Original Article

ผลการรักษาต่อมน้ำเหลืองระยะก่อนตรวจพบในผู้ป่วยมะเร็งช่องปากระยะก่อนลุกลามที่ได้รับการผ่าตัดเลาะต่อมน้ำเหลืองที่คอ รังสีรักษา หรือการเฝ้าระวัง

กิตติ จันทรพัฒนา[1]*
มนุพล ตั้งทองคำ[1]
หัชชา ศรีปลั่ง[2]
วิทูร ลีลามานิตย์[1]

Oncologic Outcomes of Clinical No in Early Stage Oral Cancer Undergoing Elective Neck Dissection, Radiation, or Observation.

Kitti Jantharapattana[1], Manupol Tangthongkum[1], Hutcha Sriplung[2], Vitoon Leelamanit[1]
[1]Department of Otolaryngology Head and Neck Surgery, [2]Epidemiology Unit,
Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla, 90110, Thailand.
***E-mail: kittient@hotmail.com**
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บทคัดย่อ:

วัตถุประสงค์: การผ่าตัด รังสีรักษา และการเฝ้าระวังล้วนเป็นวิธีการรักษาต่อมน้ำเหลืองระยะก่อนตรวจพบที่ใช้กันอยู่ในปัจจุบัน อย่างไรก็ตามยังไม่เป็นที่แน่ชัดว่าวิธีใดให้ผลการรักษาที่ดีกว่า ดังนั้นจึงทำการศึกษาเปรียบเทียบผลการรักษาต่อมน้ำเหลืองระยะก่อนตรวจพบในผู้ป่วยมะเร็งช่องปากระยะก่อนลุกลามด้วยการผ่าตัดเลาะต่อมน้ำเหลืองที่คอ รังสีรักษา หรือการเฝ้าระวัง

วัสดุและวิธีการ: ศึกษาย้อนหลังผู้ป่วยมะเร็งช่องปากระยะก่อนลุกลามจำนวน 236 ราย จากฐานข้อมูลผู้ป่วยมะเร็งศีรษะและลำคอ ภาควิชาโสต ศอ นาสิกวิทยา และแฟ้มประวัติผู้ป่วยของโรงพยาบาลสงขลานครินทร์

This study was presented at the 5th European Conference on Head and Neck Oncology
[1]ภาควิชาโสต ศอ นาสิกวิทยา [2]หน่วยระบาดวิทยา คณะแพทยศาสตร์ มหาวิทยาลัยสงขลานครินทร์ อ.หาดใหญ่ จ.สงขลา 90110
รับต้นฉบับวันที่ 2 พฤศจิกายน 2555 รับลงตีพิมพ์วันที่ 20 มกราคม 2556

โดยแบ่งผู้ป่วยเป็น 3 กลุ่มตามวิธีการรักษาต่อมน้ำเหลืองระยะก่อนตรวจพบ หลังจากนั้นติดตามผลการรักษาภายในระยะเวลา 5 ปี

ผลการศึกษา: อัตราการรอดชีวิตโดยรวมที่ 5 ปี ของกลุ่มผ่าตัด รังสีรักษา และการเฝ้าระวัง เท่ากับร้อยละ 77.7 58.8 และ 76.5 ตามลำดับ (p=0.197) อัตราการรอดชีวิตเฉพาะโรคที่ 5 ปี ของกลุ่มผ่าตัด รังสีรักษา และการเฝ้าระวัง เท่ากับร้อยละ 77.7 70.3 และ 80.9 ตามลำดับ (p=0.339) อัตราการปลอดโรคบริเวณต่อมน้ำเหลืองที่ 5 ปี ของกลุ่มผ่าตัด รังสีรักษา และการเฝ้าระวัง เท่ากับร้อยละ 84.6 79.4 และ 61.3 ตามลำดับ (p=0.062) อัตราการแพร่กระจายของโรคไปยังต่อมน้ำเหลืองที่คอ ระยะก่อนตรวจพบเท่ากับร้อยละ 24.4 โดยพบในระยะ T1 ร้อยละ 15.38 และพบในระยะ T2 ร้อยละ 28.57

