Prognostic factors of differentiated thyroid cancer patients in Hospital Universiti Sains Malaysia

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ABSTRACT

Introduction: The aim of this study was to identify the prognostic factors that influence the survival of differentiated thyroid cancer patients treated at Hospital Universiti Sains Malaysia (HUSM).

Methods: A total of 178 patients diagnosed with and treated for differentiated thyroid cancer in HUSM between January 1974 and July 2003 were included in this retrospective cohort study. The additional follow-up period was one year after the end of the recruitment phase. The data was collected from the medical records of the patients.

Results: The overall five- and ten-year relative survivals of differentiated thyroid cancer patients in HUSM were 90.6 percent (95 percent confidence interval [CI] 84.4-94.4) and 85.3 percent (95 percent CI 76.0-91.2), respectively. The significant prognostic factors for differentiated thyroid cancer were age (hazard ratio [HR] 6.9; 95 percent CI 1.7-28.6), loss of appetite (HR 10.9; 95 percent CI 2.7-43.7), tumour size (HR 3.7; 95 percent CI 1.1-13.8), regional recurrences (HR 3.2; 95 percent CI 1.1-9.8), high-risk stage (HR 19.9; 95 percent CI 4.4-90.4), and treatment (HR 0.2; 95 percent CI: 0.1-0.5).

Conclusion: The survival rates obtained in this study were slightly lower than other studies but the pattern of survival rates between groups were similar. Prognostic factors identified in this study were similar to those of other studies, suggesting that the experience of HUSM was almost similar with that of other institutions.

Keywords: cancer prognosis, cancer survival rates, differentiated thyroid cancer, thyroid cancer

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INTRODUCTION

The incidence of thyroid cancer has been observed to be increasing in the USA, Canada, Japan, Germany, the United Kingdom and eastern European and Nordic countries during the past decades[1]. This rise was also seen in Malaysia as in the year 2002, when thyroid cancer was the ninth of the ten most-frequent cancers of all cancers in all age groups of females and in younger males[2]. The overall survival rate of patients with thyroid cancer was better than any other cancer, and thyroid cancer accounted for less than 0.5% of the 20 most frequent causes of cancer death. However, although thyroid cancer is not a common malignancy, it is responsible for more deaths than all other endocrine carcinomas[1]. Information about the factors that influence its progression and survival rate is important to determine the prognosis, make therapeutic decisions and develop prevention programmes[3].

Research on prognostic factors of differentiated thyroid cancer has been done quite extensively in other countries. Most of the research was based on state and national cancer registries. A variety of factors including histological type, tumour grade, tumour stage, capsular and vascular invasion, age and sex have been analysed but results are not uniform in all the studies[1]. The information about thyroid cancer in Malaysia is scarce and there were no previous studies conducted to determine survival rates and prognostic factors of differentiated thyroid cancer patients at Hospital Universiti Sains Malaysia (HUSM). Thus, this study attempts to identify prognostic factors that influence the survival of patients diagnosed with differentiated thyroid cancer and received treatment in HUSM.

METHODS

A retrospective cohort study among patients with differentiated thyroid cancer was conducted in HUSM, Kelantan, Malaysia. All patients who met with the inclusion criteria were included in the study. The inclusion criteria included patients diagnosed to

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have differentiated thyroid cancer classified by the International Classification of Disease for Oncology (ICD-O) site codes C73[4] and received treatment in HUSM during the study period. Patients diagnosed with differentiated thyroid cancer but who refused treatment in HUSM were excluded. The study protocol was reviewed and approved by the Research and Ethics Committee, Universiti Sains Malaysia.

