Precise Intraoperative Lymph Node Identification by Isosulfan Blue of Occult Neck Lymph Node Metastases for Decision to Convert from Supraomohyoid Neck Dissection to Comprehensive Neck Dissection in Early-Stage Oral Cancer

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Original Research Article

ABSTRACT

Objective: To study the sensitivity and specificity of peritumoral isosulfan blue dye injection for localization of suspected metastatic lymph nodes.
Materials and methods: The study included all patients diagnosed with early-stage oral cancer between January 2018 and March 2020. After elevation of the skin flap, the primary site was injected peritumorally with isosulfan blue 0.3-0.5 cc at 1 cm intervals and massaged. The time at which any draining nodes turned blue was recorded and the node was then excised for frozen section. After which supraomohyoid neck dissection was performed. The frozen sections were stained with H&E and analyzed for presence of metastases. Negative sections were further analyzed using immunohistochemistry stains. Sensitivity, specificity and time of identification suspected metastatic lymph node were analyzed .
Results: Nineteen patients with early-stage oral cancer were included. The majority (78.4%) presented with tongue lesions. The mean injection amount administered was 3.62±0.83 cc, and the number of injections around the tumor were 10.26±2.31. Mean duration from time of injection to the

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identification of a blue node was 19.26±15.99 min. Nodes at Level I of the neck were the most common identified as blue nodes (57.8%). Statistical analysis comparing pathological findings with blue node identification revealed this technique has a sensitivity of 71.4% with specificity of 91.7% and an overall accuracy of 84.2% in identify metastasis lymph node.

Conclusion: Isosulfan blue injection of primary oral tumors demonstrated a high level of efficiency in identifying metastatic lesions in draining lymph nodes. This technique may be helpful in deciding intraoperatively whether to convert from supraomohyoid neck dissection to comprehensive neck dissection .

Keywords: Isosulfan blue; supraomohyoid neck dissection; comprehensive neck dissection.

1. INTRODUCTION

There is controversy regarding the management of patients during surgery of clinically negative neck. These patients have an increased risk (>20%) of occult metastasis which affects overall survival. Sentinel lymph node biopsy is an alternative diagnostic method, and its rate of detection of occult disease exceeds 95%; however, this is a technically demanding procedure, as described in the NCCN guidelines [1]. Other commonly-used methods of detecting affected localized sentinel nodes include the use of radioactive dye and lymphoscintigraphy or intraoperative handheld gamma probe imaging [2,3]. However, there are typically long waiting lists in sophisticated centers that are able to perform these procedures . In provincial hospitals where the waiting times are shorter and resection of early stage oral cancer can be performed, supraomohyoid neck dissection is the standard of care for managing oral cancer patients with clinically negative neck lymph nodes.

Intraoperatively, the finding of suspicious lymph nodes in the neck which are lymph node that enlarged>15 mm with hard consistency are sent for frozen section .The pathological result is an important factor for deciding to continue supraomohyoid neck dissection or convert to comprehensive neck dissection . Sangwan in 2015 [4], reported the sentinel lymph node by isosulfan blue had a sensitivity of 40% (but specificity of 100%) due to the fact that the isosulfan blue is absorbed in 20 minutes, whereas the duration required for skin flap elevation before identification of the lymph node is about 10-15 minutes after injection. This timing makes it difficult to identify the blue nodes as the window for observation is so narrow. The author modified the timing for use of dye injection to improve the sensitivity of lymph node identification in order to intraoperatively determine whether to continue supraomohyoid neck dissection or convert to comprehensive neck dissection due to the presence of occult disease.

2. MATERIALS AND METHODS

The diagnostic study was conducted in the Center of Excellence of Otorhinolaryngology Head and Neck Surgery Rajavithi (supertertiary care) Hospital between January 2018 and March 2020 and all patients aged at least 15 years old with diagnosis of early-stage oral cancer (T1-2) were included. Early-stage cancer was defined in accordance with the guidelines of the 8th American Joint Committee on cancer (AJCC) as primary tumor size not exceeding 4 cm and depth of invasion less than 10 mm. with no clinically palpable lymph node at the neck and/or no pathognomonic lymph node identified by CT scan. Patients were excluded if they had history of neck surgery, neck radiation treatment, or allergy to dye.

