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The Role of Sentinel Lymph Node Biopsy in Head and Neck Cancers and Its Application Areas

Review

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Abstract

The management of the clinically N0 neck in patients with head and neck cancers still remains controversial. Elective neck dissection is traditionally recommended when the subside of the head and neck, such as the oral cavity and supraglottic area, confers at least a 15–20% risk of lymphatic spread. However, elective neck dissection may cause an increase in patient morbidity and mortality rates. The emergence of sentinel lymph biopsy provides the possibility of accurate pathological staging of the cervical node with a less invasive procedure. The present review will summarize the role of sentinel lymph node biopsy and its application areas when evaluating occult metastases in patients with head and neck cancers.

Keywords: Sentinel lymph node biopsy, lymphoscintigraphy, head and neck cancer, lymphatic metastasis, diagnosis

Introduction

The most important factor affecting prognosis in head and neck cancers is lymphatic metastasis of the neck (1). Positive lymph node detected in the neck is highly important in staging and treatment of the disease. It is suggested that regional lymph node involvement reduces five year survival rate in squamous cell carcinoma (SCC) of head and neck to 50% (2). Therefore elective neck dissection (END) is recommended in some T1-T2 head and neck cancers which have latent metastasis rate of 15-20% (3). Besides it was seen in some studies that END conducted for these patients was not necessary in more than 70% of them after examination of the samplings and END was not superior to the group in which "wait and see" policy was conducted with regard to survival and neck recurrence (4, 5). Approach to N0 necks is still controversial taking into consideration that neck dissection increases mortality and morbidity of patient and raises hospital expenses.

Although diagnostic applications such as clinical examination and ultrasonography guided fine needle aspiration biopsy and visualization techniques such as positron emission tomography/ computerized tomography (PET/CT) are used in lymph node staging, these methods sometimes fail to detect lymph node metastasis. Even modern visualization techniques of our day such as PET/CT cannot detect micrometastases having sizes of 2mm and below, furthermore their sensitivity in detecting lymph nodes below the size of 10 mm is decreasing compared to ultrasonography (6). It was reported that the sensitivity of ultrasonography guided fine needle aspiration biopsy was 50% (7). Accordingly, sentinel lymph node biopsy (SLNB) method which has been frequently used in patients with the diagnosis of breast cancer and malignant melanoma (MM) has begun to be used in head and neck cancers. In this method applied for the first time by Morton et al. (8) using blue dye in MM patients, the purpose is to find the lymph node or nodes with which lymph drainage coming from cancer tissue confront for the first time. Excision and histopathological examination of these nodes called sentinel lymph nodes will give us information about neck disease. Technically SLNB method involves dynamic and static imaging after application of methylene blue and/or Tc99m radionucleotide material in multiple injections and then removal of marked lymph nodes. Generally sentinel lymph node can be found one hour after the injection by imaging techniques and marked on the skin with a permanent pen and can be counted within 24 hours after injection with probe during surgery. Indication of lymphatic map besides sentinel lymph nodes may provide us important advantages in head and neck cancers in which skip metastases may be seen. Consequently, at present SLNB method has begun to be used more frequently in head and neck cancers with overcoming technical difficulties and gaining experience.

In this paper, areas of use of SLNB in head and neck cancers and the place of its role in evaluating neck disease in the literature were reviewed.

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Clinical and Research Effects

Oral Cavity and Oropharynx Cancers

Oral cavity cancers constitute 3% in males and 2% in females of all body cancers (9). Approach to N0 neck in oral cavity SCC cancers is still a controversial issue. Some authors prefer "wait and see" policy due to the low lymphatic metastasis risk in well-differentiated oral cavity cancers particularly smaller than 2cm and have a depth of less than 4mm (10). PET/CT is recommended for lymph nodes that may be missed by examination in these patients. However it is suggested in multicenter studies and co-decisions taken in two international SLNB conferences that SLNB is a very appropriate diagnostic method for the cancers of oral cavity which is the most accessible mucosal region (11, 12).

