodes, ＜5 nodes (4%, range 3%～8%) vs. ＞5 nodes (19%, range 7%～21%).(*5*) Thus, ipsilateral neck dissection after thyroid resection to excise potential metastatic disease may be indicated in patients with high-risk differentiated thyroid cancer (DTC). To date, however, there is no direct evidence that prophylactic LN dissection may be associated with a decreased risk of recurrence and improved survival in patients with DTC(*6*) Central LN dissection also can be associated with significant morbidity including transient and/or permanent hypoparathyroidism and vocal cord paresis. If SLNB could reliably differentiate between patients with and without regional node metastasis, the ideal option in patients with clinically node-negative thyroid cancer would be to undertake central node dissection selectively in those with a positive sentinel node (SN).

POTENTIAL ADVANTAGE & PITFALLS

The risks and benefits of the SLNB procedure should first be assessed. SLNB for thyroid cancer may display potential benefits in increase the accuracy of nodal staging, the detection of metastatic lymph nodes outside the central neck, identification of skip metastasis, and the selection of patients who would benefit from complete neck dissection and optimized ^{131}I ablation therapy, avoidance of unnecessary prophylactic LN surgery, minimizing surgical morbidity.(*1*)

Although the complications of SLNB were not significant, they include hypersensitivity to isosulfan,(*7*) skin flare response to the blue dye.(*8*) There are also little increased morbidities related to the SLNB procedure, such as recurrent laryngeal nerve injury and hypoparathyroidism. In addition, removal of parathyroid glands that had been stained by the dye is well known pitfall of blue dye methods,(*9*) transient vocal cord paresis attributed to a prolonged search for the SN,(*10*) and intravascular injection of radioisotope in one patient causing early migration of the radioisotope and non-visualization of the SN.(*11*) Radioactive tracer used in lymphoscintigraphy did not harm patients, surgeons or pathologists;(*9,11,12*) however, SLNB using lymphoscintigraphy/gamma-probe is costly and time consuming, increasing operation time.

The exclusion criteria for SLNB included patients with the followings; 1) anaplastic thyroid cancer, 2) known benign disease, 3) previous surgery on the thyroid gland, 4) pregnant or actively breast-feeding, 5) known local or distant metastasis.(*13*)

The aims of this review were; to summarize the SLNB techniques used in thyroid cancer patient ; to compare the result of different methods in assessing SN detection rates, and other statistical parameters.

VITAL BLUE DYE

The SLN in thyroid cancer can be identified with either vital blue dye and/or radioactive tracer. Recently Carbon nanoparticles were used as tracer.(*14*)

Vital blue dye method is a relative convenient SLNB technique in thyroid cancer. Isosulfan blue dye (1%),(*2,8,15-17*) methylene blue (1%, 2%)(*9,14,18-24*) and Patent Blue V (0.5%, 1%, 2.5%)(*11,25-28*) were most commonly used dyes in SLNB.

For vital blue dye injection procedure, minimal mobilization thyroid gland is crucial to prevent lymphatic rupture around thyroid gland. Excessive dissection usually cause dye leak from the thyroid capsule which can ruin proper dissection due to dye staining. Small amount, usually 0.1～0.5 ml, of blue dye using a tuberculin syringe is sufficient for staining. Both intratumoral and peritumoral injection can be used. Sometimes blue dye (especially methylene blue) did not drained into lymphatic channel

especially when tumor is well encapsulated, large, or calcified. So we prefer peritumoral injection when using methylene blue. Blue stained lymphatic channel and SLN can be seen within 1～2 min after injection. All blue stained nodes are dissected and sent for frozen biopsy, Unilateral or bilateral Central Neck Dissection (CND) after SLNB can be performed following the study protocols.

The vital blue techniques are relatively easy to perform and safe. However, they have several disadvantages; the risk of lymphatic disruption from primary tumors; possible coincidental staining of parathyroid glands; and difficulty in identifying sentinel nodes in the lateral neck or mediastinum.(*1*) Staining of the parathyroid gland is a major disadvantage of the blue dye SLNB technique.

