PREDIKTOR REKURENSI KANKER PADA PASIEN DENGAN KARSINOMA SEL SKUAMOSA DI DAERAH KEPALA DAN LEHER

YS Wimardhani,* DM Walker,** JR Gibbins,** MJ Veness,** GJ Morga,** II Kalnins**
*Department Oral Medicine Faculty of Dentistry University of Indonesia
**University of Sydney Westmead Hospital NSW Australia

Abstract

Disease Recurrence Predictors for Patients with Head and Neck Squamous Cell Carcinoma

Information on reliable factors to predict patient outcome is important for deciding upon the best treatment to increase loco-regional control, overall survival and quality of life of patients with head and neck squamous cell carcinoma (HNSCC). The objective of this study was to investigate the role of clinico-pathological parameters as predictors of disease recurrence in patients with HNSCC. We studied fifty patients who were seeking treatment for primary HNSCC in Westmead Hospital between 2002-2004. Univariate analysis was used to identify any significant association between clinico-pathological parameters and disease recurrence. It was showed that age (p=0.008), cTNM stage (p=0.02), size of tumour (p=0.009) and positive tumour margin (p=0.002) predicted the risk of the development of disease recurrence. In agreement with other studies we found that some traditional factors influenced disease recurrence. A longer follow-up study should be performed to assess the significance of these factors on overall survival as well as separate studies on prognostic indicators for patients with histologically negative lymph node. *Indonesian Journal of Dentistry 2006; Edisi Khusus KPPIKG XIV:362-367*

Key words: squamous cell carcinoma, head and neck, predictor

Introduction

From recent data by Parkin *et al.* [1], 499,000 new cancers of the head and neck (mouth and pharynx, larynx ICD-9 140-149, 161, see section 1.1.1) were registered per annum worldwide in 1990, accounting for 6% overall of new cancer cases. The relative global importance of head and neck cancers has slightly declined recently. In 1980 these cancers ranked as the sixth most common malignancy, whereas by 1990 they had become the eighth most common. However, during that time period the incidence of head and neck cancer had increased slightly in developed countries. [2,3] Head and neck cancers were three times more common in men than in women worldwide, estimated as the seventh most frequent cancer in males with 376,300 new cases worldwide and as the thirteenth most common in females involving 122,700 new cases.[1,4]

The etiology of head and neck squamous cell carcinoma is complex and a number of factors are known to increase the risk of malignancy. Oral cavity cancer has been found to be associated with alcohol and tobacco consumption in developed countries and also with the use of betel in developing countries. [5,6] Other risk factors such as

ultraviolet light particularly for lip cancer, dietary factors, viruses and a family history of head and neck cancer have also been implicated with head and neck carcinogenesis.

Generally, patients with HNSCC presented with stage I and II diseases with a clinically lymph node negative at the time of the diagnosis. Despite the negative node, histopathologically positive lymph nodes obtained from the neck dissection specimens were found in approximately one third of the cases. [7] Reduction to 50% of 5-year survival rate is seen when the regional lymph node metastasis is found. [8] The development of distant metastases (DM) in patients diagnosed with HNSCC carries a very poor prognosis with few patients surviving more than two years after the diagnosis. [9] Although distant metastases from HNSCC were previously considered uncommon, 4-25% of HNSCC patients have been found to have distant disease clinically or by imaging techniques with 25-47% found to have DM at autopsy. [9-12] With improving locoregional control of HNSCC, DM has assumed increased importance as a first site of relapse.

Therefore, information on reliable factors to predict patient outcome is important for deciding upon the best treatment to increase loco-regional control, overall survival and quality of life of patients with HNSCC. In the previous published studies, some factors which include clinical as well as pathological factors affecting patient outcome have been validated but there have also been conflicting results. This study aimed to identify any clinical or pathological features in the HNSCC patients in the present study which were associated with disease recurrence. The present study has identified several factors which were significantly associated with the development of disease recurrence. The result of this study would benefit clinician to decide the best possible treatment and follow-up for patients with increasing risk of developing disease recurrence.

