INTRODUCTION

Thyroid cancer represents about 1.7% of all malignancies in humans. Survival of patients is favorable, but the disease and its treatment carries out morbidity and mortality (1). Differentiated thyroid carcinoma (DTC) account 90% of all thyroid malignancies and are the most common primary malignancy of the endocrine system, and their incidence is increasing.

Papillary thyroid carcinoma (PTC) metastasized to the regional lymph nodes in 30 to 80% of patients and up to 90% of children and adolescents. Metastasizes to the central (pretracheal and para-tracheal, level VI), upper mediastinal (level VII) and lateral (supraventricular, jugulocarotid, level II, III, IV and V) lymph nodes of the neck. Follicular thyroid carcinoma extremel rarely metastasize to the lymph node, but often metastasize to distant organs such as the lungs and bones.

Lymph nodes in the neck are most commonly classified by the American Academy of Otolaryngology and the American Joint Committee on Cancer recommendation. According to this classification, lymph nodes of the neck were divided into seven groups or levels (Figure 1).

**Key words:** Differentiated thyroid cancer, lymph node metastases, sentinel lymph nodes.
Sentinel lymph nodes are the first lymph nodes to receive the lymphatic drainage of malignant tumors. The concept of SLN has become a standard in the staging of regional spread of malignant tumors, which receives afferent lymphatic drainage. Prophylactic central neck dissection (CND) in cN0 and advanced tumors (T3 and T4) is recommended by the American Thyroid Association (ATA) to avoid the central dissection in smaller tumors. The secondary objectives of this procedure are to achieve reliable detection of LNM in clinically unaffected lymph nodes and to provide optimal and timely selective surgical treatment.

The concept of SLN has become a standard in the detection of occult LNM in case of early breast cancer and skin melanoma. The effectiveness of the method was confirmed by its inclusion in the UICC TNM classification of malignant tumors.
Pioneering study of Kelemen and coworkers (1998) on SLN for thyroid nodules inducted a series of studies that have shown that SLN biopsy may be appropriate procedure in assessment of lymph node status in patients with differentiated thyroid cancer (21).

The concept involves mapping, detection and surgical biopsy and their frozen-section and standard histopathologic analysis. The choice of markers (vital colors and/or nanocolloid), skills and experience of the surgeon in detecting (learning curve), the experience and knowledge of the pathologist in the processing of SLN are of key importance. The ratio of positive (malignant) and negative (benign) SLN presents the findings of sensitivity (Se), specificity (Sp), positive (PPV) and negative predictive value (NPV). On the basis of these findings overall accuracy of the method is calculated.

RESULTS OF SLN BIOPSY FOR DIFFERENTIATED THYROID CANCER — REVIEW OF LITERATURE

By 2012, three meta-analysis were published investigating the SLN techniques, the use of different markers and the results of methods accuracy of all relevant studies.

The first meta-analysis published by Raijmakers (2008), included 14 studies, of which in 10 were used the vital dye, and in four radiocolloid (Tc99m). The rate of SLN detection (identification rate, IR) in studies with vital dye was 83%, and 96% in four studies with radiocolloid. The data on the sensitivity of the method were available in six of the 10 studies with a vital dye, and only one of the four studies with radiocolloid in which only a percentage of false negative results was available. Sensitivity in studies with vital dye was 87.3% (79 to 93%) with a rate of false negative results of 12.7%, versus 11.3% in the only study with radiocolloid. Histologically SLN somewhat questionable because several studies have included patients with benign thyroid tumors. Percentage of thyroid malignancy in seven studies ranged from 33 to 98%, while in other studies, all patients had thyroid cancer. As a conclusion, with the real limitation, according to the detection of SLN in thyroid cancer is possible and potentially useful, but there is a need for new and more numerous prospective studies (22) (Figure 2).