Table 1 summarized the result of blue dye techniques reported. A analysis of 20 studies comprising a total 1,098 patients, demonstrated sentinel node identification rate (SNIR) of vital blue dye methods was around 82.0%. SNIR for isosulfan blue, methylene blue, and Patent Blue V was 90.7%, 81.6%, and 69.9% respectively. The SNIR of PB was lower than other two blue dye methods. Rubello et al.(*28*) indicated in their study using PB that no SLN staining was observed in 46 out of 153 patients (30.1%). And in 4 of them a normal parathyroid gland was stained and in 3 other cases, fibroadipous tissue was stained thus leading to misinterpretation of this finding as a SLN (7 cases). Moreover, in other 7 of these 46 patients (15.2%), micrometastases were found in removed LN at histopathologic examination. Other two study(*25,26*) also showed low SNIR, relatively high false negative rate of Patent Blue V. Compared to Isosulfan blue or Methylene Blue, Patent Blue V having relatively low detection rate thought to be not a good candidate for SLNB in thyroid cancer.

ISB showed uniform high SNDR around 90% except one study,(*15*) high sensitivity (90.2%), accuracy (93.3%), and low false negative rate (17.1%). Hypersensitivity reactions including anaphylaxis have been reported in 1～3% of patients administered ISB, but has not been noted in patients administered methylene blue.(*7*)

Many SLNB studies in thyroid cancer were largely carried out with methylene blue dye method. A analysis of 11 studies of methylene blue showed 81.6% (73.4～100%) of SNID which was lower than ISB and higher than PB. The sensitivity (3.1%), accuracy (92.2%), and false negative rate (12.6%) were with acceptable value. False negative rate of dye method is highly variable to the study groups from 0% to 38.9%. Source of false negative cause in dye technique may be due to spread to the lateral compartment of metastatic disease or adherence of the sentinel node to the thyroid itself thus preventing detection as a separate blue entity.(*13*) In Oct 2011, unfortunately, FDA reported (http://www.fda.gov/Drugs/DrugSafety/ucm263190.htm) on the potential drug interaction between methylene blue and serotonergic psychiatric medications. Methylene blue is not an FDA-approved drug and not commercially available at this time.

RADIOISOTOPE

The disadvantage of vital blue dye method, parathyriod staining, can be overcome by lymphoscintigraphy or an intraoperative gamma-probe procedure. The patients underwent preoperative lymphoscintigraphy after injecting one of radioisotope labeled particles such as 99mTc-tin colloid,(*9*) 99mTc-labelled nanocolloid,(*12,29*) 99mTc-labelled sulphur colloid,(*10*) or 99mTc-labelled colloidal albumin.(*11*) Small amount, usually in 0.1～0.3 ml, of radiosiotope injected intratumorally or peritumorally under US guidance. Total thyroidectomy or lobectomy was performed first in order to avoid interference by primary tumor radioactivity ('shine through' phenomenon), then a hand-held collimated gamma probe was used to scan the central compartment and the lateral compartments for 'radioactive' LN. In patients with DTC, SLNs are regarded as the lymph nodes with a lesion-to-background ratio of 2:1 or greater.(*11*) After selective excision of the SLN, the radioactivity of the lymphatic bed is monitored with the probe to verify complete surgical extirpation, while the SLN is sent to the pathology laboratory for histologic examination.(*1*)

The SNIR of Radioisotope was 98.4% (96.6%～100%) higher than that of vital blue dye techniques (Table 2). In spite of higher SNIR, only one study was available for analysis, sensitivity (66.7%), accuracy (87.7%) and false