สรุป: ผลการรักษาต่อมน้ำเหลืองระยะก่อนตรวจพบในผู้ป่วยมะเร็งช่องปากระยะก่อนลุกลาม ด้วยการผ่าตัดเลาะต่อมน้ำเหลืองที่คอ รังสีรักษา หรือการเฝ้าระวังมีความแตกต่างกันอย่างไม่มีนัยสำคัญทางสถิติ

คำสำคัญ: การผ่าตัดเลาะต่อมน้ำเหลืองที่คอ, การเฝ้าระวัง, ต่อมน้ำเหลืองระยะก่อนตรวจพบ, มะเร็งช่องปาก, รังสีรักษา

Abstract:

Objective: Surgery, radiation, and observation are the practical N0 neck management. Among these modalities, the most promising management has not been concluded yet. We aimed to evaluate oncologic outcomes comparing among the modalities in clinically N0 early stage oral cancer.

Material and Method: Clinicopathological data of 236 patients, who were diagnosed as T1 or T2, N0 squamous cell carcinoma of the oral cavity, were retrospectively reviewed. The eligible patients were classified into three groups regarding to the neck management whether elective neck dissection, elective neck radiation, or observation. Oncologic outcomes were evaluated at 5 years.

Results: Five-year overall survival rates were 77.7% for neck dissection group, 58.8% for the radiation group and 76.5 % for the observation group (p=0.197). Five-year disease specific survival rates for the same three groups were 77.7%, 70.3% and 80.9%, respectively (p=0.339), while the 5-year regional disease free survival rates were 84.6%, 79.4% and 61.3% (p=0.062), respectively. The occult regional metastasis rate was 24.4%. In subgroup analysis regarding to T stage, the occult regional metastasis rate of T1 stage was 15.38 %, and the occult regional metastasis rate of T2 stage was 28.57%.

Conclusion: The differences of oncologic outcomes of clinical N0 in early stage oral cancer undergoing elective neck dissection, radiation, and observation are not statistically significant.

Keywords: clinical N0, elective neck dissection, elective neck radiation, observation, oral cancer

Introduction

Oral cancer is the sixth leading cancer worldwide.[1] Incidence rates of oral cancer vary in men from 1-10 per 100,000 population throughout the world. In 2009, new oral cancer patient in US estimated 23,000 cases and it caused 5,300 deaths.[2] In South Central Asia, cancer of the oral cavity ranks among the three most common sites of cancer. In India, the age standardized incidence rate (ASR) of oral cancer is 12.6 per 100,000 population. In our area of study, Songkhla province, southern Thailand, the incidence of oral cancer in male is relatively high compared to other region in the country and the ASR was 10.7 per 100,000 population.[3,4]

One of the most important issues of oral cancer treatment is the relatively high rate of lymph node metastasis compared to other head and neck cancers. Occult regional metastasis is frequently found even in cases with small primary tumor. The incidence of occult lymph node metastasis from early stage oral cancer varies from 20.4 to 42%.[5-9]

In oral cancer, cervical lymph node metastasis is a significant factor to determine treatment outcomes. Many studies have demonstrated the association of recurrent disease and distant metastasis with cervical lymph node metastasis.[10,11] Cervical lymph node metastasis is considered as an essential prognostic factor to predict the survival of oral cancer patients. The more cervical lymph node metastasis tends to be the worse survival outcome.[10,11]

Regarding to a significant study, the decision analysis study in planning management of the stage No neck, the findings recommended to consider neck management if the rate of occult metastasis is more than 20%.[12] The threshold of treatment is implemented to consider management of clinical No head and neck cancer.

There are different modalities of the stage No neck management. Elective neck dissection, elective neck radiation, and observation are the commonly practiced procedures. However, among these three modalities, the most promising management for the stage No neck oral cancer is not concluded yet.