Metastasis detection rate in lymph nodes for which frozen section examination is demanded and which is removed by sentinel lymph node biopsy method is found low when compared with postoperative pathology results of the very same lymph nodes. In a study conducted by Melkane et al. (13), only micrometastatic focus was detected in 14 (33%) of the 42 positive sentinel lymph nodes. While sensitivity of intraoperative SLNB in breast cancers examined using classical pathological methods is between 47% and 74%, this rate falls to 38-47% in MM (14). This rate was found to be approximately 60% in oral cavity cancers due to the difficulties in detection of micrometastases intraoperatively (15). This has destroyed credibility of SLNB and has led to a rise in morbidity and mortality and delays in additional therapies due to secondary surgery. Therefore real-time polymerase chain reaction (PCR) was used in SLNBs conducted intraoperatively and sensitivity of this operation lasting 35 minutes on average rose to 94.2% (16, 17). Detection of micrometastases (0.2-2 mm) and isolated cancer cells in lymph node sinuses (lesions <0.2 mm) can be possible only with immunohistochemical and molecular methods. Apart from detecting SLNBs by more sensitive methods and examination of them as thin serial sections will decrease mortality and morbidity that may be caused by secondary surgery and shorten the beginning of additional therapies.

In a multicenter study conducted about oral cavity and oropharynx T1-T2 N0 cancers, SLNB method was found successful at a rate of 93% (125/134) (16). Similar results were found when SLNP alone and association of it with END were compared for diagnostic detection and sensitivities. Stoeckli (18) conducted SLNB in a T1-T2 N0 oral cavity and oropharynx study group comprising of 79 patients and performed END to patients having positive sentinel lymph node. SLNB sensitivity was found to be 98%. Recurrence was detected in two patients (6%) in a follow-up of 19 months. Therefore negative predictive value (NPV) of SLNB in this study is 94%. Mapping of lymphatic system is difficult taking into consideration that there are approximately 300 lymph nodes in the neck, there is an intensive lymphatic network and that lymph nodes are very close to cancers in head and neck region. Hence, removal of a number of lymph nodes rather than a single lymph node is recommended when SLNB is conducted. SLNB method gave an accurate result in 97% of the patients in a study in which 3 sentinel lymph nodes were removed (19). When only the first sentinel lymph node was considered a false negativity at a rate of 39% was detected. A lymph node which is full of metastatic cells may cause false negativity when it cannot be marked with radioactive material and moreover the lymph node having an impaired structure and filter function may be missed and the next lymph node can be marked. Metastases in oral cavity cancers are usually at the 1st and 2nd regions of the neck. Since front part of the tongue has direct lymphatic drainage to the 3rd region, the metastases of this region should be sought at 1., 2a, 2b and 3. sub-regions. Furthermore isolated skip metastasis can be encountered at the 4th region in the patients with oral cancer. In their studies Melkane et al. (13) encountered isolated lymph node at the 4th region only in one patient. Taking into consideration the importance of recurrence of the neck for survival of the patient, SLNB method may provide us an advantage by indicating abnormal lymphatic network and skip metastasis.

Sensitivity of sentinel lymph node biopsy method at oral cavity and oropharynx regions and NPV level falls when it is applied in floor of mouth cancer. In a study in Europe where six centers joined, it was seen that these rates fell from 97% to 80% and from 98% to 88% respectively (20). The proximity of the region where radioactive material is applied to the lymph nodes may make it difficult to detect by masking the lymph nodes. It is difficult to differentiate the sentinel lymph node from the floor of the mouth one dimensionally by gamma detector with audible warning. Therefore intraoperatively more advanced imaging techniques [fluorescence imaging, (MizuhomedicalCo Ltd.; Tokyo, Japan) and mini gamma camera (Hitachi Chemical Co. Ltd.; Tokyo, Japan)] were used 21, 22). Single photon emission computerized tomography imaging (SPECT/CT) with lymphoscintigraphy in a patient having floor of the mouth cancer was emphasized as a technique that can simultaneously display depth and radioactive distribution three-dimensionally (Surgic Eye GmbH; Munich, Germany). It was claimed that SLNB technique could reduce false negativity rate in cases with floor of the mouth cancer (23). Furthermore, masking that will take place due to proximity of lesion and lymph nodes of the neck (shine-through effect) can be reduced by excision of the lesion before scanning of the neck by gamma probe in cancers of the floor of the mouth and false negativity rates can be lowered. In the study by Kaya et al. (24) on 18 patients with oral cavity cancer, masking effect was prevented by conduction of SLNB after excision of the primary lesion and NPV and positive predictive values were found to be %100. False negativity rates in the studies are presented in Table 1.