Table 1. Results of studies using 3 kinds of blue dye technique of SLNB in PTC

Reference	No. of pts	SN identified	SNIR	SN positive	SN negative	False positive	True negative	Sensitivity (%)	Specificity (%)	Accuracy (%)	False negative rate (%)
Isosulphan blue											
Cunningham et al.(*17*) 2010	211	192	91.0	71	121	NA	NA	NA	NA	NA	NA
Takeyama et al.(*8*) 2009	8	7	87.5	3	4	1	3	75	100	86	25
Takami et al.(*16*) 2003	68	63	92.6	35	28	5	23	87	100	92	18
Arch-Ferrer et al.(*34*) 2001	22	20	90.9	17	3	0	3	100	100	100	0
Dixon et al.(*15*) 2000	14	10	71.4	6	4	NA	NA	NA	NA	NA	NA
Kelemen et al.(*2*) 1998	11	11	100.0	5	6	NA	NA	NA	NA	NA	NA
Isosulfan blue total	334	303	90.7	137	166	6	29	90.2	100	93.3	17.1
Methylene blue											
Ji et al.(*35*) 2012	114	84	73.7	24	60	13	47	64.9	100	84.5	35.1
Hao et al.(*14*) 2012	100	102†	79.0	48	54	5	49	80.6	100	93	9.9
Huang et al.(*30*) 2011	45	39	86.7	21	18	7	11	75	100	82.1	38.9
Amir et al.(*13*) 2011	94	69	73.4	14	55	3	52	82.4	100	95.7	5.5
Anand et al.(*24*) 2009	70	55	78.6	14	41	0	41	100	100	100	0
Lee et al.(*9*) 2009	54	50	92.6	19	31	5	26	79	100	90	21
Bae et al.(*23*) 2009	11	9	81.8	5	4	1	3	83	100	89	25
Roh and Park(*22*) 2008	50	46	92.0	14	32	4	28	78	100	91	13
Wang et al.(*21*) 2008	25	22	88.0	19	3	0	3	100	100	100	0
Falvo et al.(*20*) 2006	18	18	100.0	12	6	0	6	100	100	100	0
Fukui et al.(*18*) 2001	22	21	95.5	7	14	2	12	78	100	90	14
Methylene blue total	603	515	81.6	197	318	40	278	83.1	100	92.2	12.6
Patent blue V											
Rubello et al.(*28*) 2006	153	107	69.9	36	71	0	71	100	100	100	0
Chow et al.(*26*) 2004	15	10	66.7	7	3	1	2	87	100	90	33
Tsugawa et al.(*25*) 2002	38	27	71.1	16	11	3	8	84	100	89	27
Patent blue V total	206	144	69.9	59	85	4	81	93.7	100	97.2	4.7
Blue dye methods total	1,098	923	82.0	372	551	43*	377*	86.1*	100*	93.3*	11.4*

*Calculated in 17 out of 20 studies, †The total number of identified sentinel nodes were 102 nodes. The author calculated sensitivity, specificity, accuracy, and false negative rate based on this number. SN = sentinel node; SNIR = sentinel node identification rate.

negative rate (16.3%) is not satisfactory.

The radiotracer technique has several advantages, including the absence of lymphatic disruption during surgery, potential identification of the SLN outside the central compartment, and no uptake of the tracer by the parathyroid glands.(*28*)

The radioisotope method also has disadvantages. The 'shine through' phenomenon where the SLN close to primary lesion may be obscured by the lesion, may be problematic in the central compartment, where the lymph nodes are located close to the thyroid lesions. This results in high radioactivity counts throughout the entire lymphatic basin, obscuring the ability to localize the drained SLN. In addition, using a radiocolloid for lymphatic mapping is more costly and time consuming than the vital blue technique and requires equipment for radiotracer detection(*1*).

COMBINED METHOD

The combination of lymphoscintigraphy, intraoperative gamma-probe and vital blue dye approaches may also be used to detect SLN. A analysis of 3 studies using combined methods(*9,11,30*) showed SNIR of 97.9%, sensitivity of 90.7%, accuracy of 94.6%, and false negative rate of 11.4% (Table 2). Two comparison study(*9,30*) of methylene bule alone vs. combined methylene bule & radioisotope technique showed improved SNIR, sensitivity, accuracy, and false negative rate in combined method group (Table 3).

The results of 26 studies of three different SLNB technique were summarized in Table 4. SNIR of vital blue dye was improved with radioisotope technique. The false negative rate, 11.4%～16.3%, was similar among the three methods. The clinical significance of false-negative LN in DTC has not yet been determined. The sensitivity of SLNB for SLN detection is also increased by serial sectioning of LN allowing histological examination at multiple level. immunohistochemistry (IHC) staining is more sensitive than hematoxylin and eosin staining in detecting tumor cells. The use of IHC staining on SLNB samples may increase the number of patients found to have LN metastases. IHC assessment of the SN with anticytokeratin/

Table 2. Results of studies using radioisotope vs. combined methods (both blue dye and radioisotope) techniques of SLNB in thyroid cancer

