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Analysis of relevant risk factor and recurrence prediction model construction of thyroid cancer after surgery.

Shuai Lin[1#], Min Wang[2#], Jingqiang Zhu[3], Yanchun Gao[1*]

[1]Department of Thyroid Breast Surgery, Affiliated Hospital of North Sichuan Medical College, Nanchong, PR China

[2]Affiliated Hospital of North Sichuan Medical College, Nanchong, PR China

[3]Thyroid and Parathyroid Surgery Center, West China Hospital of Sichuan University, Chengdu, PR China

[#]These authors contributed equally to this work.

Abstract

Objective: To explore relevant risk factors of thyroid cancer after surgery, and build prediction of thyroid cancer recurrence.

Methods: Clinical data of thyroid cancer patients who diagnosed by surgical treatment and pathology from June, 2009 to December, 2012 were given retrospective analysis, follow-up for recurrence conditions after surgery; this study used Kaplan-Meier method to calculate recurrence rate after surgery of patients, drew survival curve without recurrence of patients.

Results: This study included 376 cases with thyroid cancer who met conditions, there were 86 male cases, 290 female cases; the age was from 16 to 81 y old. The average age was 43.5 ± 8.1 y old. The follow-up time was from 1 to 58 months. Median follow-up time was 24 h. There were 97 cases (25.8%) with recurrence during follow-up. Survival time without recurrence was from 1 to 58 months. Survival rate without recurrence in the first, second and third year were 96.8%, 92.5% and 87.9% respectively. Multiple factors regression model analysis found that maximum of tumor equal to or more than 4 cm. Surgical mode was unilateral resection of lobe with isthmus. Pathological type was undifferentiated carcinoma. No lymph node dissection was independent risk factors of recurrence of thyroid cancer after surgery ($P<0.05$). Prediction model was $h(t)=h_0 \exp(3.798\chi_1+2.721\chi_2+5.972\chi_3+2.679\chi_4)$.

Conclusion: Large tumor size, lobectomy plus isthmectomy, high degree of malignancy histopathology and without lymph node dissection are the main risk factors for thyroid cancer recurrence.

Keywords: Thyroid cancer, Recurrence, Risk factors, Cox regression model.

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Introduction

Thyroid cancer is the most common thyroid malignant tumor, accounting for 0.2% to 1% of general malignant tumor [1]. During the past 20 years, the incidence of thyroid cancer has increased sharply all over the world mainly due to increased detection using ultrasonography [2], and the incidence rate of thyroid cancer in Korea is the highest in the world [3]. And Chen et al. found that thyroid nodules were highly prevalent in men in China [4]. The treatment of thyroid cancer is manly surgical treatment, including thyroid cancer surgery and lymph node dissection. But the anatomic structure of thyroid is complex, the surgery cannot clean it completely, so it is easily to have recurrence after surgery. Evidence-data [5] show that in the studies of relating to 13 thyroid cancer recurrence from 1972 to 2012, there are 3511 in total, 414 recurrences after surgery. The total recurrence rate is 11.59%. Therefore, learning relevant risk factors of recurrence in patients after thyroid cancer surgery is benefit for identifying patients with recurrence risk, which has important clinical significance for treating patients. However, the risk factor for thyroid cancer recurrence has not yet been established clearly. So the aim of this study is to explore its relevant risk factors and establish recurrence prediction model through analyzing clinical and follow-up data of thyroid cancer patients during surgical time from June, 2009 to December, 2012 in affiliated hospital of North Sichuan Medical College, which will provide relevant scientific basis for thyroid cancer treatment and preventing recurrence.

Materials and Methods

General data

This study collected case information materials of 376 thyroid cancer patients continuously, who were diagnosed by pathology, surgical treatment in our hospital from June 1st, 2009 to December, 31st, 2012. There were 85 male cases, 290

female cases. The age was from 16 to 81 y old. The average age was 43.5 ± 8.1 y old. Complete information data of patients included general conditions, disease features, pathological features, treatment, prognosis, which all come from health record management system of information center in affiliated hospital of North Sichuan Medical College. This research was approved by the affiliated hospital of North Sichuan Medical College according to the declaration of Helsinki promulgated in 1964 as amended in 1996, the approval number is 2009003.

Study methods

This study collected cases information data of patients respectively from health record management system in hospital, including (1) Demographic characters, such as sex, age, height, weight, marriage conditions, education etc.; (2) disease features: such as tumor size, tumor invasion degree (T1: tumor diameter equal to or less than 1 cm, limited in thyroid; T2: the diameter more than 1cm or equal to or less than 4cm, limited in thyroid; T3: tumor more than 4cm, limited in thyroid; T4: tumor out of thyroid membrane), whether had lymph node metastasis, long-distance metastasis, surgical mode, pathological type etc.; (3) family history, smoking history and wine drink history etc.