Data was collected from patients' medical records at the Department of Oncology and Radiotherapy and Unit of Records at HUSM. Age, sex, race, marital status, time of follow-up, symptoms, diagnostic tests, histological type, tumour size, metastases, stage, treatment, recurrences and status of the patients were documented by coding. Patients were classified as high and low risk according to AMES (age, metastases, extra-capsular tumour extent, size) risk-group definition[5]. Individual subjects were anonymised and the principal investigator kept individual identifiers, such as name and address, confidential. A single researcher retrieved the required information from the medical records by coding it onto the checklist form. Staff nurses also helped to ascertain any clinical information (such as symptoms, diagnostic tests and treatments given to the patients), when the data were not clear in the medical records.

An additional follow-up period after the end of the recruitment period was from August 1, 2003 to July 31, 2004. The survival status of a patient was obtained from the follow-up visits to the oncology clinic after discharge. Patients without follow-up treatment were contacted through telephone calls to their house or workplace. Information on the time and cause of death were obtained from the death certificates in the medical records for deaths that occurred in the hospital, or from the patient's closest relative (usually children) who was contacted to determine the time and cause of death, for deaths which occurred out of the hospital.

The outcome variable, survival time, referred to the time from diagnosis to death of a patient. A death was considered as a terminal event, if the death was due to thyroid cancer or complications of its treatment. A patient was considered as censored if the patient was alive at the end of the study period. If the patient died during the study period because of other causes unrelated to thyroid cancer or its complications, it was treated as a censored case. Any patients who were lost to follow-up were also considered as censored. Censored survival time was obtained for these patients.

Data entry and analysis were performed with STATA version 8.0 (Los Angeles, CA, USA). Kaplan-Meier Product Limit survival curves were used to calculate the probability of surviving a given length of time. The statistical difference of the survival probabilities between subgroups was evaluated using the log-rank test. Univariate Cox proportional hazards model was applied to determine potential prognostic factors. Level of significance was set at 0.05. Variables that were found statistically significant in univariate analysis ($p<0.20$) and also proven to be significant in other studies were included in multivariate analysis.

Multivariate analysis, using the Cox proportional hazards model, was used to identify the prognostic factors. Significance of clinically meaningful interaction terms was also tested. The final model was chosen based on the consideration of statistical significance as well as the clinical significance of the variables. The inspection of log cumulative hazard curve plotted against log time and Schoenfeld residuals were used to check the proportional hazards assumptions. Time-varying covariates were not present in this study. Martingale residuals to assess adequate functional form, Cox-Snell residuals to evaluate the model fitness, deviance residuals and influential statistics to determine the presence of outliers and its influence on the model, were performed. Results were tabulated with crude and adjusted hazards ratios, 95% confidence intervals and p-values.

RESULTS

A total of 178 subjects were studied. 33 patients died, of which 18 died of differentiated thyroid cancer and the rest of other causes. The mean (standard deviation) and median (interquartile range) survival time of thyroid cancer patients were 48 months (60 months) and 24 months (48 months), respectively, and ranged from two months to 264 months. The mean (standard deviation) and median (interquartile range) follow-up time were 72 months (60 months) and 48 months (five months), respectively and ranged from 12 months to 360 months. The overall five- and ten-year relative survivals of thyroid cancer patients in HUSM were 90.6% (95% CI 84.4-94.4) and 85.3% (95% CI 76.0-91.2), respectively.

The characteristics of the differentiated thyroid cancer patients in HUSM and the log-rank test analysis of all the studied variables are shown in Table I. Significant differences in survival duration among subgroups were seen in the variables of age, loss of appetite, histological type, regional recurrences, stage and metastases. The prognostic factors that influence the survival of differentiated thyroid cancer patients in HUSM are listed in Table II. Age, loss of appetite, tumour size, regional recurrence, stage, and

Table I. Characteristics of 178 patients with differentiated thyroid cancer in HUSM.