Reference	No. of patients	SN identified	SN IR (%)	Positive SN	Negative SN	False negative	True negative	Sensitivity (%)	Specificity (%)	Accuracy (%)	F(−) rate (%)
Radioisotope method											
Boschin et al.(*12*) 2008	65	65	100	34	31	NA	NA	NA	NA	NA	NA
Carcoforo et al.(*36*) 2007	59	57	96.6	14	43	7	36	66.7	100	87.7	16.3
Stoeckli et al.(*10*) 2003	1	1	100	1	0	NA	NA	NA	NA	NA	NA
Rettenbacher et al.(*29*) 2000	4	4	100	2	2	NA	NA	NA	NA	NA	NA
Radioisotope total	129	127	98.4	51	76	7	36	66.7	100	87.7	16.3
Combined method (blue dye+radioisotope)											
Huang et al.(*30*) 2011	45	45	100	24	21	3	18	88.9	100	93.3	14.3
Lee et al.(*9*) 2009	43	42	98	21	21	2	19	91.3	100	95.2	9
Catarci et al.(*11*) 2001	7	6	86	4	2	0	2	100	100	100	0
Combined total	95	93	97.9	49	44	5	39	90.7	100	94.6	11.4

SN = sentinel node; SNIR = sentinel node identification rate.

Table 3. Comparison of methylene blue only vs. combined methylene blue & radioisotope SLNB study in thyroid cancer

Reference	No. of patients	SN identified	SNIR (%)	Positive SN	Negative SN	False negative	True negative	Sensitivity (%)	Specificity (%)	Accuracy (%)	F(−) rate (%)
Huang et al.(*30*) 2011											
Methylene blue (MB)	45	39	86.7*	21	18	7	11	75	100	82.1	38.9
MB+^{99m}Tc sulfur colloid	45	45	100*	24	21	3	18	88.9	100	93.3	14.3
Lee et al.(*9*) 2009											
Methylene blue (MB)	54	50	92.6*	19	31	5	26	79	100	90	21
MB+^{99m}Tc tin colloid	43	42	98*	21	21	2	19	91.3	100	95.2	9

*Statistically significant, $P<0.005$. SLNB = sentinel lymph node biopsy; SN = sentinel node; SNIR = sentinel node identification rate.

Table 4. Results of three different SLNB techniques (vital blue dye, radioisotope, and combined) in thyroid cancer

Method	No. of studies	No. of patients	SN identified	SN detection rate (%)	Positive SN	Negative SN	False negative	True negative	Sensitivity (%)	Specificity (%)	Accuracy (%)	F(−) rate (%)
Blue dye total	20	1,098	923	82.0	372	551	43	377	86.1	100	93.3	11.4
Isosulfan blue	6	334	303	90.7	137	166	6	29	90.2	100	93.3	17.1
Methylene blue	11	603	515	81.6	197	318	40	278	83.1	100	92.2	12.6
Patent blue V	3	206	144	69.9	59	85	4	81	93.7	100	97.2	4.7
Radiosotope	4	129	127	98.4	51	76	7	36	66.7	100	87.7	16.3
Combined total	3	95	93	97.9	49	44	5	39	90.7	100	94.6	11.4

SLNB = sentinel lymph node biopsy; SN = sentinel node; SNIR = sentinel node identification rate.

antithyroglobulin antibody showed evidence of nodal metastases in an additional 15% of patients (7 of 47 sentinel nodes).(*3*) In addition, metastatic nodes can be detected by improved molecular biologic techniques, including real-time PCR and reverse transcriptase-PCR assays, using primers and/or probes for genes that may be over-expressed in certain tumors. The use of PCR-based molecular markers has resulted in high sensitivity and reproducibility for detecting tumor cells in lymph nodes.(*1*)

NEW TRACER

Recently Hao et al.(*14*) reported SLNB using Carbon nanoparticles (CNs) as tracers for SLNB in thyroid microcarcinoma patients and compare the efficacies with methylene blue (MB) (Table 5). The staining rate of cervical level VI LN, sensitivity, specificity, accuracy rate, and false negative rate were superior in CNs group compared to MB group (Table 4). They suggested the CNs method a feasible and repeatable technique in the screening and selection of patients who are most likely to benefit from cervical LN dissection.