Materials And Methods

Subjects

Fifty patients diagnosed with squamous cell carcinomas from the head and neck region during 2002-2004 were included in this study. All the participants in this study gave their signed informed witnessed consent. This study has been approved by the Western Sydney Area Health Service Human Research Ethics Committee and was carried out according to the Committee's recommendations. They were referred to the Head and Neck Cancer Service, Westmead Hospital, NSW, Australia.

Variables

The clinical and pathological variables were documented in each patient's hospital record and the details stored in the Department of Radiation Oncology were abstracted. Ethical approval was obtained from the Western Sydney Area Health Services Human Research Ethic Committees. The follow-up period for the 50 patients in this study started from the date of the beginning of treatment until disease recurrence or the completion of the study.

Statistical analysis

SPSS for Windows (Version 11.0) was used to analyze the data and the statistical analysis was performed with the assistance of Dr Karen Byth, Consultant Statistician, Westmead Hospital. Probability value of 5% or less was considered significant and probability value less than 10% was considered as approaching significance. Odds ratios (OR) and their 95% confidence intervals (CI) were used to quantify the degree of association.
The effect of clinical and pathological features of the HNSCC cases on disease recurrence was analyzed using Cox's regression model to assess their prognostic significance. Multivariate analysis was performed using the Cox's regression model, for variables found to be statistically significant or approaching significant by univariate analysis, to determine whether they had dependent or independent prognostic significance. Kaplan-Meier survival curves were built for the variables determined by multivariate analysis to be significantly associated with disease recurrence

Results

Disease recurrence was recorded in 14 (28%) of 50 patients after completion of treatment. The results of statistical analysis of the correlation between clinico-pathological factors and disease recurrence are summarized in Table 1. The results showed that age, tumour stage, T stage, positive margin and perineural invasion were associated with the development of disease recurrence by univariate analysis.

Table 1. Prognostic Factors Significantly Associated with an Increased Risk of Disease Recurrence in 50 Patients With HNSCC. Determined by Univariate Cox Regression Analysis

Univariate Cox regression analysis Disease recurrence				
Variable	**Value of variable**	**p value**	**Hazard ratio**	**95% CI**
1. Age (per year of age)		**0.008**	**1.069**	**1.018-1.123**
2. Gender		0.6	1.3	0.4-4.0
3. Smoking	Non-smokers	-	1	-
	Ex-smokers	0.2	4.2	0.5-36.0
	Current smokers	0.5	2.1	0.3-17.4
4. Alcohol consumption	Alcohol drinkers	0.6	1.4	0.4-5.0
5. Stage (per increase stage)		**0.02**	**1.9**	**1.1-3.3**
6. T stage (per increase Tstage)		**0.009**	**2.3**	**1.2-4.3**
7. N stage (per increase N stage)		**0.1**	**1.4**	**0.6-6.5**
8. Histology (+ vs – LN)		0.3	1.9	0.2-1.8
9. K5 RT-PCR (+ vs – LN)		**0.3**	**2.1**	**0.4-10.5**
10. Histology (single vs multiple)		0.9	1.1	0.2-5.4
11. ECS (+ vs -)		**0.9**	**1.1**	**0.3-3.5**
12. Tumour grade	Low	-	1	-
	Intermediate	0.2	2.7	0.6-12.9
	High	0.1	4.1	0.7-24.5
13. Tumour grade (per increase grade)		**0.1**	**2**	**0.9-4.4**
14. Site		**0.9**	**0.9**	**0.5-1.7**
15. Previous SCC		0.1	2.3	0.8-7.1
16. Margin (+ vs -)		**0.002**	**8.6**	**2.2-33.3**
17. Depth of invasion (per mm)		0.1	1.073	0.974-1.182
18. Maximum diameter of tumor (per mm)		**0.1**	**1.019**	**0.981-1.059**
19. Perineural invasion*		**0.06**	**3.2**	**0.9-10.6**
20. Vascular/lymphatic invasion		**0.9**	**1**	**0.1-7.7**
21. Radiotherapy		0.7	1.2	0.4-3.5
22. Chemotherapy		**0.9**	**1.5**	**0.2-11.1**

Key: + =positive; - =negative: vs=versus; F=female; M=male; LN=lymph node; CI=confidence interval;

Table 2. Prognostic Factors Significantly Associated with an Increased Risk of Disease Recurrence in 50 Patients with HNSCC Determined by Multivariate Cox Regression Analysis