Some previous studies failed to show statistically significant differences in survival between patients received elective neck treatment and observation.[13-15] A number of studies, however, found a significant survival benefit in patients underwent the elective neck treatment.[6,16-18] In terms of effectiveness of treatment modality, a retrospective study comparing elective neck dissection with elective neck radiation showed that there was no statistically significant difference of both modalities to control of subclinical nodal metastasis.[19]

Until now, there is no a directly comparative study among elective neck dissection, elective neck radiation, and observation in the specific group as stage I/II oral squamous cell carcinoma. The aim of this study is to evaluate oncologic outcomes comparing among elective neck dissection, radiation and observation in clinically No early stage oral cancer.

Material and Method

The Ethic Committee at Faculty of Medicine, Prince of Songkla University approved the study protocol. Clinicopathological data of 236 patients

who were diagnosed as squamous cell carcinoma of the oral cavity at the Department of Otolaryngology Head and Neck Surgery, Prince of Songkla University between January 1992 and June 2010 were reviewed.

All patients were defined as stage T1 (tumor is 2 cm or less in greatest dimension) or T2 (tumor is more than 2 cm but 4 cm or less in greatest dimension) N0 by physical examination and/or imaging documentation (ultrasonography or computed tomography) at time of receiving treatment for the primary tumor. Aim of treatment was curative intent. The treatment modality for primary tumor eradication was surgery and/or radiation and the treatment modality for the neck was surgery, radiation, or observation. The decision on the treatment resulted on the multidisciplinary tumor board recommendation which was on the principle of early stage oral cancer treatment. For the primary tumor, a single primary treatment modality either surgery or radiation was offered to the individual patient regarding to patient's medical condition, performance status and risks of general anesthesia. If there was an adverse result of the primary treatment, such as incomplete resection of the primary tumor, the appropriate adjuvant treatment was administrated. For the neck management, the patient who received radiotherapy at the primary tumor also received elective neck radiation. The patient who underwent surgery at the primary tumor received either elective neck dissection or observation.

The eligible patients were classified into three groups regarding to the neck management, whether elective neck dissection, elective neck radiation, or observation. The elective neck dissection group had received selective, modified, or radical neck dissection. The dissected cervical lymph nodes included at least level I to III or IV. The elective neck radiation group had undergone external beam radiation at neck with the conventional technique. The irradiated area at neck included at least ipsilateral level I to V. The observation group had not had any treatment at the neck, yet received careful tumor surveillance once a month in the first year, then every two months in the second year, then every three months in the third year, and then every six months until to 5 years or so. Physical examination and/or radiologic investigation were periodically performed to detect emerging disease. If the recurrent disease was found, the appropriate salvage treatment was offered to the curable patients.

Clinical follow-up data with at least of 24 months post treatment until death was included in the study. The study period of each patient was during the date of clinical diagnosis and the date of last examination. The medical record was reviewed in details of disease recurrences and survival. Three groups of study were directly compared with respect to overall survival, disease specific survival and regional disease free survival. The incidence of occult metastasis at neck node was analyzed from histopathology of neck dissection specimens in the elective neck dissection group.

Descriptive statistics were described in frequency and percentage or median and range. Kaplan-Meier curve was used to describe survival probability of cancer cases by various variables. The probability of survival at 5 year and its 95% confidence interval were calculated using standard Kaplan-Meier estimate. Statistical test p-values for difference in survival curve were obtained by

the method described by Harrington and Fleming (1982).[20] All statistical methods were performed using R statistical software version 2.13.0.[21]

Results

Two hundred thirty six patients were eligible for this study. One hundred thirty three patients were male and 103 patients were female. Median age of patients was 64 years (range 24-88 years). The primary tumor was staged as follows: T1 stage was 114 (48.3%) patients and T2 stage was 122 (51.7%) patients. Subsites distribution of primary tumor and details of population are shown in Table 1.

The eligible patients received primary tumor eradication as surgery (n=109), radiation (n=60), or surgery with radiation (n=67). For the neck management, 41 patients received elective neck dissection, 127 patients received elective neck radiation and 68 patients underwent observation.