LATERAL SLNB

The incidence of lateral LN metastasis in PTC varies from 15.9～80.0%.(*19,31*) The lateral skip metastasis rate in patients with thyroid cancer has been reported to be as high as 20%.(*1*) Contrast to numerous central SLNB reports in thyroid carcinoma, lateral compartment SLNB study is scanty because prognostic significance of occult lateral LN metastasis in PTC is still controversial. The rationale of lateral SLNB, early identification and removal of occult lateral LN in preclinical stage, may be helpful in avoiding secondary operation due to recurrence in the lateral compartment.

Dzodic et al.(*19*) reported a lateral SLNB study. Methylene blue dye was applied peritumorally in 40 patients with DTC. Both SLN and non-SLN in the lower third of the jugulo-carotid chain were dissected prior to total thyroidectomy and routine dissection of the central neck compartment. All LN were examined by frozen section and standard histology. Modified Radical Neck Dissection (MRND) was performed in 9 cases of LN metastasis in the lateral neck compartment. The SLN identification rate was 92.5%. Metastases in SLNs were revealed by frozen section histology in 7 cases, leading to immediate MRND. In 2 false-negative cases SLN metastases were revealed on standard histology and MRND was performed 1 week later. The specificity of the method was 100%, sensitivity 77.7%, negative predictive value 94%, positive predictive value 100%, with overall accuracy of 95%. In this study he found that SLN biopsy in the jugulo-carotid chain using methylene blue dye mapping may be a feasible and valuable method for estimating LN status in the lateral neck compartment.

We reported lateral SLNB study using radioisotope in 2011. A randomized clinical trial in 94 patients with PTC larger than 1 cm and/or with clinically suspicious central neck node metastasis was conducted in order to evaluate the efficacy of lateral SLNB in the prevention of lateral neck recurrence. Preoperative lymphoscintigraphy was obtained after intratumoral injection of a 99mTc-tin colloid under ultrasound guidance. After total thyroidectomy or

Table 5. Comparison of the results using carbone nanoparticles (CN) vs. methylene blue (MB) dye technique of sentinel lymph node biopsy in papillary thyroid cancer [Hao et al.(*14*) 2012]

Dye	Volume injected (ml)	No. of patients	SN* identified	SN IR (%)	Positive SN	Negative SN	Sensitivity (%)	Specificity (%)	Accuracy (%)	F (−) rate (%)
CN	0.1～0.5 (suspension= 1 ml : 50 mg)	100	126	91	77	49	93.3	100	97	5.2
MB	0.1～0.5	100	102	79	48	54	80.6	100	93	9.9

The CN and MB were injected peritumorally after mobilization of thyroid gland. *The total number of identified sentinel nodes were 126 and 102 nodes in 100 patients of each group respectively. The author calculated sensitivity, specificity, accuracy, and false negative rate based on this number. SLNB = sentinel lymph node biopsy; SN = sentinel node; SNIR = sentinel node identification rate.

lobectomy, SLNB was performed in the lateral neck nodes. When metastasis detected in SLNs upon frozen biopsy, an immediate MRND was performed. The SNIR was 63.8%. SLNs metastasis was found in 19 patients (31.7%). This clinically occult lateral metastasis was only related to the total number of metastatic LNs in the central compartment. We found SLNB a useful method for evaluating the occult lateral neck LN status in patients with PTC, especially in the cases of central neck node metastasis.

Tracing the lymphatic flow for blue dye uptake in lateral cervical area is not easy. On the contrary, searching and localization of the SLN with a radioisotope in the lateral neck is easily accomplished with a gamma probe and lymphoscintigraphy, even when the SLN is located in the upper (level I or II) or contralateral neck.

SLNB has not yet found a place in the therapy for thyroid cancer. Doherty(*32*) pointed out several reasons for this: (1) sentinel node biopsy in the confined area of the neck is technically challenging; (2) the most common node basin for PTC metastasis is the level VI nodes, an area that has already been exposed during thyroidectomy and can be dissected with limited additional morbidity; (3) ultrasound evaluation of the lateral neck is sensitive for identification of non-palpable node metastases; and (4) lateral neck recurrence is uncommon after effective adjuvant treatment with radioiodine.

