

# Management for the N0 Neck of SCC in the Oral Cavity

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## 1. Introduction

The oral cavity is the most predominant location in the head and neck region for primary malignant tumors, and more than 90 % cancer consists of squamous cell carcinoma (SCC). (Shah and Patel 2003) SCC has a high propensity to early and extensive lymph node metastases. Regarding cancer stage distribution at diagnosis, regional spread is more frequent in cancers of oral cavity and pharynx compared to other cancers, including such as prostate, breast, lung and bronchus, and colorectum (Figure 1). (Jemal *et al.* 2010) Therefore, clinicians for cancers of the oral cavity and pharynx have to regard regional metastasis as most important. Advanced SCC of the oral cavity has regional metastasis frequently, and even in small tumors (T1 or T2) has a relatively high propensity of regional lymph node

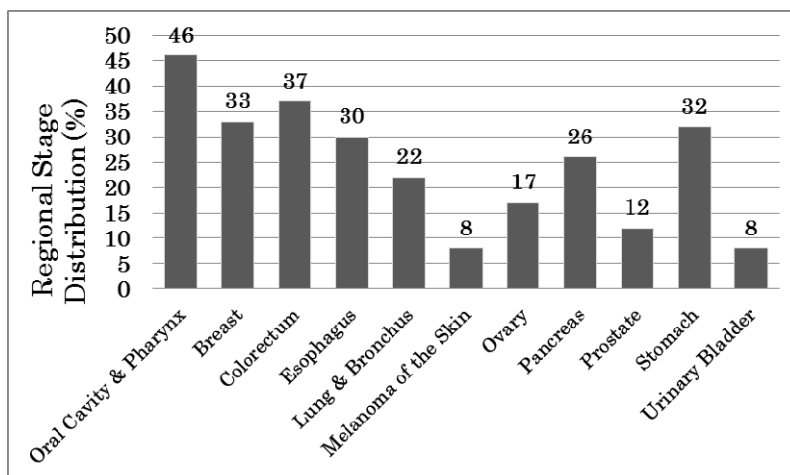


Fig. 1. Regional stage distribution of selected cancers, United States, 1999 to 2005.  
Source: Horner M, Ries L, Krapcho M, et al, eds. SEER Cancer Statistics Review, 1975-2006.  
Bethesda, MD: National Cancer Institute; 2009.

metastasis. The five-year relative survival rate of patients who present with tumors localized at the primary site without dissemination to regional lymph nodes is 82%. (SEER, Oral cancer statistics, <http://seer.cancer.gov/statfacts/html/oralcav.html>) On the other hand, once dissemination to regional lymph nodes takes place, the survival rate reduces to nearly 50%. Advancement of regional disease, such as extracapsular spread and multiple nodal metastases, has influenced survival. (Myers *et al.* 2001; Shaw *et al.* 2009) Clearly, the regional status is the most significant independent prognostic factor, (Okura 2002; Shah *et al.* 1993; Taniguchi and Okura 2003) and appropriate management of the cervical lymph nodes is essential for control of disease. (Ferlito *et al.* 2006) In this chapter, we review the literature to ascertain whether elective neck dissection should be performed for cN0 neck or wait-and-see policy is safe and adequate.

### 1.1 Treatment of clinical N0 (cN0) neck

The management of neck disease in head and neck cancer, including oral cavity cancer, has been considered one of the most important aspects of treatment. When nodal metastases are present, nobody can deny the important effect of therapeutic neck dissection in the prognosis of head and neck cancer patients. However, the role of elective neck dissection has been a matter of discussion. Even the patients with clinically negative nodes (cN0) may still harbor occult metastasis, although advances in imaging techniques such as computed tomography, magnetic resonance, ultrasound sonography (US), and positron emission tomography have increased the accuracy of nodal metastases (Figure 2).