Multivariate Cox regression analysis Disease recurrence			
Variable	p value	Adjusted Hazard Ratio	95% CI
1. Age (per year of age)	0.04	1.080	1.002-1.163
2. Margin (+ vs -)	0.001	11.1	2.6-48.1

Key: CI=confidence int erval

Variables with prognostic significance or approaching prognostic significance by univariate analysis for disease recurrence were age, alcohol consumption, stage, cT stage, cN stage, tumour grade, previous history of HNSCC, margin, depth of invasion and perineural invasion were further analyzed ant the independent predictors found to be significantly associated with disease recurrence by multivariate analysis were age (per year of age) (p=0.04) and status of excision margin (p=0.001). (Table 2). Table 2 summarizes the factors significantly associated with disease recurrence determined by multivariate analysis.

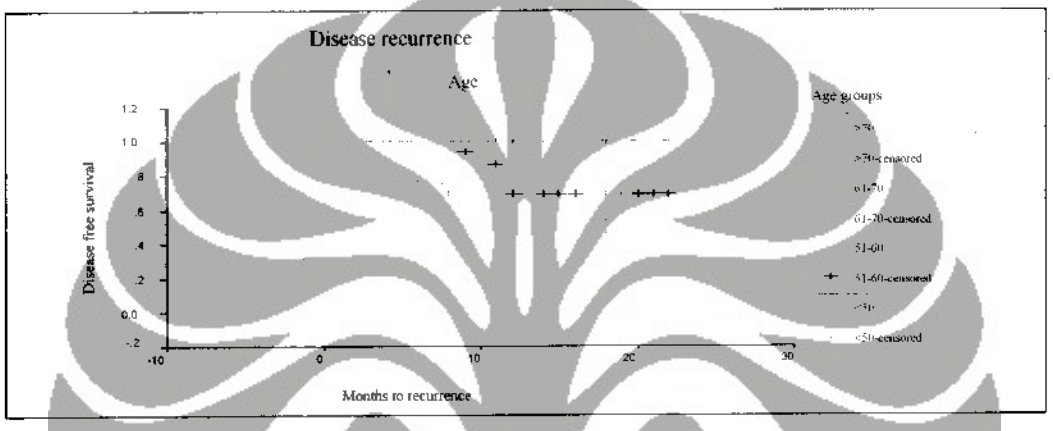

Figure 1. Age (per year) was significantly associated with disease recurrence when analyzed using univariate Cox regression analysis (p=0.008) and determined as an independent predictor for disease recurrence by multivariate analysis (p=0.04).