Laryngeal Cancers

Although there are many studies in the literature investigating SLNB method in oral cavity and oropharyngeal cancers, studies

Table 1. Data obtained from sentinel lymph node biopsies in head-neck cancers

Study	Year	Region of lesion	Number of patients	True positive SLN	False negative SLN	True negative SLN
Civantos (15)	2003	Oral cavity	18	10	1	7
Werner (19)	2004	Oral cavity and oropharynx	55	12	2	41
Stárek (29)	2006	Parotid gland	6	2	1	3
Stoeckli (18)	2007	Oral cavity and oropharynx	79	29	1	48
Alkureishi (20)	2010	Oral cavity and oropharynx	134	42	4	79
Lawson (25)	2010	Larynx	29	22	0	73
Melkane (13)	2012	Oral cavity	174	42	6	118
Cabrera (27)	2015	Thyroid	23	7	3	13

SLN: sentinel lymph node

about laryngeal cancers are fewer both in number and number of cases. Therefore NPVs in these studies are usually found high. Lawson et al. (25) in their study found sensitivity of SLNB method in 29 patients having supraglottic laryngeal cancer to be 100% and NPV as 100%. In this study it is suggested that particularly the evaluation of prelaryngeal area should be made carefully. Prelaryngeal lymph node in one patient could not be detected because of its proximity to the primary lesion. However, the sensitivity of the method was not affected since another positive sentinel lymph node was detected. Nevertheless Flach et al. (26) suggested that at present SLNB is not an advantageous method due to the difficulties of detection of sentinel lymph node positivity intraoperatively. Therefore, this method can be used for mapping of the neck in approaching to the contralateral neck postoperatively. As long as reliable and sensitive methods are not used in detection of intraoperative micrometastases, SLNB method may be more appropriate in laryngeal cancers if particularly transoral laser surgery will be conducted.

Thyroid Cancers

Prophylactic neck dissection in well-differentiated thyroid cancers is still a controversial issue. SLNB method is recommended with the thought that central and lateral neck dissection will increase morbidity in N0 neck. Cabrera et al. (27) in a study of 23 cases having been detected papillary thyroid cancer, found the false negativity rate as 13%. They linked this rate to the insufficiency of radioactive material injection to each of the thyroid lobes due to multifocal lesion in the thyroid tissue and the proximity of thyroid tissue and the central neck dissection area. Additionally an association has been detected among the size of the cancer, spread outside of the thyroid, angio-lympathic spread and the number of sentinel lymph nodes. Lee et al. (28) have found that the metastasis at the rate of 30% (24/80) they detected in the lateral neck by SLNB is associated with central neck metastasis. Besides, result of SLNB and frozen section was positive and there was no statistically significant difference between the study groups having been conducted lateral neck dissection and the control group having been given postoperative radioactive iodine at the end of a follow-up of 39 months with regard to regional recurrence (28).

Parotid Salivary Gland Cancers

Even though SLNB studies regarding parotid salivary gland cancers date back to 60 years before, a fast progress could not be made in this issue. SLNB studies in the literature about parotid salivary gland are very few compared to other regions of head and neck with regard to number of cases. In a pilot study of 6 cases conducted in 2006, 2 positive sentinel lymph nodes and 1 false negative result were obtained (29). In a case of parotid mucoepidermoid carcinoma in which three-dimensional imaging and navigation was used, it was emphasized that lymphoscintigraphy was more reliable and less invasive with this new technique (30).

Skin Cancers

Sentinel lymph node biopsy is also frequently used in head and neck skin cancers. Especially MM cases metastasize to the neck at varying rates according to Breslow thickness. Accordingly, the studies performed in this area have demonstrated that SLNB is the most important prognostic factor in MM cases not having any lymph node involvement clinically (31). However there is a controversy in the literature about the use of SLNB in skin SCC cancers. Krediet et al. (32) who found diagnostic value of SLNB low, do not recommend this method and have claimed that it is sufficient to follow-up these patients closely for 3 month periods along two years.

Conclusion

The negative effects of the presence of occult metastasis in N0 necks on the prognosis of head-neck cancers and survival are clinically known and many health centers routinely use SLNB for preventing these effects. Its rate of application is increasing every day owing to its high sensitivity and safety with the existence of NPV and low mortality and morbidity compared to END. Because of insufficiencies in the detection of intraoperative sentinel lymph nodes, its sensitivity can be elevated by performing sentinel lymph node biopsies by using thinner sections and evaluating through molecular and immunohistochemical methods, rather than using conventional methods. It is suggested that the application area and rate of this technique, which is less frequently used in some regions of the head and neck such

as the floor of the mouth and the parotis, can be increased with new techniques in the future.