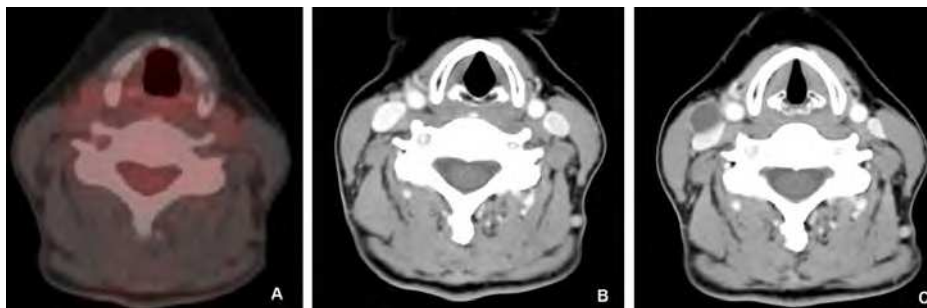


Fig. 2. Imagings of a patient with T2N0M0 SCC of the oral tongue.

A, preoperative positron emission tomography; B, preoperative enhanced computer tomography; C, enhanced computer tomography two months after transoral excision of the tumor. Preoperative assessment shows no involved node in the neck (A, B). Note late cervical nodal metastasis in the right side of the neck (Level III, C).

Table 1 shows the results of neck metastases and of each imaging study per patient with SCC of the oral tongue. CT had 70% accuracy, MRI had 74%, and US had 83% accuracy. Among the three image techniques US had the highest accuracy, although the accuracy was dependent on the observer. Our policy is essentially wait-and-see, and most of false-negative nodes were detected within 12 months after the initial transoral excision. In this study of oral tongue 66 (69%) patients with cN0 neck received intraoral excision alone, and 16 (17%) developed late lymph node metastases. The rate of occult metastases was 17% for SCC of the oral tongue and 21% for SCC of the oral cavity. Since the occult metastatic rate of head and neck cancer ranges from 17–50% (average, 28%) in the literature (Table 2), the optimal method of management of clinical N0 neck remains controversial.

	CT		MRI		US	
	-	+	-	+	-	+
Pathologically negative <sup>1</sup>	65	15	27	5	39	3
Pathologically positive						
Therapeutic neck dissection	2	24	1	16	1	12
Elective neck dissection	5	0	2	0	1	0
Regional recurrence	16	1	7	0	6	2
Loco-regional recurrence	4	0	2	0	2	0
Total	92	40	39	21	49	17
Sensitivity	52%		62%		67%	
Specificity	81%		84%		93%	
Positive predictive value	63%		76%		82%	
Negative predictive value	74%		73%		83%	
Accuracy	70%		74%		83%	

Table 1. Image accuracy of nodal positivity in patients with SCC of the oral tongue.

<sup>1</sup>Pathologically negative includes patients who performed intraoral excision alone with no regional recurrence; CT, computed tomography; MRI, magnetic resonance imaging; US, ultrasound sonography; -, negative; +, positive. Number indicates patient number.

The N0 neck can be treated electively or can be carefully observed (wait-and-see), and the decision can be made from each own clinical experience (Table 1). Randomized controlled trial (RCT) is desired to determine which is preferred, however RCT is not easy task. So far four RCTs of the small sample size had been performed. Vandembrouck *et al.* (Vandembrouck *et al.* 1980) demonstrated that the survival rates were similar between two treatment arms in 75 patients with oral cavity cancer, whereas Fakih *et al.* (Fakih *et al.* 1989) (n = 70) and Klingerman *et al.* (Klingerman *et al.* 1994) (n = 67) found that elective neck dissection had significant benefit for patients with tumor thickness of more than 4 mm. In 2009, Yuen *et al.* (Yuen *et al.* 2009) demonstrated that disease-free survival was quite similar between two arms in 71 patients with SCC of the oral tongue. Thus, these four RCTs failed to impact on clinicians due to the inconsistency and small number of cases studied. In 1994 Weiss *et al.* (Weiss *et al.* 1994) created a decision tree analysis and demonstrated that when the probability of occult cervical metastasis is more than 20%, the neck should be electively treated. Since then a large number of studies (Dias *et al.* 2001; Ferlito *et al.* 2006; Greenberg *et al.* 2003; Haddadin *et al.* 1999; O'Brien *et al.* 2000; Sano and Myers 2007; Wei *et al.* 2006) supported their recommendation and preferred elective treatment for N0 neck, (Andersen *et al.* 1996; Bourcier *et al.* 2005; Brazilian 1998; Byers *et al.* 1998; Dias *et al.* 2001; Ferlito *et al.* 2006; Franceschi *et al.* 1993; Greenberg *et al.* 2003; Haddadin *et al.* 1999; Huang *et al.* 2008; Kaya *et al.* 2001; O'Brien *et al.* 2000; Sano and Myers 2007; Wei *et al.* 2006; Yuen *et al.* 1997) because their occult metastatic rates were much higher than 20% (Table 2). Currently, the National Cancer Comprehensive Network's adopted practice guidelines have recommended elective neck dissection for clinical N0 cancer of the oral cavity, oropharynx, hypopharynx and supraglottic larynx. (NCCN, 2011) These guidelines apply to the performance of elective neck dissections as part of treatment of the primary tumor.