Table 1 Characteristics of study subjects by neck management group

Characteristics	Elective neck dissection	Elective neck radiation	Observation	Total
Gender				
Male	24	79	30	133
Female	17	48	38	103
Age				
Median (Range)	53 (24-86)	63 (28-88)	68 (29-86)	64 (24-88)
T stage				
T1	13 (31.7%)	45 (35.4%)	56 (82.4%)	114 (48.3%)
T2	28 (68.3%)	82 (64.6%)	12 (17.6%)	122 (51.7%)
Subsites				
Oral tongue	32	72	24	128
Floor of mouth	5	27	11	43
Buccal mucosa	3	12	6	21
Upper gingiva	0	1	0	1
Lower gingiva	1	4	6	11
Upper lip	0	0	1	1
Lower lip	0	2	11	13
Hard palate	0	6	8	14
Retromolar trigone	0	3	1	4
Primary tumor treatment				
Surgery	41	0	68	109
Radiation	0	60	0	60
Surgery and radiation	0	67	0	67

In elective neck dissection group, all 41 patients had definitive surgery at the primary tumor. All patients underwent ipsilateral neck dissection. Three patients underwent bilateral neck dissection. Selective neck dissection was performed in 37 patients, modified radical neck dissection was performed in two patients, and radical neck dissection was performed in two patients. Thirteen patients (31.7%) were T1 stage and 28 patients (68.3%) were T2 stage.

In elective neck radiation group, 60 patients received definitive radiation and 67 patients received surgery with radiation at the primary tumor. One hundred twenty-five (98.4%) patients received radiation dosage 50-70 Gy. Forty-five patients (35.4%) were T1 stage and 82 patients (64.6%) were T2 stage.

In observation group, all 68 patients underwent definitive surgery at primary tumor then careful head and neck examination were followed as the previously described schedule. Fifty-six (82.4%) patients were T1 stage and 12 patients (17.6%) were T2 stage.

Comparison of the outcomes among three studied groups is demonstrated as Kaplan-Meier survival curves. Five-year overall survival of observation, elective neck radiation, and elective neck dissection group were 76.5% (95% confidence interval; CI, 63.5-92.2), 58.8% (95%CI, 49.4-70.0), and 77.7% (95%CI, 63.3-95.4) respectively. The difference was not statistically significant (p=0.197). Figure 1

Five-year disease specific survival of observation, elective neck radiation, and elective neck dissection group were 80.9% (95%CI, 67.9-96.4), 70.3% (95%CI, 61.3-80.5), and 77.7% (95%CI, 63.3-95.4) respectively. The difference in disease specific survival was not statistically significant (p=0.339). Figure 2

Five-year regional disease free survival of observation, elective neck radiation, and elective neck dissection group were 61.3% (95%CI, 48.6-77.4), 79.4% (95%CI, 71.3-88.4), and 84.6% (95% CI, 72.8-98.3) respectively. Again, the difference in regional disease free survival was not statistically significant (p=0.062). Figure 3

During the follow up period, regional disease free interval was observed in each group. Median regional disease free interval was 3 months (range 1-13 months) in the radiation group, 5 months (range 2-21 months) in the surgery group, and 9 months (range 1-24 months) in the observation group.

Over the period of study, 54 patients had relapse at the primary site. According to modality of the primary tumor eradication, 23 patients received definitive radiation, 13 patients received definitive surgery, and 18 patients received surgery and radiation. Thirty-four patients developed regional failure and 8 patients had locoregional failure (Table 2). Salvage neck treatment; such as surgery, radiation, or chemoradiation was given in 31 patients depend on the previously received treatment and patients' physical condition. Twenty-three patients underwent salvage neck dissection. Eight patients underwent salvage neck radiation or chemoradiation. The others received palliative care. The results of salvage treatment were unsatisfactory. Of the 31 patients who received salvage treatment, only 10 patients survived without of evidence of disease at last contact.