The second meta-analysis by Balasubramanian and Harrison (2011) cover 24 relevant original studies on the role of SLN biopsy in thyroid cancer published until February 2010. In 17 studies vital dye was used as a marker, in four radiocolloid, while in the two studies, the combination of these two markers was used. Detection rate (IR) was 83.7%, 98.4% and 96% successively.

Figure 2. Detection rate of SLN in Raijmakers’s meta-analysis


Figure 3. Detection rate of SLN in Balasubramanian’s meta-analysis
Analysis of sensitivity, specificity and overall accuracy of the method was possible in 12 studies with a vital stain, and only by one study with radiocolloid and combined method. The percentage of false negatives was successively 7.7%, 16% and 0%. Lymph node metastasis in the SLN were observed in 42.9% of patients, whereas in eight studies, which is used for additional immuno-histochemical analysis, micro-metastases verified in another 14.8% of patients. Balasubramanian and Harrison concluded that SLNb method has high expectation and with its implementation can be avoided prophylactic dissection in almost 57% of patients with thyroid cancer and clinically negative lymph nodes (23) (Figures 3 and 4).

Finally, the third meta-analysis by Kaczka and associates (2012) included 25 studies, which according to the techniques of marking and detection of SLN was divided into three groups. The first group of 18 study used the vital dye, in the second group of four studies, radiocolloid was used, and in the third group the two studies used a combined technique. SLN detection rate in patients was 83.1% in the first group, 98.8% in the second group and 97.8% in the third group. In two studies of the third group, Catraci have shown better result of detection with radiocolloid relative to the vital dye (83.3% versus 50%), while Lee showed a better IR with vital dye (93% versus 88.4%) (24, 25, 26).

This meta-analysis showed the advantage in IR of peritumoral injection of the vital dye compared to intratumoural application (92.2% to 71.8%). It also showed a better detection rate of SLN using methylene blue (Methylene blue), compared to isosulfan blue (Isosulfan blue) and patent blue (Patent blue) — (91.9% versus 86.1% and 68.3%). There were no differences in the rate of detection of intratumoral and peritu...
moral applications of radiocolloids. Lymph node metastasis in the SLN were detected successively in 40.8%, 39.9% and 52.1% of cases (24) (Figure 5).

Disparity of histopathological findings of primary thyroid tumor, involvement of benign tumors and cancers with different biological behavior, relatively few studies have been undertaken a complete surgical exploration of central and lateral neck compartments and the lack of data on the statistical reliability of the testing methods, represent real constraints.

In the experimental study of Li and associates in laboratory rabbits, the advantage of methylene blue staining in speed, depth of penetration and persistence of staining compared to other vital colors have been shown (27).

Thevarajah and associates in the review paper analyzed the side effects and allergic reactions to the use of vital blue dye in the detection of SLN in breast cancer in the period from 1985 to 2002. They concluded that isosulfan blue cause significant allergic reactions, even life-threatening. Therefore, the use of methylene blue strongly recommended as an equally effective and safe alternative in the detection SLN (28).

The results of previous prospective study by Dzodic and associates (2006) are included in all three meta-analysis. Also, by 2011, our concept SLN biopsy in the lateral compartment was only published in the relevant literature. We used a 1% solution of methylene blue as peritumoral injection in 40 patients with thyroid cancer in the period from 2001 to 2004. Lymph node metastases in the lateral neck compartment were histologically confirmed in 22.5% of patients with clinically unaffected lymph nodes (cN0). SLN detection rate was 92.5%, sensitivity 77.7%, specificity 100%, positive predictive value of 100%, negative predictive value 94%, while the overall accuracy of the method was 95% (29).

Unlike other studies that were based on the identification of the SLN biopsy in the central neck compartment, in this study the path of the vital dye was followed to the lymph nodes in lateral compartment with the idea to check them histologically in the case of metastases and perform selective lateral neck dissection.