Another reason of the preference for elective neck dissection is less morbidity of supraomohoid neck dissection (SOHND) compared to classical radical neck dissection. (Spiro *et al.* 1996) For primary tumors in the oral cavity the regional lymph nodes at highest risk for early dissemination by metastatic cancer are limited to Levels I, II, and III

Author, year	Primary site	T stage	Patient number	% of occult metastasis	Neck treatment
Ho, 1992	OT	T1-2	28	42	obs
Lim, 2004	OT	T1-2	56	32	obs
Goto, 2005	OT	T1-2	88	26	obs, END
Lim, 2006	OT	T1-2	54	28	obs, SOHND
Keski-Säntti, 2006	OT	T1-2	80	30	obs, END
Kligerman, 1994	OC	T1-2	67	43	obs, SOHND
Brazilian H&N, 1998	OC	T2-4	148	28	mRND, SOHND
Kaneko, 2002	OC	T1-4	868	17	obs, END
Amaral, 2004	OC	T1-2	117	23	END
Smith, 2004	OC	T1-2	150	28	obs, END
Zbären, 2006	OC	T1-3	100	20	SOHND
Clark, 2006	OC	T1-4	105	34	obs, END
Mathew lype, 2008	OC	T1-4	219	27	SOHND
Okura, 2009	OC	T1-4	165	21	obs, END
Kraus, 1996	OC, OP	T1-4	44	32	SOHND
Nieuwenhuis, 2001	OC, OP	T1-2	161	21	obs
Duvvuri, 2004	OC, OP	T1-2	359	25	obs, END
O'Brien, 2008	OC, OP	T1-4	108	30	END
Spiro, 1996	H&N	-	268	25	SOHND
van den Brekel, 1999	H&N	T1-4	77	18	obs
Coatesworth, 2002	H&N	T1-4	63	30	END
Gourin, 2008	H&N	T1-4	337	50	END
Total			3662	28	

Table 2. Analysis of occult metastasis.

OT, oral tongue; OC, oral cavity; OP, oropharynx; H&N, head and neck; obs, observation; END, elective neck dissection; SOHND, supraomohyoid neck dissection; mRND, modified radical neck dissection.

in the supraomohyoid triangle. Skip metastasis to Levels IV and V in the absence of metastatic disease at Levels I, II, or III is exceedingly rare.(Shah *et al.* 1993) Compared to radical neck dissection SOHND reduces morbidity, including spinal accessory nerve disorder which results in diminished or absent function of the sternocleidomastoid muscle and upper portion of the trapezius muscle, and reduces cosmetic deformity. In addition, SOHND is considered as effective as comprehensive procedures for staging the clinically negative neck, when the neck is treated electively. It is intrinsic in the philosophy of a preventive treatment, to make it the less morbidity possible without losing oncologic results. However, this elective policy results in overtreatment of the neck, when the neck actually has no involved nodes. The less shoulder morbidity accompanied with SOHND is nonzero. Approximately 20% of patients who received SOHND had a shoulder pain even with conserving the accessory nerve.(Van Wilgen *et al.* 2004) Such overtreatment should be avoided when patients have no involved nodes in the neck.