The issue of whether it is important to remove small amounts of occult disease in lateral neck, or whether they can be effectively managed by radioiodine therapy, will require careful clinical study.(*32*)

POTENTIAL BENEFITS IN MTC

ATA guideline recommend that Medullary thyroid cancer (MTC) patients with suspected limited local metastatic disease to regional LN in the central compartment (with a normal US examination of the lateral neck compartments), in the setting of no distant metastases should typically undergo a total thyroidectomy and level VI compartmental dissection. A minority of the Task Force favored prophylactic lateral neck dissection when LN metastases were present in the adjacent paratracheal central compartment. Grade: B Recommendation.(*33*)

MTC has a high rate of LN metastases that are suboptimally detected preoperatively in the central compartment by US or intra-operatively by the surgeon, and re-operation is associated with a higher rate of surgical complications. For these reasons, most authors advocate for a total thyroidectomy and prophylactic central neck dissection in the setting of MTC patients without advanced local invasion or cervical node or distant metastases. Because surgical modality plays a major role and issue on prophylactic lateral neck dissection is still not settle down in MTC, it is important to detect and treat occult nodal diseases in lateral neck. In this context, the SLNB especially with radioctive tracer technique may provide useful information of occult lateral neck nodal diseases in MTC.

REFERENCES

1. Roh JL, Koch WM. Role of sentinel lymph node biopsy in thyroid cancer. Expert Rev Anticancer Ther 2010;10:1429-37.
2. Kelemen PR, Van Herle AJ, Giuliano AE. Sentinel lymphadenectomy in thyroid malignant neoplasms. Arch Surg 1998;133:288-92.
3. Balasubramanian SP, Harrison BJ. Systematic review and meta-analysis of sentinel node biopsy in thyroid cancer. Br J Surg 2011;98:334-44.
4. Wada N, Duh QY, Sugino K, Iwasaki H, Kameyama K, Mimura T, et al. Lymph node metastasis from 259 papillary thyroid microcarcinomas: frequency, pattern of occurrence and recurrence, and optimal strategy for neck dissection. Ann Surg 2003;237:399-407.
5. Randolph GW, Duh QY, Heller KS, LiVolsi VA, Mandel SJ, Steward DL, et al. The prognostic significance of nodal metastases from papillary thyroid carcinoma can be stratified based on the size and number of metastatic lymph nodes, as well as the presence of extranodal extension. Thyroid 2012;22:1144-52.
6. Zeiger MA. Evolution in the surgical management of well-differentiated thyroid cancer or not: to dissect or not dissect the central lymph node compartment. J Surg Oncol 2010;101:101-2.
7. Montgomery LL, Thorne AC, Van Zee KJ, Fey J, Heerdt AS, Gemignani M, et al. Isosulfan blue dye reactions during sentinel lymph node mapping for breast cancer. Anesth Analg 2002;95:385-8.
8. Takeyama H, Tabei I, Uchida K, Morikawa T. Sentinel node biopsy for follicular tumours of the thyroid gland. Br J Surg 2009;96:490-5.
9. Lee SK, Choi JH, Lim HI, Kim WW, Kim SM, Choe JH, et al. Sentinel lymph node biopsy in papillary thyroid cancer: com-