During 2011, two studies that have analyzed results SLNb lateral neck compartment were published. Ikeda presented the results of detection SLNb with Indocyanin green peritumoral application in 12 patients with PTC. The rate of detection was 100% as well as sensitivity, specificity and overall accuracy of the method. Lymph node metastases in the lateral compartment were confirmed in 31.7% of cN0 patients. Approximately 93% of SLN was located in the ipsilateral compartment in the level III and IV, 4.6% in level II and 2.3% in the third level. The sensitivity and accuracy of the method were not tested in this study (30).

CONCLUSIONS AND PERSPECTIVES

Based on the three meta-analysis it could be concluded that SLN biopsy is a safe and feasible, with high reliability in predicting occult lymph node metastases in differentiated thyroid carcinoma. Using vital dye is cheap and does not require technical equipment. The sensitivity of the method is increasing, while the complementary immunohistochemical and molecular techniques evolve. SLNb for thyroid cancer may prove practical use in precise staging of cervical lymph node status, detection LNM outside the central compartment, the selection of patients who will benefit with adequate and timely selective neck dissection and optimize application of ablative radiiodine therapy.

Currently, there is no direct evidence that SLNb could associated with long-term prognosis in terms of locoregional relapse and survival of patients with thyroid cancer.

Controlled prospective clinical studies on a larger number of patients and longer follow-up period will determine the clinical significance of occult LNM and their early detection method SLNb in patients with thyroid cancer.

The authors have no conflict of interests.

Abbreviations:

TC — Differentiated thyroid carcinoma
PTC — Papillary thyroid carcinoma
UICC — Union International Against Cancer
LNM — Lymph node metastases
ATA — American Thyroid Association
CND — Central neck dissection
MRND — Modified radical neck dissection
SLN — Sentinel lymph node
SLNB — Sentinel lymph node biopsy
Sažetak

KONCEPT STRAŽARSKIH LIMFNIH NODUSA KOD DIFERENTOVANOG TIROIDNOG KARCINOMA

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Diferentovani tiroidni karcinomi (DTK) čine do 90% svih tiroidnih maligniteta i najčešće su primarni maligniteti endokrinog sistema. Njihova učestalost je u značajnom porastu u poslednje tri decenije, a posebno malih papilarnih tiroidnih karcinoma (PTK). U vreme dijagnoze, učestalost limfonodalnih metastaza (LNM) iznosi od 80 do 90%. U poslednjih 15 godina, LNM su prepoznate kao loš prognostički faktor za pojavu lokoregionalnog relapsa bolesti (LRR) i cancer-spektralnog preživljavanja. Postoji generalna saglasnost da su disekcije vrata indikovane kod klinički suspektnih LNM. Predmet aktuelnih kontroverzi predstavlja hirurški postupak sa okulutnim LNM koje preoperativnom dijagnostikom ostaju neprepoznate (cN0). Opseg operacije na limfnim nodusima kreće se od teorije „sačekati i videti” takoçoane „zapadne kole” argumentovane ulogom primene ablativne terapije J131 i učestalošću peroperativnih komplikacija (povrede povratnog

laringealnog nerva i hipoparatiroidizma) posebno kod manje iskusnih timova, do obstranih profilaktičkih dijekcija centralne i lateralne regije vrata takozvan „ja-panske škole” zbog ograničene upotrebe radioaktivnog joda u terapijske svrhe kao i značajno manjeg operativnog morbidećeta ukoliko se disekcija uraditi u primarnom aktu. Uprkos visokoj prevalencij okulutnih LNM, postoje kontroverze u dijagnostici, dugoročnom prognostičkom značaju i opseg operacija na limfnim nodusima, motivisale su neke autore da koncept provere stražarskih limfnih nodusa (SLN) primene kod pacijenata sa DTK, imajući u vidu odlične rezultate kod karcinoma dojke i melanoma kože. U ovom pregledu prikazani su sumirani rezultati relevantnih studija i tri meta analize pouzdansosti i primenljivosti koncepta SLN kod pacijenata sa diferentovanim tiroidnim karcinomom.

Ključne reči: Diferentovani tiroidni karcinom, limfonodalne metastaze, stražarski limfni nodus.

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