## 1.2 Decision tree analysis

Upon returning decision tree analysis of Weiss *et al.*, the decision tree is based on an analysis of the utility of the management options taking into account the incidence of node

involvement, complications of treatment, and disease control rates. (Weiss *et al.* 1994) In sensitivity analysis they defined the expected utility to a function of the occult metastatic rate. They concluded that cN0 necks should be treated electively when the occult metastatic rate is more than 20%. The 20% of threshold has likely exerted a great influence on the management of cN0 necks, because they estimated curable probabilities using data of reviews published in the 1980s. Weiss *et al.* have however alluded that the values will change and the threshold will be altered with the times. The recommendation for elective neck dissection in more than two decades has to be reconsidered with the current data. Accordingly we have reconfigured the decision tree sensitivity analysis with our current disease control rates to determine optimal therapy based on a current set of underlying assumptions. (Okura *et al.* 2009) Two decision tree strategies for the management of cN0 neck was compared; elective neck dissection or wait-and-see. In sensitivity analysis the expected utility for each strategy is a function of occult metastatic rate according to Weiss study. The higher utility value is preferable to the lower one, and the intersection indicates the treatment threshold.

### 1.3 Formula of the threshold for the treatment of cN0 neck

The treatment threshold between elective neck dissection and observation was estimated with three ( $a-c$ ) probabilities of survival;  $a$  = the curable probability (5-year overall survival rate) of the patients received elective neck dissection with no neck recurrence,  $b$  = the curable probability of the observed patients with late neck metastasis,  $c$  = the curable probability of the observed patients with no neck recurrence. These three probabilities are different in each institution. With the sensitivity analysis, the treatment threshold (Rx) can be calculated through the following:

$$Rx = (c - 0.97a) / (0.00376 - 0.0776a - 0.94b + c).$$

When clinicians calculate their own 3 probabilities ( $a-c$ ) of being cured, they can estimate their own threshold for treatment of cN0 neck using this formula. The formula will be put to practical use and will estimate the current threshold. Our calculated threshold of the occult rate between the two strategies was 44.4% (Table 3). In our practice a patient with SCC of the oral cavity and N0 neck should be carefully observed if the probability of occult cervical metastasis is less than 44.4%. Only if the probability is greater than 44.4%, elective neck dissection might be warranted. Since the probability  $c$  is the survival rate for patients with no involved nodes who do not have occult metastases,  $c$  is expected to be a high rate. The probability  $a$  is the survival rate for patients who received elective neck dissection and should be lower than  $c$ , because some have occult metastases. If the occult metastatic rate is 0%, then the probability  $a$  would be quite same to  $c$ . A high occult metastatic rate and poor survival for patients with occult metastases contribute to a difference in probability between  $a$  and  $c$ .

Table 3 shows the treatment threshold in various three probabilities according to the formula. For instance, assuming that  $c$  is fixed to 80% and  $a$  is 65% gives Rx more than 30% when  $b$  is not less than 20%. Rx becomes greater in proportion to the increase of  $b$ , because the denominator in the formula is decreased. Assuming that  $a$  is 70%, Rx is more than 22%. Assuming that the difference between  $a$  and  $c$  is 5% ( $a = 75\%$ ), Rx is 13% when  $b = 20\%$  and 16% when  $b = 30\%$ , respectively. These Rx rates are too lower, however Rx goes up to more than 30% when  $b$  is more than 54%. Furthermore, providing that the difference between  $a$  and  $c$  is decreased to 2%, Rx is below 20% when  $b$  is less than 50%. For giving Rx > 30%,  $b$  needs more than 64%. It is therefore necessary for giving Rx high percentage to build up

high  $b$  probability as well as the positive difference between  $a$  and  $c$ . First, we have to raise the successful salvage rate for patients with late neck metastases. In Table 3 when  $b$  is more than 60%, Rx is invariably over 24%.

$a$	$b$	$c$	Rx	
60%	50%	60%	21%	Weiss et al.
87.8%	71.3%	94.5%	44.4%	Okura et al.
65%	20%	80%	30%	
65%	30%	80%	36%	
70%	20%	80%	22%	
70%	30%	80%	26%	
70%	40%	80%	32%	
70%	50%	80%	43%	
75%	20%	80%	13%	
75%	30%	80%	16%	
75%	40%	80%	20%	
75%	54%	80%	30%	
75%	60%	80%	40%	
78%	30%	80%	9%	
78%	40%	80%	12%	
78%	50%	80%	16%	
78%	60%	80%	24%	
78%	64%	80%	31%	
78%	70%	80%	51%	

Table 3. Three probabilities ( $a$ - $c$ ) and treatment threshold (Rx).