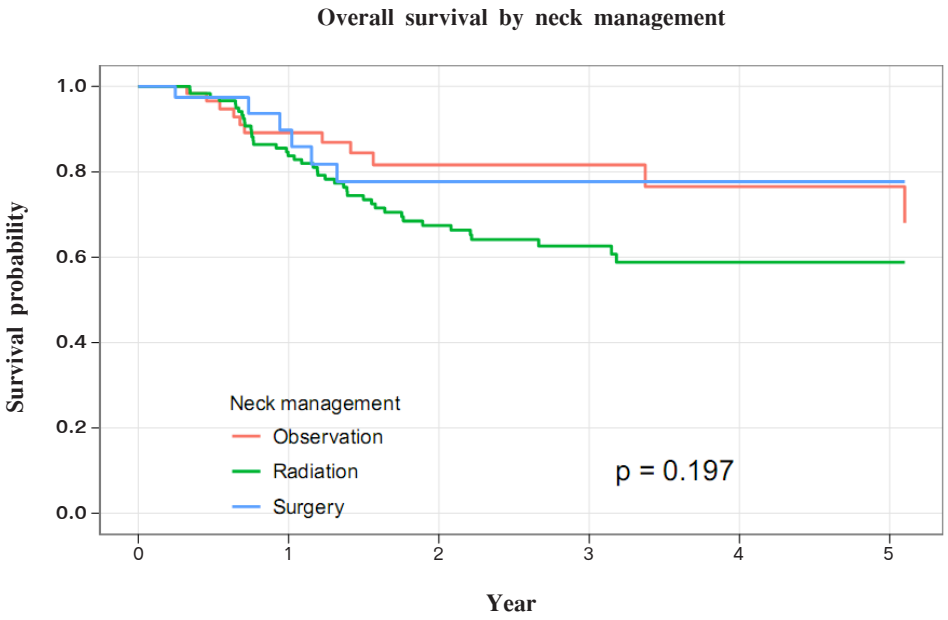

Figure 1 Overall survival of the early stage oral cancer, comparison among surgery, radiation, or observation

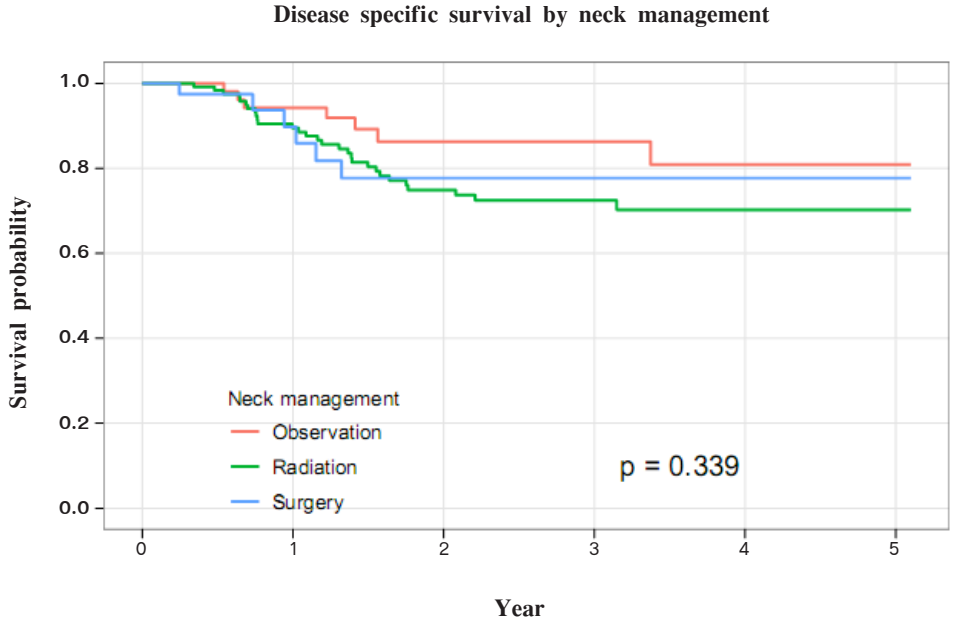

Figure 2 Disease specific survival of the early stage oral cancer, comparison among surgery, radiation, or observation