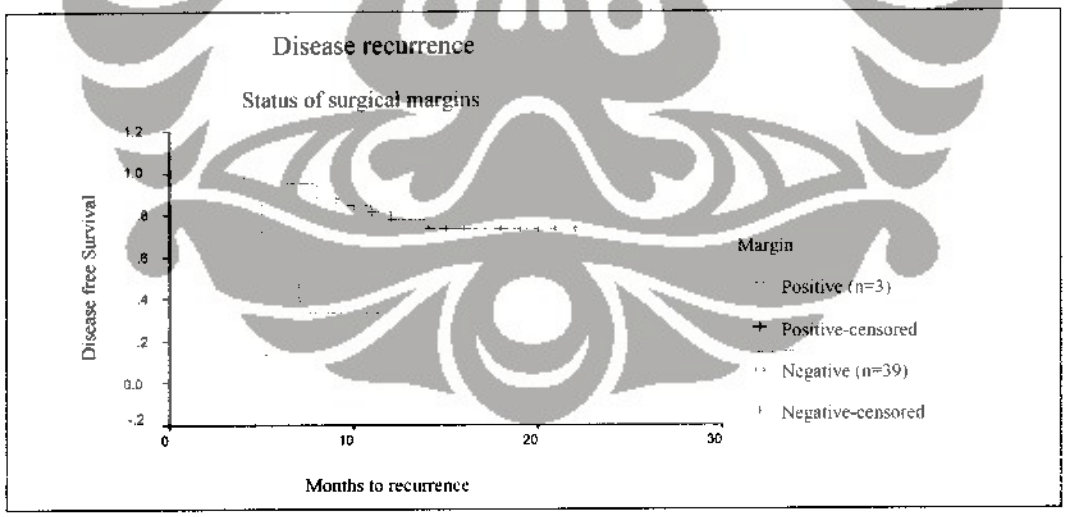

Figure 2. The presence of tumour in the surgical margin assessed by histology was significantly associated with disease recurrence by univariate Cox regression analysis (p=0.002) and determined as an independent predictor for disease recurrence by multivariate analysis (p=0.004). At one year follow-up, patients with tumour in the surgical margin had 77% 1-year disease free survival rate compared with 38% of patients with negative tumour margin.

Kaplan Meier survival curves for disease recurrence of these two independent variables by multivariate analysis are shown in Figures 1, 2.

Discussion

In this study, some clinical and pathological features of the patients predicted the risk of the development of disease recurrence by univariate analysis. These variables were age, clinical TNM stage, clinical T stage, tumour margin and perineural invasion (Table1). These findings were similar to other results of previous investigations. [13,14] Furthermore, multivariate analysis revealed that age (per year of age) (p=0.04) and status of excision margin (p=0.001) were independently associated with the risk of disease recurrence.

A significant association between increasing age and disease recurrence was found by multivariate analysis in the present study. This observation was similar to those of other workers, [13,14] although these authors investigated homogeneous groups with carcinoma of the tongue. Further investigation on other factors related with patients' co-morbidity might help explained the results gained in this study.

Status of surgical margins was found to be a independently significant predictor for disease recurrence although the classification of positive surgical margins in this study did not include the specimens that have close margins (margin less than 0.5mm) and this finding was in concordance with previous results [13,15-17]. Some studies have reported contrary results, indicating that further molecular analysis to assess specific mutation in p53 gene in microscopically negative surgical margins was needed [18]. A significant association between the findings of histologically lymph node metastases and disease recurrence was not found in this investigation. This result may reflect the success of the loco-regional control in the head and neck region with the application of adjuvant radiotherapy in patients with histologically positive lymph nodes [19,20]. Four (29%) patients who experienced recurrences in this study did not have histologically positive lymph nodes and did not receive adjuvant radiotherapy however, Cox regression analysis showed that patients treated without radiotherapy had 1.2 times more likely to develop disease recurrences (Table 1). A short follow-up period in this study may also affect the lack of association between histologically positive lymph nodes and disease recurrence.

A study with longer time period to continually monitor the patients included in this study is required. This would reveal the clinical relevance of the finding of disseminated tumour cells in lymph nodes. A five year follow up period of these patients may have shown the clinical relevance of the finding of these cells[21], although a study of breast cancer suggested that patients should be followed up to twelve years to determine an accurate clinical significance of the presence of micrometastases.[22] The archival material of primary tumours of the patients included in this study could be used for further study to determine the expression of some metastatic markers within the specimen using immunohistochemistry.

Conclusion

In agreement with other studies we found that some traditional factors influenced disease recurrence. A longer follow-up study should be performed to assess the significance of these factors on overall survival as well as separate studies on prognostic indicators for patients with histologically negative lymph node.

References

1. Parkin D, Pisani P, Ferlay J. Estimates of the Worldwide Incidence of 25 Major Cancers in 1990. *Int J Cancer* 1999; 80:827-41.
2. Schantz S, Yu G. Head and Neck Cancer Incidence Trends in Young Americans, 1973-1997, with a Special Analysis for Tongue Cancer. *Arch Otolaryngol Head Neck Surg* 2002; 128:268-74
3. Canto M, Devesa S. Oral Cavity and Pharynx Cancer Incidence Rates in the United States, 1975-1998. *Oral Oncol* 2002; 38:610-17
4. Parkin D, Pisani P, Ferlay J. Estimates of the Worldwide Incidence of Eighteen Major Cancers in 1985. *Int J Cancer* 1993; 54:594-606
5. Murti P, Gupta P, Bhonsle R, Daftary D, Mehta F, Pindborg J. Effect on the Incidence of Oral Submucous Fibrosis of Intervention in the Areca Nut Chewing Habit. *J Oral Pathol Med* 1990; 19:99-100
6. Sinor P, Gupta P, Murti P, Bhonsle R, Daftary D, Mehta F, Pindborg J. A Case-Control Study of Oral Submucous Fibrosis with Special Reference to the Etiologic Role of Areca Nut. *J Oral Pathol Med* 1990; 19:94-8
7. McDonald L, Walker D, Gibbins. Cervical Lymph Node Involvement in Head and Neck Cancer