Rx of our study (2009) was two times or more as high as that of Weiss study (1994). Rx is calculated with each  $a$ ,  $b$  and  $c$  using the formula.

#### 1.4 Predictors of occult metastases

The management of cN0 neck of SCC of the oral cavity is not necessarily wait-and-see (observation). In our study the overall occult rate was 21%, relatively low compared to other studies (Table 2) and our policy is wait-and-see. Notwithstanding, one-fifth of patients with cN0 neck need late neck dissection when all necks of those patients were observed. Patients with higher probability of occult metastases are encouraged to be selected with other predictors. For instance, our occult metastatic rate was 14% for T1 lesions, 23% for T2 lesions, and 30% for T3 lesions, respectively (Table 4).

T stage	Incidence	Rate
T1	21/152	14%
T2	54/232	23%
T3	16/53	30%
T4	7/38	18%
Total	98/475	21%

Table 4. Incidence and rate of occult metastases according to T stage.

The rate is increased in proportion of the increase of T stage, except for T4. The increase of primary lesions compels us to consider elective treatment, although the highest rate for T3 is still lower than our treatment threshold (44.4%). Other predictors of occult metastases are essential to management of cN0 necks.

Numerous studies have reported that histologic tumor thickness correlates closely with lymph node metastases in SCC of the oral cavity.(Asakage *et al.* 1998; Byers *et al.* 1998; Fukano *et al.* 1997; Lim *et al.* 2004; O-Charoenrat *et al.* 2003; Spiro *et al.* 1986; Yamazaki *et al.* 2004; Yuen *et al.* 2000) Patients with more than 3 - 6 mm of histologic tumor thickness recommends to treated electively because of high risk of metastases. However accurate preoperative assessment of the thickness in biopsy section is no easy task. It is occasionally difficult to reach an invasive front on biopsy, and the tumor thickness on biopsy is not necessarily the greatest. In order to detect tumor thickness more accurately, sequential sections are desirable but not pragmatic. Accordingly, multi-sliced imaging techniques should be useful and convenient.

Recently, the correlation between histologic tumor thickness and magnetic resonance imaging (MRI) tumor thickness was demonstrated (Iwai *et al.* 2002; Lam *et al.* 2004; Preda *et al.* 2006). Then MRI tumor thickness seems to become a candidate of occult metastatic predictor, although these studies did not reach to demonstrate the relation with MRI tumor thickness and regional metastases. We have verified MRI tumor thickness in patients with oral tongue SCC.(Okura *et al.* 2008) Coronal MRI was preferred to measure tumor thickness than axial image (Figure 3).

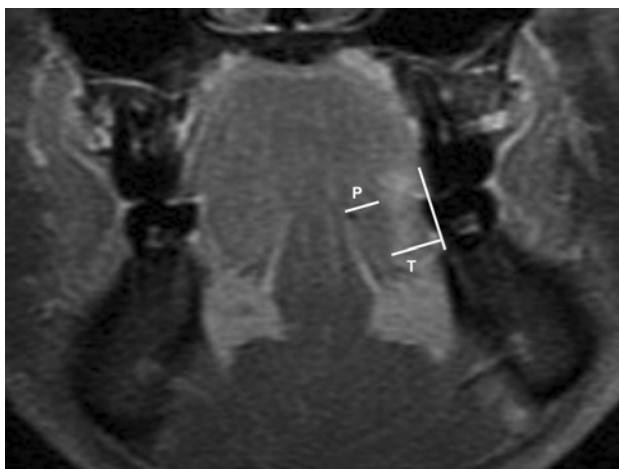


Fig. 3. Coronal contrasted-enhanced T1-weighted MRI shows tumor thickness (T) and paralingual distance (P). A vertical white line is a reference line connecting two tumor-mucosa junctions. A horizontal white line drawn perpendicular to the reference line represents radiologically is tumor thickness (T). The image shows that a high-intensity area, paralingual spatium, extends from the medial border of the sublingual space to the deep lingual artery along the genioglossus. The white line (P) is the paralingual distance between the tumor and the paralingual spatium.