Surgery commenced with Schobinger incision and elevation of the skin flap from the level of the cricoid to the mandibular area. The skin flap was repositioned, and the primary site was peritumorally infiltrated with 0.3-0.5 cc of isosulfan blue at 1 cm intervals to a maximum of 5 cc and was then massaged. At this point, the search commenced for blue nodes in the neck with elevation of the prepared skin flap. The time was recorded upon identification of a blue node which was then excised and prepared for frozen section. The waiting time for the blue node identification was recorded. The duration of waiting until 30 minutes if no blue node identification which result was recorded as "not found". Supraomohyoid neck dissection was then commenced All pathological result of lymph node from supraomohyoid neck dissection were compared to the frozen section of blue node. The frozen section was confirmed with H&E stain of permanent section and immunohistochemistry of AE1/AE3 in the case of a negative result from frozen section and H&E stain. Analysis of

sensitivity, specificity, and time of identification of blue node was performed using SPSS version 22, and a p-value <0.05 was considered statistically significant.

3. RESULTS

Nineteen patients were included, of whom 73.7% were male. Their mean age was 52.3±12.5 years, and the sites of oral cancer in this study were tongue (78.9%), floor of mouth (15.8%), and buccal mucosa (5.3%). The mean amount of isosulfan blue injected was 3.62±0.83 cc with mean number of injection sites of 10.26±2.31 and time to identification of blue nodes of 19.26±15.99 minutes, as shown in Table 1. The majority (64.7%) of lymph nodes identified were at neck level I.

The group with pathological neck lymph node metastasis from supraomohyoid neck dissection was not statistically different from the group with no metastasis in terms of gender, age, site, amount of isosulfan blue injected, number of injections, or time to identification, as displayed in Table 2; however, the results of frozen sections of blue nodes significantly correlated with the pathological report of lymph node metastasis from supraomohyoid neck dissection specimens.

Lymph node identification from blue node predictions of metastasis were analyzed, and the results are shown in Table 3. The positive predictive value was 100%, and the sensitivity and specificity were 71.4% and 91.7% respectively, as shown in Table 4.

4. DISCUSSION

Staging of neck cancer in early-stage oral cancer determines adjuvant treatment. Selective neck dissection in the neck area levels I-III/I-IV is often performed. Even though sentinel lymph node biopsy is recommended in the NCCN guidelines version 2020 [1] for early-stage management as an alternative modality to selective neck dissection , it requires high levels of expertise, materials and equipment that is available only in medical school or supertertiary hospitals . In other settings, supraomohyoid neck dissection is the treatment of choice for head and neck surgeons treating clinically negative neck lymph node metastasis in oral cancer. Supraomohyoid neck dissection carries a recurrence rate of 5.4% in the pN0 neck, 16.6 % in the p N+ neck [2] The comprehensive neck dissection is the gold standard of treatment for positive neck so it is a common practice of head and neck surgeons

during selective neck dissection to reassess nodes intraoperatively by direct palpation and inspection. Suspected nodes are sent for histological assessment by frozen section. If results are positive, the operation is converted to comprehensive neck dissection. But the intraoperative assessment of lymph nodes appropriate for frozen section is the problem. Fin [5,6] report accuracy of intraoperative node assessment for metastasis of head and neck cancer has a sensitivity of only 56% and specificity of 70%, which is of questionable the benefit, raising concerns regarding the intraoperative selection of nodes for histological examination for determination of whether to conduct a selective or comprehensive neck dissection.

Dye injection was previously reported for detection sentinel lymph nodes. The detection rates of colored dye injection reported for localization have been found to vary from 10-92.3% [7-9] with sensitivity of 40-87.5%, and NPV of 77-98% [4,7-9] with no false positives in any case (specificity of 100%). The procedure can be executed from start to finish in the operating room; is available for use in oncological surgery general practice such as in breast cancer and melanoma. Sangwan [4] reported of isosulfan blue injection for sentinel lymph node and discussed the duration of skin flap elevation and the time required for transit from the injection site to the sentinel node. It was proposed that the dye be injected before skin flap elevation, as the lymph node may lose its color due to systemic absorption after approximately 20 minutes. Recently Vishnoi [10] reported of prospective study outcome of sentinel lymph node biopsy in early-stage squamous cell carcinoma of the oral cavity with methylene blue dye alone and found detection rate of 84.6% with PPV 100% and NPV 93.9% . The distribution of sentinel lymph node reported in the area of IA, IB, IIA and III. Also Elshamaa MM [11] reported sentinel lymph node in oral cancer by methylene blue which found detection rate of 75% . Compare to this study, a modified technique of isosulfan blue injection was evaluated as a means to improve detection rate and the timing of blue node detection. The skin flap was elevated before injecting the dye and the number of peritumoral injections were increased. The overall maximum volume of isosulfan blue was no more than 5 cc, and a detection rate of 89.4% (17/19) was achieved. Confirmation of frozen section in the sentinel node by H&E stain and immunohistochemistry