Variable	n (%)	χ^2 test[a] (df[b] = 1)	p-value
Age		9.19	0.002
<40 years	84 (52.8)		
≥40 years	94 (47.2)		
Sex		0.81	0.367
Female	145 (81.5)		
Male	33 (18.5)		
Race		3.58	0.058
Malay	154 (86.5)		
Others	24 (13.5)		
Marital status		0.42	0.519
Married	155 (87.1)		
Single	23 (12.9)		
Goitre		3.69	0.055
Solitary nodule	107 (60.1)		
Multinodular goitre	71 (39.9)		
Palpable lymph nodes		0.81	0.367
Yes	33 (18.5)		
No	145 (81.5)		
Loss of appetite		8.92	0.002
Yes	12 (6.6)		
No	166 (93.4)		
Shortness of breath		0.38	0.790
Yes	18 (10.1)		
No	160 (89.9)		
Dysphagia		0.39	0.740
Yes	18 (10.1)		
No	160 (89.9)		
Hoarseness of voice		2.05	0.152
Yes	19 (10.7)		
No	159 (89.3)		
Tumour size		0.99	0.321
<4 cm	72 (59.6)		
≥4 cm	106 (40.4)		
Histological type		4.01	0.045
Papillary	138 (77.5)		
Follicular	40 (22.5)		
Local recurrence		5.32	0.022
Yes	33 (18.5)		
No	145 (81.5)		
Regional recurrence		5.32	0.022
Yes	59 (33.1)		
No	119 (66.9)		
Distant metastases		66.66	<0.001
Yes	18 (10.1)		
No	160 (89.9)		
Stage		32.10	<0.001
Low-risk	127 (71.3)		
High-risk	51 (28.7)		
FNAC[c]		1.71	0.191
Yes	158 (88.8)		
Biopsy alone	20 (11.2)		
Treatment		0.15	0.695
Surgery alone	24 (13.5)		
Surgery with RAI[d] therapy and/or radiotherapy	154 (86.5)		

[a] Log-rank test was applied

[b] Degree of freedom

[c] Fine needle aspiration cytology

[d] Radioactive iodine

Table II. Multivariate analysis of cancer deaths in 178 patients with differentiated thyroid cancer.

Variables	n	Coefficient *(b)*	Wald statistics	Crude HR[a]	Adjusted HR	95% CI[b] of adjusted HR	p-value
Age							
<40 years	94			1.00	1.00		
≥40 years	84	1.94	2.69	10.33	6.94	1.69-28.63	0.007
Loss of appetite							
No	166			1.00	1.00		
Yes	12	2.39	3.37	10.85	10.90	2.72-43.67	0.001
Tumour size							
<4 cm	72			1.00	1.00		
≥4 cm	106	1.32	2.03	1.27	3.72	1.04-13.82	0.042
Regional recurrence							
No	119			1.00	1.00		
Yes	59	1.15	2.06	3.53	3.17	1.02-9.82	0.045
Stage							
Low-risk	127			1.00	1.00		
High-risk	51	2.99	3.87	3.17	19.88	4.37-90.43	0.000
Treatment							
Surgery alone	24			1.00	1.00		
Surgery with RAI[c] therapy and/or radiotherapy	154	-1.93	-3.62	0.37	0.19	0.05-0.41	<0.001

[a] Hazard ratio

[b] Confidence interval

[c] Radioactive iodine

surgery plus radioactive iodine (RAI) therapy and/or radiotherapy were statistically significant factors for survival.

Interaction terms were tested between the significant factors and no meaningful interaction terms were found. The log cumulative hazard plot against log time and Schoenfeld residuals showed that the proportional hazards assumption was fulfilled. Martingale and Cox-Snell residuals showed that no transformation was necessary and the model was fit. The deviance residual and influence statistics indicated there were no significant outliers.