Eighty-one % MRI permitted us the measurement of tumor thickness, however the remaining 19% could not be interpreted because of the interference of artifacts. There are some patients unsuitable for MR scan. Notwithstanding, MRI tumor thickness was related to lymph node metastases, and the mean of tumor thickness in patients with nodal metastases was twice length of that without nodal metastases. The thicker tumor thickness is, the higher the probability of lymph node metastases is (Table 5). Using logistic regression model, MRI tumor thickness was able to predict nodal metastasis in SCC of the oral tongue. Multivariate logistic regression function showed that if tumor thickness was 9.7mm, then the probability of metastases was 20%. Tongue cancer varies in the growth pattern, endophytic or exophytic. Even if tumor thickness is similar in size, the position of the invasive front is different between endophytic and exophytic tumors. In order to observe where tumor cells invade, the paralingual distance between the invasive front and the paralingual spatium of tongue was measured (Figure 3). The paralingual spatium is loose connective tissue, which locates between the genioglossus muscle and the intrinsic tongue muscles to sublingual space. Lingual nerve and lingual artery run through this spatium, and the lingual artery is the landmark of this spatium. The paralingual distance was significantly related to lymph node metastases. The probability of nodal metastasis was in inverse proportion to the paralingual distance, and the probability was 20% at 5.2 mm of paralingual distance (Table 5). The two MRI parameters were more reliable than preoperative assessment of clinical N staging because of the log likelihood ratio. In our practice, when MR tumor thickness is more than 9.7 mm or paralingual distance is less than 5.2mm, we take elective neck dissection into consideration.

Probability of lymph node metastasis (%)	Tumor thickness (mm)	Paralingual distance (mm)
10%	7.1	6.5
20%	9.7	5.2
25%	10.6	4.7
30%	11.5	4.3
40%	12.9	3.6
50%	14.2	3.0

Table 5. Lymph node metastasis and measured MRI distances in SCC of the oral tongue.

Entering 5.2 mm of paralingual distance into the cut-off point resulted in 82% of specificity, 70% of sensitivity, and 14% of occult metastatic rate. The specificity of paralingual distance is higher than that using other images and the occult metastatic rate is the lowest (Table 1). Thus, MRI distances are useful to detect occult metastases of the oral tongue. Other endeavor to improve the accuracy of detecting occult metastases will be required.

## 2. Survival

In our study overall survival was similar, whether patients with cN0 neck are observed or electively treated. The 5-year overall survival rate for observed patients was 89%, and the rate for patients received elective neck dissection was 86% (Figure 4). On the other hand, patients with cN 1-3 neck had significantly lower overall survival (54% at 5-year) than those with cN0 neck.



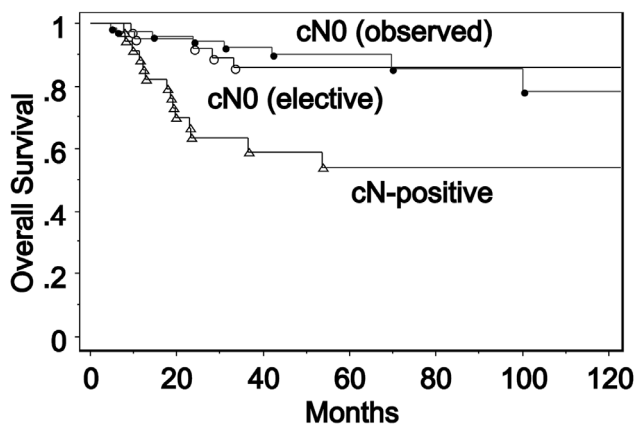


Fig. 4. Overall survival according to clinical N stage. Clinical N0 necks were treated with two treatment arms: observation and elective neck dissection.