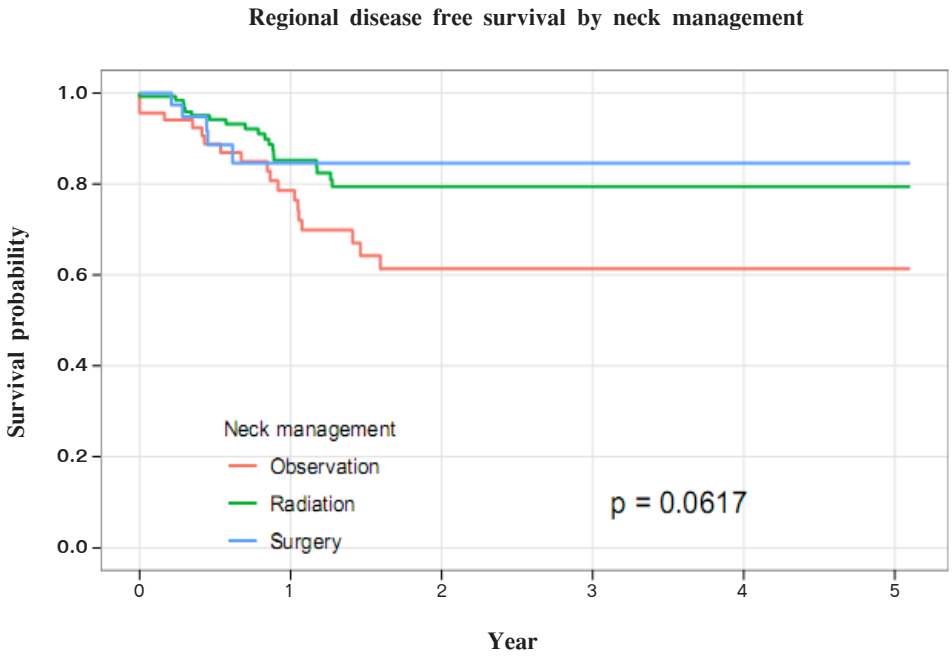

Figure 3 Regional disease free survival of the early stage oral cancer, comparison among surgery, radiation, or observation

Table 2 Locoregional recurrence subjects by primary tumor treatment

Site of recurrence	Primary tumor treatment (%)			
	Surgery	Radiation	Surgery and radiation	Total
Local	13	23	18	54
Regional	20	2	12	34
Locoregional	3	5	0	8

Histopathologic examination of 41 neck dissection specimens revealed regional metastatic disease in 10 patients. The calculated occult regional metastasis rate was 24.4% (10/41). In subgroup analysis regarding to T stage, the calculated occult regional metastasis rate of T1 stage was 15.38% (2/13), and the calculated occult regional metastasis rate of T2 stage was 28.57% (8/28). Of the positive metastatic neck patients, seven patients had one metastatic node, one patient had two metastatic nodes, a patient had three metastatic nodes, and a patient had five metastatic nodes. Adjuvant radiation treatment was given in five patients and adjuvant chemoradiation was given in one patient.

Discussion

Our results demonstrate that the differences of overall and disease specific survival among elective neck dissection, elective neck radiation, or observation are not statistically significant. At 5 year follow up period: overall survival of elective radiation group was 58.8%, elective neck dissection group was 77.7%, and observation group was 76.5%; disease specific survival of elective radiation group was 70.3%, elective neck dissection group was 77.7%, and observation group was 80.9%. However, the results indicate the relatively higher overall survival of the surgery group. This would result of the younger age patients in the surgery group compared to the others. Median age of patients in surgery group was 53 years whereas the radiation and observation group had median age of 63 and 68 years respectively. Over 10 years younger age is a significant factor to determine the better overall survival in surgery group. The results, moreover, suggest the relatively better disease specific survival of the observation group. This finding would result of the more advanced T stage patients in surgery and radiation group. The number of T2 stage patients received elective neck dissection and elective neck radiation were 68.3% and 64.6%, respectively. Whereas the number of T2 stage patients received observation was only 17.6%. The disproportion of stage population could be a factor to determine the different disease specific survival. To eliminate the uncontrolled confounders commonly found in a retrospective study, a prospective controlled study is needed.