Follow-up

This study acquired recurrence conditions and survival time without recurrence through follow-up. Observation start point was surgical treatment time of patients. Terminal point was recurrence of thyroid cancer of patients. The observation ending time was March, 31st, 2014; survival time without recurrence referred to the time from observation start point to terminal events (recurrence patients) or observation ending time (patients without recurrence). All patients used outpatient or phone call to do follow-up. Patients were regarded as losing follow-up without continuous visit, with visit decline, cannot connect patients and their families over three times.

Statistical management

This study input case information and follow-up data of patients into Epidata3.10 data base, used SPSS 16.0 software to do statistical management for data and materials, Kaplan-Meier method to calculate recurrence rate of patients, drew survival curve without recurrence of patients, then adopted multiple factors Cox regression model to analyse independent risk factors of patients after surgery. $P<0.05$, there were statistical differences.

Results

General conditions

There were 409 thyroid cancer patients with surgery in central affiliated hospital of North Sichuan Medical College from June, 2009 to December, 2013, of which, there were 24 cases excluded because of incomplete data, two cases were excluded who died of other diseases, 7 cases were regarded as follow-up lost because of incoordination and losing connection, 376 thyroid cancer patients were included who met criteria. General conditions and disease features seen in Table 1.

Follow-up results

The follow-up time was from the surgical time of patients to March, 31st, 2014. The follow-up was from 1 month to 58 month. Median follow-up time was 24 months. There were 97 patients have recurrence (25.8%). Survival time without recurrence was from 1 to 58 months. The average survival time without recurrence was 52.7±1.7 months. Survival rate without recurrence in 1-3 y after thyroid cancer surgery of patients were 96.8%, 92.5% and 87.9% respectively.

Table 1. *General conditions and disease features of thyroid cancer patients.*

Variables	Category	Cases	Variables	Category	Cases
Sex	Male	86 (22.9)	Neoplasm staging	T1	98 (26.1)
	Female	290 (77.1)		T2	105 (27.9)
Age/years old	43.5 ± 8.1			T3	120 (31.9)
BMI/(kg.m^{-2})	≤ 24	135 (35.9)		T4	53 (14.1)
	24~28	192 (51.1)	Capillary infiltration	No	330 (87.8)
	≥ 28	49 (13.0)		Yes	46 (12.2)
Education	Primary school and below	98 (26.1)	Lymph node dissection	No	292 (77.7)
	High school	180 (47.9)		Yes	84 (22.3)
	Junior college	56 (14.9)	Surgical mode	Total thyroidectomy	163 (43.4)
	Undergraduate and over	42 (11.2)		Subtotal thyroidectomy	114 (30.3)
Maximum diameter of tumor/cm	≤ 2	48 (22.9)		Resection of lobe with isthmus	99 (26.3)

	2~4	158 (42.0)	Surgical margin	negative	322 (85.6)
	≥4	132 (35.1)		positive	54 (14.4)
Lymph node metastasis	No	281 (74.7)	Pathological type	Papillary carcinoma	198 (52.7)
	Yes	95 (25.3)		FTC	73 (19.4)
Long-distance metastasis	No	317 (84.3)		Cephaloma	64 (17.0)
	Yes	59 (15.7)		Undifferentiated cancer	41 (10.9)

Notes: Percentage in brackets

Cox regression analysis of recurrence risk factors of thyroid cancer patients after surgery

This study took survival results (recurrence of thyroid cancer patients after surgery) and survival time (survival time without recurrence) as dependent variables, various relevant factors (demographic features, diseases features, family history, smoking and drinking winwe history) as independent variables, which were given multiple Cox ratio risk regression model analysis (the screening methods of variables: Forward, LR, inclusive criteria of variables α=0.05, exclusive criteria was 0.1). Results showed that maximum diameter of tumor equal to or more than 4 cm. The surgical method was unilateral resection of lobe with isthmus. Pathological type was undifferentiated carcinoma. No lymph node dissection was independent risk factors of thyroid cancer patients after surgery ($P<0.05$, Table 2).

Multiple factors prediction model of recurrence after thyroid cancer surgery

According to results of multiple Cox regression model analysis, this study fit risk function model expression of thyroid cancer patients after surgery: $h(t)=h_0 \exp(3.798\ \chi^1+2.721\ \chi^2+5.972\ \chi^3+2.679\ \chi^4)$. The greater the functional index number, the greater risk function h (t), the poorer the prognosis of patients, the higher the recurrence risk. PI was $PI=3.798\ \chi^1+2.721\ \chi^2+5.972\ \chi^3+2.679\ \chi^4$.