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References

1. Yamauchi K, Kogashiwa Y, Nakamura T, Moro Y, Nagafuji H, Kohno N. Diagnostic evaluation of sentinel lymph node biopsy in early head and neck squamous cell carcinoma: a meta-analysis. Head Neck 2015; 37: 127-33. [CrossRef]
2. Layland MK, Sessions DG, Lenox J. The influence of lymph node metastasis in the treatment of squamous cell carcinoma of the oral cavity, oropharynx, larynx, and hypopharynx: N0 versus N+. Laryngoscope 2005; 115: 629-39. [CrossRef]
3. Pillsbury HC 3rd, Clark M. A rationale for therapy of the N0 neck. Laryngoscope 1997; 107: 1294-315. [CrossRef]
4. Goudakos JK, Markou K, Nikolaou A, Themelis C, Vital V. Management of the clinically negative neck (N0) of supraglottic laryngeal carcinoma: a systematic review. Eur J Surg Oncol 2009; 35: 223-9. [CrossRef]
5. Rodrigo JP, Shah JP, Silver CE, Medina JE, Takes RP, Robbins KT. Management of the clinically negative neck in early-stage head and neck cancers after transoral resection. Head Neck 2011; 33: 1210-9. [CrossRef]
6. Hart RD, Nasser JG, Trites JR, Taylor SM, Bullock M, Barnes D. Sentinel lymph node biopsy in N0 squamous cell carcinoma of the oral cavity and oropharynx. Arch Otolaryngol Head Neck Surg 2005; 131: 34-8. [CrossRef]
7. Kowalski LP, Medina JE. Nodal metastases: predictive factors. Otolaryngol Clin North Am 1998; 31: 621-37. [CrossRef]
8. Morton DL, Wen DR, Wong JH, Economou JS, Cagle LA, Storm FK. Technical details of intraoperatively lymphatic mapping for early stage melanoma. Arch Surg 1992; 127: 392-9. [CrossRef]
9. Aliyev A, Akyıldız S, Duygun ÜA, Göde S, Uluöz Ü, Yavuzer A. Erken evre oral kavite kanserlerinde sentinel lenf nodu biyopsisi: 13 boyun diseksiyonunun sonuçları. İzmir Atatürk Eğitim Hastanesi Tıp Dergisi 2009; 47: 35-40.
10. Martínez-Gimeno C, Rodríguez EM, Vila CN, Varela CL. Squamous cell carcinoma of the oral cavity: a clinicopathologic scoring system for evaluating risk of cervically lymph node metastasis. Laryngoscope 1995; 105: 728-33. [CrossRef]
11. Civantos F Jr, Zitsch R, Bared A, Amin A. Sentinel node biopsy for squamous cell carcinoma of the head and neck. J Surg Oncol 2008; 97: 683-90. [CrossRef]
12. Civantos FJ, Zitsch RP, Schuller DE, Agrawal A, Smith RB, Nason R. et al. Sentinel lymph node biopsy accurately stages the regional lymph nodes for T1-T2 oral squamous cell carcinomas: results of a prospective multi-institutional trial. J Clin Oncol 2010; 28: 1395-400. [CrossRef]
13. Melkane AE, Mamelle G, Wycisk G, Temam S, Janot F, Casiraghi O, et al. Sentinel node biopsy in early oral squamous cell carcinomas: a 10-year experience. Laryngoscope 2012; 122: 1782-8. [CrossRef]
14. Ferris RL, Kraus DH. Sentinel lymph node biopsy versus selective neck dissection for detection of metastatic oral squamous cell carcinoma. Clin Exp Metastasis 2012; 29: 693-8. [CrossRef]
15. Civantos FJ, Gomez C, Duque C, Pedroso F, Goodwin WJ, Weed DT et al. Sentinel node biopsy in oral cavity cancer: correlation with PET scan and immunohistochemistry. Head Neck 2003; 25: 1-9. [CrossRef]
16. Ferris RL, Xi L, Seethala RR, Chan J, Desai S, Hoch B et al. Intraoperative qRT-PCR for detection of lymph node metastasis in head and neck cancer. Clin Cancer Res 2011; 17: 1858-66. [CrossRef]