DISCUSSION

In this study, the survival probabilities for differentiated thyroid cancer was lower than the study by Gilliland et al[3], but similar pattern of survival rates were seen. The mean age (39 years) in this study was similar to that reported by McConahey et al[6], older than the study from Mazzaferri and Young[7], and younger than in the study by Harach et al[8]. Older age was associated with lower relative survival. This could be caused by the rapid metastasis progression in patients aged 40 years old and above[9]. The female to male ratio of the patients in this study (4.4:1) was higher than the ratio in other countries such as 3:1 in the USA, 3.4:1 in Singapore, and 4.1:1 in Finland[2] but was considerably lower than the ratio of 13:1 seen in Japan[6]. Similar with other studies[10,11], the survival probabilities between males and females were not significantly different. Higher percentage of thyroid cancer was seen in Malays compared to non-Malays. According to National Cancer Registry, Malays had lower risk of cancer for all sites except for thyroid cancer and lymphoma. Those differences might be due to genetics and environmental factors such as dietary habits[2].

Many studies have demonstrated that the extension of disease at diagnosis correlates significantly with disease outcome[5,10,12,13]. Survival probabilities for symptoms such as goitre, palpable lymph nodes, shortness of breath, dysphagia, and hoarseness of voice were more than 80%, except for loss of appetite. Lower survival rates were also found in patients with tumours of size 4 cm and larger, compared to patients with tumours less than 4 cm in size. Survival probabilities for patients with local and regional recurrences and distant metastases were lower compared to patients without these symptoms and were similar to other studies[3]. Large tumours and enlarged lymph nodes (in regional recurrences) indicated that there was an airway obstruction, which was one of the major causes of death in thyroid cancer. These symptoms also might have caused loss of appetite among the patients. Similar to other studies[1,13], distant metastases were seen more frequently in the

lungs, followed by bones and brain. This study had two cases of brain metastases, and both of the affected patients had died.

Lower survival probabilities in the high-risk group could be due to the higher percentage of older patients and presentation with metastases seen in this group, compared to the low-risk group. Papillary thyroid cancer patients in this study had a significant better relative survival compared to follicular thyroid cancer, which was similar to other studies[5,12]. Follicular thyroid cancer patients usually present with local and regional recurrences, which could be the cause of higher mortality in these patients[11]. The survival probabilities for patients who had fine needle aspiration cytology were higher compared to the patients who had biopsy alone; the latter group also had a higher percentage of solitary thyroid nodule and bone metastases. Patients who had a combination of surgery, RAI therapy and radiotherapy had higher survival probabilities compared to patients who did not undergo these treatments. Similar to this study, other studies[7,10,12,13] reported RAI ablation of remnant thyroid tissue after surgery decreased mortality rates in differentiated thyroid cancer patients. Patients who had undergone surgery plus radiotherapy also had a better survival rate compared to those who did not receive these treatments[9,14].

The limitations of data collected from the existing medical records need to be considered in any interpretation of findings in this study. Histological classifications of tumours were based on review of pathological reports that were attached to the medical records and not subject to a standardised review. Information such as family history, irradiation and dietary habits, which could also be prognostic factors for thyroid cancer, was not available in the patient's medical records and was not studied. Missing values also had to be managed in collecting data from records. In addition, short follow-up period and small number of observations could result in small number of outcome events, which could affect the accuracy and precision of the regression coefficient for independent variables. Since this was a retrospective cohort study, selection bias might have occurred. Estimates of the survival might be biased due to a correlation between unobserved factors associated with treatment selection and outcomes, such as patient's preference. Furthermore, treatment was not controlled in this study and may influence survival estimates. Selection of a treatment was different from another as it was determined by stage and extension of the disease. Associations with treatment were strongly biased by selection factors and were not readily interpretable.

Although, papillary and follicular thyroid cancers are among the most curable cancers, high-risk patients for recurrence disease or death should be identified earlier. Most of these patients could be identified at the time of diagnosis by using well-established prognostic indicators. Besides that, therapeutic strategies and the extent of surgery depend on factors that influence the prognosis of thyroid cancer patients. Thus, identification of subgroups of patients with poorer prognoses might be of value in focusing treatment effort and reducing unnecessary mortality. In conclusion, this study identified age, loss of appetite, tumour size, regional recurrence, stage, and surgery plus RAI therapy and/or radiotherapy as prognostic factors for differentiated thyroid cancer patients in HUSM.

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