Table 1. The characteristics of data collection

Factor	n (%)
Gender	
Male	14 (73.7)
Female	5 (26.3)
Age (mean±S.D.)	52.32±12.55
Site	
Tongue	15 (78.9)
FOM	3 (15.8)
Buccal	1 (5.3)
Comorbid	
No	9 (47.4)
Yes	10 (52.6)
Isosulfan (cc) (mean±S.D.)	3.62±0.83
No. injections (mean±S.D.)	10.26±2.31
Time to identification (mean±S.D.)	19.26±15.99
Neck level at which blue node was identified	
Level I	11 (64.7)
Level II	6 (35.3)

Values are presented as number (percent), mean±SD

Table 2. Comparison of characteristics of lymph node metastasis with no lymph node metastasis from pathological examination of supraomohyoid neck dissection specimens

Factor	Lymph nodes from supraomohyoid neck dissection		p-value
	Metastasis (pathological report) n (%)	No Metastasis (pathological report) n (%)	
Gender			1.000^F
Male	5 (35.7)	9 (64.3)	
Female	2 (40.0)	3 (60.0)	
Age (mean±S.D.)	49.14±9.1	54.17±14.19	0.415^T
Site			0.217^F
Tongue	6 (40.0)	9 (60.0)	
FOM	0 (0.0)	3 (100.0)	
Buccal	1 (100.0)	0 (0.0)	

Factor	Lymph nodes from supraomohyoid neck dissection		p-value
	Metastasis (pathological report) n (%)	No Metastasis (pathological report) n (%)	
Neck level of Blue node identification			0.600[F]
Level I	3 (27.3)	8 (72.7)	
Level II	3 (50.0)	3 (50.0)	
Comorbidity			0.650[F]
No	4 (44.4)	5 (55.6)	
Yes	3 (30.0)	7 (70.0)	
Isosulfan (cc) (mean±S.D.)	3.41±1.19	3.73±0.58	0.524[T]
No. injections (mean±S.D.)	10.00±1.63	10.42±2.68	0.715[T]
Time to identification (mean±S.D.)	15.29±16.73	21.58±15.80	0.423[T]
Frozen section result of blue nodes			<0.001*[F]
Positive for malignancy	5	0	
Negative for malignancy	1	11	

*Values are presented as number (percent), mean±SD; *= statistically significant at p-value<0.05; F= A p-value from Fisher's exact test; T=A p-value from independent t-test*

Table 3. Comparison of number of patients: Frozen section report with metastasis /no metastasis by the identified blue node to all lymph node from supraomohyoid neck dissection specimen

Report of Identified blue node by frozen section	Pathological report of lymph node metastasis from supraomohyoid neck dissection		Total
	Metastasis	No Metastasis	
	n	n	
Positive for metastasis	5	0	5
Negative for metastasis	1	11	12
Not found	1	1	2

Table 4. Analysis of sensitivity and specificity of isosulfan blue in prediction of lymph node metastasis

Parameter	Result
Detection Rate	89.4 %
Sensitivity	71.4 %
Specificity	91.7 %
Accuracy	84.2 %
Positive Predictive Value (PPV)	100.0 %
Negative Predictive Value (NPV)	91.7 %

revealed a false negative in 1 case (sensitivity of 71.4% and specificity of 91.7%). All subjects has at least supraomohyoid neck dissection, so the false negative result of the frozen section provided accurate staging for use in determining adjuvant treatment.