17. Ferris RL, Xi L, Raja S, Hunt JL, Wang J, Gooding WE et al. Molecular staging of cervical lymph nodes in squamous cell carcinoma of the head and neck. Cancer Res 2005; 65: 2147-56. [CrossRef]
18. Stoeckli SJ. Sentinel node biopsy for oral and oropharyngeal squamous cell carcinoma of the head and neck. Laryngoscope 2007; 117: 1539-51. [CrossRef]
19. Werner JA, Dünne AA, Ramaswamy A, Dalchow C, Behr T, Moll R, et al. The sentinel node concept in head and neck cancer: solution for the controversies in the N0 neck? Head Neck 2004; 26: 603-11.
20. Alkureishi LW, Ross GL, Shoaib T, Soutar DS, Robertson AG, Thompson R, et al. Sentinel node biopsy in head and neck squamous cell cancer: 5-year follow-up of a European multi center trial. Ann Surg Oncol 2010; 17: 2459-64. [CrossRef]
21. Yamauchi K, Nagafuji H, Nakamura T, Sato T, Kohno N. Feasibility of ICG fluorescence-guided sentinel node biopsy in animal models using the Hyper Eye Medical System. Ann Surg Oncol 2011; 18: 2042-7. [CrossRef]
22. Mathelin C, Salvador S, Huss D, Guyonnet JL. Precise localization of sentinel lymph nodes and estimation of their depth using a prototype intraoperative mini gamma-camera in patients with breast cancer. J Nucl Med 2007; 48: 623-9. [CrossRef]
23. Bluemel C, Herrmann K, Müller-Richter U, Lapa C, Higuchi T, Wild V, et al. Freehand SPECT-guided sentinel lymph node biopsy in early oral squamous cell carcinoma. HeadNeck 2014; 36: E112-6.
24. Kaya İ, Gode S, Ozturk K, Turhal G, Aliyev A, Akyıldız S, et al. The value of sentinel lymph node biopsy in oral cavity cancers. Turk Arch Otorhinolaryngol 2015; 53: 62-6. [CrossRef]
25. Lawson G, Matar N, Nollevaux MC, Jamart J, Krug B, Delos M, et al. Reliability of sentinel node technique in the treatment of N0 supraglottic laryngeal cancer. Laryngoscope 2010; 120: 2213-7. [CrossRef]
26. Flach GB, Bloemena E, vanSchie A, Hoekstra OS, vanWeert S, Leemans CR, et al. Sentinel node identification in laryngeal cancer: feasible in primary cancer with previously untreated neck. Oral Oncol 2013; 49: 165-8. [CrossRef]
27. Cabrera RN, Chone CT, Zantut-Wittmann D, Matos P, Ferreira DM, Pereira PS, et al. Value of sentinel lymph node biopsy in papillary thyroid cancer: initial results of a prospective trial. Eur Arch Otorhinolaryngol 2015; 272: 971-9. [CrossRef]
28. Lee SK, Lee JH, Bae SY, Kim J, Kim M, Lee HC et al. Lateral neck sentinel lymph node biopsy in papillary thyroid carcinoma, is it really necessary? A randomized, controlled study. Surgery 2015; 157: 518-25. [CrossRef]
29. Stárek I, Koranda P, Zboøil V, Mrzena L. Sentinel lymph node biopsy in parotid gland carcinoma. Clin Nucl Med 2006; 31: 203-4. [CrossRef]
30. Schilling C, Gnanasegaran G, McGurk M. Three-dimensional imaging and navigated sentinel node biopsy for primary parotid malignancy: new application in parotid cancer management. Head Neck 2014; 36: E91-3.
31. Gershenwald JE, Thompson W, Mansfield PF, Lee JE, Colome MI, Tseng CH, et al. Multi-institutional melanoma lymphatic mapping experience: the prognostic value of sentinel lymph node status in 612 stage I or II melanoma patients. J Clin Oncol 1999; 17: 976-83.
32. Krediet JT, Beyer M, Lenz K, Ulrich C, Lange-Asschenfeldt B, Stockfleth E, et al. Sentinel lymph node biopsy and risk factors for predicting metastasis in cutaneous squamous cell carcinoma. Br J Dermatol 2015; 172: 1029-36. [CrossRef]