parison study of blue dye method and combined radioisotope and blue dye method in papillary thyroid cancer. Eur J Surg Oncol 2009;35:974-9.
10. Stoeckli SJ, Pfaltz M, Steinert H, Schmid S. Sentinel lymph node biopsy in thyroid tumors: a pilot study. Eur Arch Otorhinolaryngol 2003;260:364-8.
11. 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.
12. 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.
13. Amir A, Payne R, Richardson K, Hier M, Mlynarek A, Caglar D. Sentinel lymph node biopsy in thyroid cancer: it can work but there are pitfalls. Otolaryngol Head Neck Surg 2011;145:723-6.
14. Hao RT, Chen J, Zhao LH, Liu C, Wang OC, Huang GL, et al. Sentinel lymph node biopsy using carbon nanoparticles for Chinese patients with papillary thyroid microcarcinoma. Eur J Surg Oncol 2012;38:718-24.
15. Dixon E, McKinnon JG, Pasieka JL. Feasibility of sentinel lymph node biopsy and lymphatic mapping in nodular thyroid neoplasms. World J Surg 2000;24:1396-401.
16. Takami H, Sasaki K, Ikeda Y, Tajima G, Kameyama K. Detection of sentinel lymph nodes in patients with papillary thyroid cancer. Asian J Surg 2003;26:145-8.
17. Cunningham DK, Yao KA, Turner RR, Singer FR, Van Herle AR, Giuliano AE. Sentinel lymph node biopsy for papillary thyroid cancer: 12 years of experience at a single institution. Ann Surg Oncol 2010;17:2970-5.
18. Fukui Y, Yamakawa T, Taniki T, Numoto S, Miki H, Monden Y. Sentinel lymph node biopsy in patients with papillary thyroid carcinoma. Cancer 2001;92:2868-74.
19. Dzodic R, Markovic I, Inic M, Jokic N, Djurisic I, Zegarac M, et al. Sentinel lymph node biopsy may be used to support the decision to perform modified radical neck dissection in differentiated thyroid carcinoma. World J Surg 2006;30:841-6.
20. Falvo L, Marzullo A, Palermo S, Biancafarina A, De Stefano M, Vanni B, et al. The sentinel lymph node in papillary cancer of the thyroid including histological subtype. Ann Ital Chir 2006; 77:13-8.
21. Wang JD, Deng XC, Jin XJ, Zhang C, Zhou JQ, Zhou QY, et al. [Surgical exploration of the sentinel lymph nodes in the papillary thyroid carcinoma]. Rev Laryngol Otol Rhinol (Bord) 2008;129:285-7.
22. 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.
23. Bae JS, Park WC, Song BJ, Jung SS, Kim JS. Endoscopic thyroidectomy and sentinel lymph node biopsy via an anterior chest approach for papillary thyroid cancer. Surg Today 2009;39: 178-81.
24. Anand SM, Gologan O, Rochon L, Tamilia M, How J, Hier MP, et al. The role of sentinel lymph node biopsy in differentiated thyroid carcinoma. Arch Otolaryngol Head Neck Surg 2009;135: 1199-204.
25. Tsugawa K, Ohnishi I, Nakamura M, Miwa K, Yokoyama K, Michigishi T, et al. Intraoperative lymphatic mapping and sentinel lymph node biopsy in patients with papillary carcinoma of the thyroid gland. Biomed Pharmacother 2002;56 Suppl 1:100s-3s.
26. Chow TL, Lim BH, Kwok SP. Sentinel lymph node dissection in papillary thyroid carcinoma. ANZ J Surg 2004;74:10-2.
27. Peparini N, Maturo A, Di Matteo FM, Tartaglia F, Marchesi M, Campana EP. Blue-dye sentinel node mapping in thyroid carcinoma: debatable results of feasibility. Acta Chir Belg 2006;106: 523-7.
28. 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.
29. Rettenbacher L, Sungler P, Gmeiner D, Kässmann H, Galvan G. Detecting the sentinel lymph node in patients with differentiated thyroid carcinoma. Eur J Nucl Med 2000;27:1399-401.
30. Huang O, Wu W, Wang O, You J, Li Q, Huang D, et al. Sentinel lymph node biopsy is unsuitable for routine practice in younger female patients with unilateral low-risk papillary thyroid carcinoma. BMC Cancer 2011;11:386.
31. Lee SK, Kim SH, Hur SM, Choe JH, Kim JH, Kim JS. The efficacy of lateral neck sentinel lymph node biopsy in papillary thyroid carcinoma. World J Surg 2011;35:2675-82.
32. Doherty GM. Sentinel lymph node biopsy for papillary thyroid cancer: commentary on the efficacy of lateral neck sentinel lymph node biopsy in papillary thyroid carcinoma by Se Kyung Lee et al. World J Surg 2011;35:2683.
33. American Thyroid Association Guidelines Task Force, Kloos RT, Eng C, Evans DB, Francis GL, Gagel RF, et al. Medullary thyroid cancer: management guidelines of the American Thyroid Association. Thyroid 2009;19:565-612.
34. Arch-Ferrer J, Velázquez D, Fajardo R, Gamboa-Domínguez A, Herrera MF. Accuracy of sentinel lymph node in papillary thyroid carcinoma. Surgery 2001;130:907-13.
35. Ji YB, Lee KJ, Park YS, Hong SM, Paik SS, Tae K. Clinical efficacy of sentinel lymph node biopsy using methylene blue dye in clinically node-negative papillary thyroid carcinoma. Ann Surg Oncol 2012;19:1868-73.
36. 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. Eur J Surg Oncol 2007;33:1075-80.