Discussion

As a whole, thyroid cancer generally has a good prognosis with a 5 y survival rate of 98% [6]. The malignant degree of thyroid cancer is relatively low, the growth is slow. Patients can survive for years without any symptoms. Once have symptoms of hoarseness, bucking, hemoptysis, unsmooth swallow, arthralgia, it shows the thyroid cancer has developed to a certain degree; routine examination, such as ultrasound, CT, MRI, thyroxine scanning etc. cannot identify accurate range and whether has metastasis of focus. Thyroid cancer of different pathological types and its biological behaviour have great differences. Different surgical treatments have different therapeutic effects on thyroid cancer [7], which will cause high recurrence rate of thyroid cancer. Although patients with thyroid cancer have excellent prognosis and survival, some researchers found that recurrence occurs in 5%-21% of patients with thyroid cancer [8,9]. Recurrence rate of patients' data in our study reach to 25.8%. Ti was very close to the literature report.

Table 2. *Multiple factors Cox analysis of thyroid cancer patients after surgery.*

Risk factors	n	RR (95% CI)	B	χ^2 value	P value
Maximum diameter of tumor (χ_1)					
≤ 1 cm	48	1			
1~4 cm	158	1.236 (0.715~2.136)	0.212	0.575	0.448
≥ 4 cm	132	3.798 (2.069~6.981)	1.334	17.926	< 0.001
Surgical mode (χ_2)					
Total or subtotal thyroidectomy	277	1			
Unilateral Resection of lobe with isthmus	99	2.721 (1.507~4.321)	0.941	11.885	0.001
Pathological type (χ_3)					
Papillary carcinoma	198	1			
FTC	73	1.259 (0.256~6.190)	0.231	0.081	0.777

Cephaloma	64	0.836 (0.450~1.552)	0.179	0.322	0.571
Undifferentiated cancer	41	5.972 (2.463~9.395)	1.787	9.734	0.002
Lymph node dissection (χ_4)					
Yes	292	1			
No	84	2.679 (1.761~4.130)	0.992	20.806	< 0.001

Yao et al. [1] find that recurrence risk of maximum diameter equal to or more than 4 cm is 6.236 times than diameter less than 4 cm. At present, surgical treatment are the main treatment mode of treating thyroid cancer, which has reached common cognition around the world. There still have arguments about selection of initial surgical mode and surgical range. American Thyroid Association (ATA) [10] thinks that thyroid cancer with a diameter of >4 cm, with extra glandular infiltration, with lymph node metastasis and with distant metastasis can be given complete resection of thyroid; European NCCN guide thinks that primary focus more than 4 cm, which is the symbol of complete resection of thyroid; JSTS [11] thinks that when focus more than 5 cm is suggested to be given complete resection of thyroid; at the same time, recurrence rate of patients with different surgical mode have different reports. Evidence-based data [5] show that recurrence rate of total thyroidectomy and subtotal thyroidectomy lower than unilateral resection of lobe with isthmus of patients. However, Yao et al. found that the recurrence rate of resection of lobe with isthmus was lower [1]. Data in this group also verify the recurrence rate of unilateral resection of lobe with isthmus higher than total thyroidectomy and subtotal thyroidectomy (RR=2.721). The more severe the histological malignant degree, the higher the recurrence of patients after surgery (OR=5.927) [1], this study also concludes the similar results. We also find that the recurrence risk of patients without lymph node dissection is 2.679 times than patients with lymph node dissection. Another study emphasized that the number of metastatic lymph nodes in the central compartment is a significant predictor of recurrence [12]. Therefore, for thyroid cancer patients, we should complete examination before surgery, evaluate metastasis location of patients as much as possible, identify resection range of cancerous focus to avoid recurrence after surgery.

In conclusion, the recurrence factors of thyroid cancer patients are wide and complex, which have correlations with disease severe degree etc., also with surgical modes. But selection of surgical modes also influenced by tumor pathological type etc. Therefore, we should be careful for selecting surgical mode of thyroid cancer, and combine with experience of physicians, consider conditions of patients themselves comprehensively. From comprehensive treatment, we should select individualized treatment program to prevent and treat recurrence of thyroid cancer patients.

Several limitations of this study should be considered. Firstly, all patients were collected from the same hospital. Further studies are needed to unravel this. Secondly, the sample size is not big enough. However, the study setting is a modern, high level comprehensive medical institution with sophisticated clinical diagnosis facilities and medical record management. Thus, the data used can be deemed reliable.

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***Correspondence to**

Yanchun Gao

Department of Thyroid Breast Surgery

Affiliated Hospital of North Sichuan Medical College

PR China