Compared to sentinel node biopsy,which meta-analysis of high sensitivity and specificity [12,13] but required complexity of preoperative preparation and intraoperative procedures such as lymphangiography, gamma probe, single-photon emission computed tomography (CT) which no available in provincial hospitals where early stage oral cancer can be performed, the modified procedure for using intraoperative dye as a method for determining whether to end operation or proceed with comprehensive neck dissection holds promise . For the sentinel node negative, there are no further information of the other lymph nodes. Rigual et al [5] reported a 6 % recurrence rate in sentinel node negative patients. The author therefore proposed dye injection for selection of lymph node for frozen section in order to determine whether to continue supraomohyoid neck dissection or convert to comprehensive neck dissection based on the evidences from the blue nodes which directly drain from primary tumor.

A limitation of this study was its small number of early-stage patients. Further studies are needed in order to determine the benefit of this modified dye injection procedure. Upon confirmation, this technique may provide a new guide for management of negative neck of early stage oral cancer.

5. CONCLUSION

Isosulfan blue injection after elevation of skin flap and multiple peritumoral injection is highly efficient in identification of directly drainage lymph nodes from primary tumor. In practice, it is a feasible option for indicating whether selective or comprehensive neck dissection should be performed.

CONSENT AND ETHICAL APPROVAL

The study approved by Rajavithi Hospital research ethics committee and Informed consent was obtained from patients.

COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES

1. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology Head and Neck Cancers version 2;2020.
2. Nawaz AKK, Nazriya R. Reliability of sentinel lymph node biopsy in head and neck squamous cell carcinoma. International Journal of Otorhinolaryngology and Head and Neck Surgery. 2016;2(2):105-109.
3. Civantos FJ, Werner JA, Bared A. Sentinel biopsy in cancer of oral cavity. Operative Techniques in Otolaryngology. 2005;16:275-85.
4. Sangwan P, Nilakanta A, Patnalk U, Mishra A, Sethi A. Sentinel lymph node localization using 1% isosulfan blue dye in cases of early oral cavity and oropharyngeal squamous cell Carcinoma. Indian J otolaryngol Head Neck Surg. 67 (suppl 1):S56-S61.
5. Rigual N, Loree T, Frustino J, Jayaprakash V, Cohan D, Sullivan M, Kuriakose M.A. Sentinel Node Biopsy in Lieu of Neck Dissection for Staging Oral Cancer . JAMA Otolaryngology Head and Neck Surg 2013;139:779-782
6. Finn S, Toner M, Timon C. The node-negative neck: accuracy of clinical intraoperative lymph node assessment for metastatic disease in head and neck cancer. Laryngoscope. 2002;112(4):630–633.
7. Minamikawa T, Umeda M, Komori T. Reliability of sentinel lymph node biopsy with squamous cell carcinoma of the oral

cavity. Oral Surgery Oral Medicine Oral Pathology Oral Radiology and Endodontics.2005;99(5):532±8.

8. Ramamurthy R, Kottayasamy Seenivasagam R, Shanmugam S, Palanivelu K. A prospective study on sentinel lymph node biopsy in early oral cancers using methylene blue dye alone. Indian journal of surgical oncology. 2014;5(3):178±83

9. Vishnoi JR, Kumar V, Gupta S, Agrawal P, Jamal N, Misra S, et al. Sentinel lymph node biopsy in early oral cancer using methylene blue dye alone: A tertiary care cancer centre experience from india. Eur J Cancer. 2015;51:S573±S4.

10. Vishnoi JR, Kumar V, Gupta S, Chaturvedi A, Misra S, Akhtar N, et al. Outcome of sentinel lymph node biopsy in early-stage squamous cell carcinoma of the oral cavity

with methylene blue dye alone: A prospective validation study. British Journal of Oral and Maxillofacial Surgery 2019;57:755–759

11. Elshamaa MM, Fata MM, Swaify GA, Hegab SS, Tayel HY .Sentinel Lymph node biopsy as a prognostic tool in early oral cancer using methylene blue dye. Alexandria Dental Journal;2020.

12. Kim DH, Kim Y, Kim SW, Hwang SH. Usefulness of Sentinel Lymph Node Biopsy for Oral Cancer:A Systematic Review and Meta-Analysis. Laryngoscope, 2021;131:E459–E465.

13. Govers TM, Hannink G, Merkx M AW., Takes RP, Rovers M. Sentinel node biopsy for squamous cell carcinoma of the oral cavity and oropharynx : A diagnostic meta-analysis . Oral Oncology. 2013;49:726-732.