The outcome depends on the extent of the occult metastases at the time they are detected, which correlates with the intensity of follow-up.(Cheng and Schmidt 2008) In our practice, follow-up took place at every month in the first year, at two months in the second year, at three months in the third year, at four months in the fourth year, and 6 months in the fifth year. CT scan and ultrasound sonography were performed every half year. The follow-up is basic management, and the optional examinations are appended individually. For instance, patients with higher risk of lymph node metastases have ultrasound examination more times, and patients with higher risk of distant metastases have positron emission tomography test or pulmonary CT scan. It is important to understand which risks are high.

### 3. Conclusion

At present, it is impossible to set the incidence of occult metastases to zero. Additionally, more sensitive parameters or markers associated with the presence of nodal metastasis are encouraged to be developed. The continued advancement will have a significant impact on the evaluation, management and outcome of patients with the oral cavity. For the current management for the cN0 neck, the important points are: Clinicians have to comprehend their own threshold between observation and elective neck dissection. For that purpose, it is necessary to estimate the occult metastatic rate and three probabilities of survival ( $a$ ,  $b$ ,  $c$ ). Then, the best policy of the management of cN0 necks is able to be controlled and determined. Extended operations with less morbidity in surgical oncology have been pursued to improve the outcomes. However, these extended operations are not necessarily wise. Recently, extended para-aortic nodal dissection did not improve the survival of patients with gastric cancer,(Sasako *et al.* 2008) and axillary lymph node dissection should be considered unnecessary for woman with T1-2 invasive breast cancer.(Giuliano *et al.* 2011) Thus, some extended operations do not seem to be the standard treatment.

In SCC of the oral cavity, elective neck dissection does not also seem to be superior to a wait-and-see policy, and vice versa. Current studies, retrospective and prospective, have been unable to give us definitive recommendations regarding the management of the cN0

neck in those patients. However, the cN0 necks might be conserved more frequently without the decline of survival by means of the improvement of nodal assessment and the higher salvage rate of late lymph node metastases.

#### 4. Acknowledgment

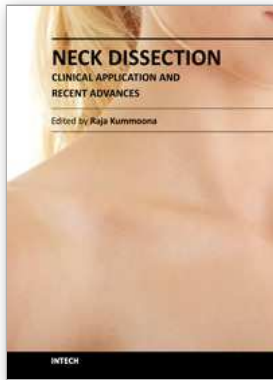
This work was conducted at the first department of Oral & Maxillofacial Surgery, Osaka University Dental Hospital in Japan. This work is supported in part by Grants from Ministry of Education, Science and Culture, Japan. We would like to express great gratitude to Chief professor Mikihiko Kogo and all clinical members in Osaka University Dental Hospital. We have furthermore to thank our secretary, Ms. Aya Okano to support this work.

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## **Neck Dissection - Clinical Application and Recent Advances**

Edited by Prof. Raja Kummoona

ISBN 978-953-51-0104-8

Hard cover, 164 pages

**Publisher** InTech

**Published online** 22, February, 2012

**Published in print edition** February, 2012

Neck Dissection - Clinical Application and Recent Advances is a leading book in neck surgery and represents the recent work and experiences of a number of top international scientists. The book covers all techniques of neck dissection and the most recent advances in neck dissection by advocating better access to all techniques of neck dissection; e.g. Robotic surgery (de Venice) system, a technique for detection of lymph node metastasis by ultra sonography and CT scan, and a technique of therapeutic selective neck dissection in multidisciplinary treatment. This book is essential to any surgeon specializing or practicing neck surgery, including Head Neck Surgeons, Maxillofacial Surgeons, ENT Surgeons, Plastic and Reconstructive Surgeons, Craniofacial Surgeons and also to all postgraduate Medical & Dental candidates in the field.

### **How to reference**

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Masaya Okura, Natsuko Yoshimura Sawai, Satoshi Sumioka and Tomonao Aikawa (2012). Management for the N0 Neck of SCC in the Oral Cavity, Neck Dissection - Clinical Application and Recent Advances, Prof. Raja Kummoona (Ed.), ISBN: 978-953-51-0104-8, InTech, Available from: <http://www.intechopen.com/books/neck-dissection-clinical-application-and-recent-advances/management-of-cn0-neck-of-scc-in-the-oral-cavity>

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