Detectable as Expression of a Spliced Transcript of Type II Keratin K5. *Oral Oncol* 1998; 34:276-83
8. Puri S, Fan CY, Hanna E. Significance of Extracapsular Lymph Node Metastases in Patients with Head and Neck Squamous Cell Carcinoma. *Curr Opin Otolaryngol Head Neck Surg* 2003; 11:119-23
9. Calhoun K, Fulmer P, Weiss R, Hokanson J. Distant Metastases from Head and Neck Squamous Cell Carcinomas. *Laryngoscope* 1994; 104:1199-1205.
10. Vikram B. Changing Patterns of Failure in Advanced Head and Neck Cancer. *Arch Otolaryngol* 1984; 110:564-5
11. Bhatia R, Bahadur S. Distant Metastasis in Malignancies of the Head and Neck. *J Laryngol Otol* 1987; 101:925-8
12. Snow G. Follow-up in Patients Treated for Head and Neck Cancer: How Frequent, How Thorough and For How Long? *Eur J Cancer* 1992; 28:315-6
13. El-Husseiny G, Kandil A, Jamshed A, Khafaga Y, Saleem M, Aliam A, Al-Rajhi N, Al-Amro A, Rostom A, Abuzeid M, Ottieschan A, Flores A. Squamous Cell Carcinoma of the Oral Tongue: An Analysis of Prognostic Factors. *Br J Oral Maxillofac Surg* 2000; 38:193-9
14. Yamazaki H, Inoue T, Yoshida K, Imai A, Yoshioka Y, Tanaka E, Shimamoto S, Nakamura S, Inoue T, Nakamura H, Furukawa S, Shimizutani K. Influence of Age on the Results of Brachytherapy for Early Tongue Cancer. *Int J Radiat Oncol Biol Phys* 2001; 49: 931-6
15. Smeele L, Leemans C, Langendijk J, Tiwari R, Slotman B, van Der Waal I, Snow G. Positive Surgical Margins in Neck Dissection Specimens in Patients with Head and Neck Squamous Cell Carcinoma and The Effect of Radiotherapy. *Head Neck* 2000; 22: 559-63
16. Jones K, Lodge-Rigal R, Reddick R, Tudor G, Shockley W. Prognostic Factors in the Recurrence of Stage I and II Squamous Cell Cancer of The Oral Cavity. *Arch Otolaryngol Head Neck Surg* 1992; 118: 483-5
17. Loree T, Strong E. Significance of Positive Margins in Oral Cavity Squamous Carcinoma. *Am J Surg* 1990;160:410-414
18. Brennan J, Mao L, Hruban R, Boyle J, Eby Y, Koch W. Molecular Assessment of Histopathological Staging in Squamous-Cell Carcinoma of The Head and Neck. N Engl J Med 1995; 332:429-35
19. Parsons J, Mendenhall W, Stringer S, Amdur R, Hinerman R, Villaret D, Moore-Higgs G, Greene B, Speer T, Cassisi N. Squamous Cell Carcinoma of the Oropharynx: Surgery, Radiation Therapy, or Both. *Cancer* 2002; 94: 2967-80
20. Smeele L, Leemans C, Reid C, Tiwari R, Snow G. Neck Dissection for Advanced Lymph Node Metastasis before Definitive Radiotherapy for Primary Carcinoma of The Head and Neck. *Laryngoscope* 2000; 110:1210-4
21. Woolgar J. Micrometastasis in Oral/oropharyngeal Squamous Cell Carcinoma: Incidence, Histopathological Features and Clinical Implications. *Br J Oral Maxillofac Surg* 1999; 37:181-6
22. Rosen P, Saigo P, Braun D, Weathers E, Brachia A, Kinney D. Maxillary Micro- and Macro Metastases in Breast Cancer. *Ann Surg* 1981; 194:585-91