In terms of regional recurrence, again there is no statistically significant difference among elective neck dissection, elective neck radiation, or observation in controlling subclinical metastasis of oral cancer over a 5-year follow up period. Regional disease free survival of elective neck radiation, elective neck dissection, and observation group were 79.4%, 84.6%, and 61.3% respectively. Nonetheless, our results demonstrate a trend toward better regional control in patients managed by elective neck dissection. This finding would result of the relatively higher local control of the patients treated primary tumor with surgery. In our series, 16 in 109 (14.67%) patients who received definitive surgery at primary site developed local recurrence. Moreover, a number of patients in the surgery group received postoperative adjuvant treatment such as radiation or chemoradiation, if the adverse pathological result of the dissected neck is revealed. Therefore the emergence of recurrence is relatively less in the surgery group.

In our series, the results of salvage neck treatment were unsatisfactory. Over the period of study, 42 patients developed regional failure. Salvage neck treatment; such as surgery, radiation, or chemoradiation was given in 31 patients depend on the previously received treatment and patient conditions. Twenty-three patients underwent salvage neck dissection. Eight patients underwent salvage neck radiation or chemoradiation. Of the 31 patients who received salvage neck treatment, only 10 patients survived without of evidence of disease at last contact. Poor salvage rate has been reported in previous studies as well.[8,13,22]

The prevalence of occult lymph node metastasis in early stage oral cancer reported in the former studies varies from 20.4 to 42%.[5-8] Our study shows the rate of occult neck node metastasis was 24.4%. Subgroup analysis showed that

the rate of occult neck node metastasis were 15.38% in T1 stage and 28.57% in T2 stage. These numbers are comparable to the previous literatures. We also found that over 75% of elective neck dissection was negative for metastatic regional disease. This indicates that elective neck dissection might be an undue treatment for the patients without occult lymph node metastasis. The more predictable strategies, such as tumor thickness evaluation, sentinel lymph node biopsy, and molecular analysis, would be the keys to select the right patient to receive the right treatment.

Histopathologic thickness evaluation is an option to indicate the patients at greatest risk for metastatic disease. Many studies have published that tumor thickness exceeds 4 mm are associated with the high proportion of occult neck metastasis.[23-25] It is sensible to treat clinically negative neck in patients with more than 4 mm thick tumor.

Sentinel lymph node biopsy has been an important role in treatment of breast cancer and melanoma so far. Currently it becomes an acceptable option for head and neck cancer. Rationale of sentinel lymph node biopsy for the management of the cN0 neck is to lessen the morbidity associated with the traditional modified radical neck dissection. Recently many studies published about using sentinel lymph node biopsy in oral cancer. The results suggested that sentinel node biopsy correctly predicts a pathological negative neck in high proportion of patients.[26]

Nowadays molecular analysis is widely used for determination of cancer treatment. The increasing focus on the investigation of molecular markers will enhance cervical lymph node metastasis prediction. Recent studies report that using complementary deoxyribonucleic acid (cDNA) microarray analysis to determine the presence of lymph node metastasis at the time of diagnosis.[27,28] Further development of the biological investigations would provide the means of anticipation for cervical lymph node metastases.

Conclusion

In conclusion, our results indicate that the oncologic outcomes of clinically No in early stage oral cancer are not significantly different among the common treatment modalities. Loco-regional control tends to be superior in the patients who received surgery.

References

1. Mahboubi E. The epidemiology of oral cavity, pharyngeal and esophageal cancer outside of North America and Western Europe. Cancer 1977; 40: 1879 - 86.
2. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2009. CA Cancer J Clin 2009; 59: 225 - 49.
3. Thongsuksai P, Sriplung H, Phungrassami T, et al. Cancer incidence in Songkhla, southern Thailand, 1990-1994. Southeast Asian J Trop Med Public Health 1997; 28 (Suppl 3): 1 - 10.
4. Sriplung H, Sontipong S, Martin N, et al. Cancer incidence in Thailand, 1995-1997. Asian Pac J Cancer Prev 2005; 6: 276 - 81.
5. Yuen AP, Lam KY, Chan AC, et al. Clinicopathological analysis of elective neck dissection for No neck of early oral tongue carcinoma. Am J Surg 1999; 177: 90 - 2.
6. Lydiatt DD, Robbins KT, Byers RM, et al. Treatment of stage I and II oral tongue cancer. Head Neck 1993; 15: 308 - 12.
7. Ho CM, Lam KH, Wei WI, et al. Occult lymph node metastasis in small oral tongue cancers. Head Neck 1992; 14: 359 - 63.

8. Teichgraeber JF, Clairmont AA. The incidence of occult metastases for cancer of the oral tongue and floor of the mouth: treatment rationale. Head Neck Surg 1984; 7: 15 - 21.
9. Spiro RH, Huvos AG, Wong GY, et al. Predictive value of tumor thickness in squamous carcinoma confined to the tongue and floor of the mouth. Am J Surg 1986; 152: 345 - 50.
10. Jones AS. Prognosis in mouth cancer: tumour factors. Eur J Cancer B Oral Oncol 1994; 30B: 8 - 15.
11. Mamelle G, Pampurik J, Luboinski B, et al. Lymph node prognostic factors in head and neck squamous cell carcinomas. Am J Surg 1994; 168: 494 - 8.
12. Weiss MH, Harrison LB, Isaacs RS. Use of decision analysis in planning a management strategy for the stage N0 neck. Arch Otolaryngol Head Neck Surg 1994; 120: 699 - 702.
13. Yii NW, Patel SG, Rhys-Evans PH, et al. Management of the N0 neck in early cancer of the oral tongue. Clin Otolaryngol Allied Sci 1999; 24: 75 - 9.
14. Yuen AP, Ho CM, Chow TL, et al. Prospective randomized study of selective neck dissection versus observation for N0 neck of early tongue carcinoma. Head Neck 2009; 31: 765 - 72.
15. D'Cruz AK, Siddachari RC, Walvekar RR, et al. Elective neck dissection for the management of the N0 neck in early cancer of the oral tongue: need for a randomized controlled trial. Head Neck 2009; 31: 618 - 24.
16. Dias FL, Kligerman J, Matos de Sa G, et al. Elective neck dissection versus observation in stage I squamous cell carcinomas of the tongue and floor of the mouth. Otolaryngol Head Neck Surg 2001; 125: 23 - 9.
17. Capote A, Escorial V, Munoz-Guerra MF, et al. Elective neck dissection in early-stage oral squamous cell carcinoma--does it influence recurrence and survival? Head Neck 2007; 29: 3 - 11.
18. Yuen AP, Wei WI, Wong YM, et al. Elective neck dissection versus observation in the treatment of early oral tongue carcinoma. Head Neck 1997; 19: 583 - 8.
19. Chow JM, Levin BC, Krivit JS, et al. Radiotherapy or surgery for subclinical cervical node metastases. Arch Otolaryngol Head Neck Surg 1989; 115: 981 - 4.
20. Harrington DP, Fleming TR. A class of rank test procedures for censored survival data. Biometrika 1982; 69: 553 - 66.
21. Team RDC. R: a language and environment for statistical computing. Vienna: R Foundation for Statistical Computing; 2011.
22. Keski-Santti H, Atula T, Tornwall J, et al. Elective neck treatment versus observation in patients with T1/T2 N0 squamous cell carcinoma of oral tongue. Oral Oncol 2006; 42: 96 - 101.
23. Kurokawa H, Yamashita Y, Takeda S, et al. Risk factors for late cervical lymph node metastases in patients with stage I or II carcinoma of the tongue. Head Neck 2002; 24: 731 - 6.
24. Asakage T, Yokose T, Mukai K, et al. Tumor thickness predicts cervical metastasis in patients with stage I/II carcinoma of the tongue. Cancer 1998; 82: 1443 - 8.
25. Sparano A, Weinstein G, Chalian A, et al. Multivariate predictors of occult neck metastasis in early oral tongue cancer. Otolaryngol Head Neck Surg 2004; 131: 472 - 6.
26. Civantos FJ, Zitsch RP, Schuller DE, 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.
27. O'Donnell RK, Kupferman M, Wei SJ, et al. Gene expression signature predicts lymphatic metastasis in squamous cell carcinoma of the oral cavity. Oncogene 2005; 24: 1244 - 51.
28. Roepman P, Wessels LF, Kettelarij N, et al. An expression profile for diagnosis of lymph node metastases from primary head and neck squamous cell carcinomas. Nat Genet 2005; 37: 182 - 6.