Oncologie
DOI: 10.32604/oncologie.2020.012445
Article

Analysis of the Effects of Different Surgical Procedures for the Treatment of Thyroid Cancer on the Expression Levels of IL-17, IL-35, and SIL-2R and the Prognostic Factors

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Abstract: To analyze the effects of different surgical procedures for the treatment of thyroid cancer on the expression levels of serum interleukin-17 (IL-17), IL-35, soluble interleukin-2 receptor (SIL-2R), and the prognostic factors. Seventy-eight patients with differentiated thyroid cancer were selected and grouped as control group (CG) (n = 39, underwent subtotal thyroidectomy) and observation group (OG) (n = 39, underwent total thyroidectomy). The serum IL-17, IL-35, and SIL-2R expression levels; the incidence of complications; and the differentiated thyroid carcinoma (DTC) relapse rate were compared between the two groups. The serum IL-17 and SIL-2R levels were lower in the OG than in the CG on the third, fifth, and seventh days after the operation, but the IL-35 levels were higher than those in the CG ($p < 0.05$). There were no cases of relapse in the OG, and the DTC relapse rate was lower than that of the CG (15.38%) ($p < 0.05$). The differences in age; lesion diameter; serum IL-17, IL-35, and SIL-2R expression levels; AJCC thyroid cancer stage; and disease type between DTC relapse and relapse-free patients were statistically significant ($p < 0.05$). Older age; higher IL-17, lower IL-35, and higher SIL-2R expression levels; higher AJCC thyroid cancer stage; and disease type were positively correlated with DTC relapse ($p < 0.05$). Compared with subtotal thyroidectomy, total thyroidectomy for the treatment of thyroid cancer has greater advantages in improving immune inflammation and reducing the relapse rate. Older age; higher IL-17, lower IL-35, and higher SIL-2R expression levels; higher AJCC thyroid cancer stage; and disease type are independent risk factors affecting thyroid cancer relapse after surgery. These findings can reference the selection of clinical surgery procedures in the treatment of thyroid cancer.

Keywords: Thyroid cancer; SIL-2R; prognostic; IL-17; different surgical procedures; IL-35

1 Introduction

Thyroid cancer accounts for approximately 1% of the malignant tumors in the body, which can be divided into the differentiated type and the undifferentiated type according to histology [1,2]. Differentiated thyroid carcinoma (DTC) accounts for approximately 90% of thyroid malignancies, with a low degree of malignancy and better prognosis after standardized treatment. However, some patients with DTC still have high invasiveness and die from distant metastases [3,4]. At present, total thyroidectomy and subtotal thyroidectomy are commonly used for DTC treatment. Due to the lack of accurate preoperative assessment and the operator's uncertainty about the principles of DTC diagnosis and treatment, choosing the appropriate treatment method remains controversial. Additionally, the impact of the two surgical procedures on prognosis is uncertain. In recent years, studies have found that interleukin-17 (IL-17), IL-35, and soluble interleukin-2 receptor (SIL-2R) are closely related to the occurrence and development of thyroid cancer. The effects of different surgical procedures on their expression levels and whether they can be used for preoperative evaluation require further discussion [5,6]. In this study, 78 patients with DTC were selected to observe the effects of different surgical procedures on the expression levels of serum IL-17, IL-35, and SIL-2R and the prognostic factors. A discussion of the findings follows.

2 Material and Methods

2.1 General Information

A total of 78 DTC patients admitted to our hospital from January 2015 to December 2017 were selected and grouped according to different surgical procedures they had undergone. There were two groups with 39 patients each. (1) The inclusion criteria were as follows: met the DTC diagnostic criteria [7]; no history of radiotherapy or chemotherapy; no history of taking iodine preparation before surgery; voluntary signing of informed consent; no serious lung or liver dysfunction; first thyroid surgery treatment; and unilateral lesions. (2) The exclusion criteria were as follows: adhesions of the thyroid tumor and large vessels in the trachea and neck; accompanied by a diffuse goiter; lymph node metastasis; unable to tolerate surgery; contraindications to anesthesia; and loss to follow-up due to various reasons. All patients included in this study were informed about the study purpose and volunteered to participate. This study was confirmed and approved by the ethical committee department of Linyi Tumor Hospital (Linyi, Shandong, China).

2.2 Methods

Preoperative treatment. To determine the boundary, number, and calcification conditions of the thyroid nodules, the thyroid and neck lymph node ultrasound examination and thyroid function examination were completed before the operation in both groups, and a cervical CT examination was performed as appropriate. Patients with hyperthyroidism were given medical treatment to reduce their basal metabolic rate to normal or close to normal and to keep the pulse rate less than 90 times/min.

Each patient in the control group (CG) underwent subtotal thyroidectomy. After anesthetization and tracheal intubation, the shoulders were raised in the supine position, the head was tilted back, and small sandbags were fixed on both sides of the patient's head with exposed neck. An arc-shaped incision was made along the dermatoglyph at the location of two horizontal fingers above the incisura on the sternum. The skin and subcutaneous tissue were cut in turn, and the upper and lower flaps were pulled and then separated along the loose tissues behind the platysma, up to the lower edge of thyroid cartilage and down to the incisura of sternum stem. The incision was protected and pulled apart. The anterior jugular veins on both sides were sutured with No. 4 silk thread. After cutting the fascia and separating the sternocleidomastoid muscle and the anterior cervical muscle group, the deep fascia was longitudinally cut through the midline of the neck to separate the muscle group and reach the thyroid capsule. By careful separation of the thyroid suspensory ligament through the inner side of the upper pole and incision and ligation of the ligament, the thyroid gland was separated. The middle thyroid vein in the central section of the gland periphery was separated, ligated, and cut with the thyroid gently pulled inside. The inferior thyroid vein was ligated and cut after separation of the lower pole along the thyroid periphery. The inferior thyroid artery generally does not need to be exposed or ligated to protect the recurrent laryngeal nerve. After the back of the thyroid isthmus was separated via the front of the lower trachea to determine the boundary of the gland, a wedge-shaped thyroidectomy resection was performed. The resection volume depends on the patient's thyroid function and condition. Generally, the residual glandular tissue should cover the parathyroid gland and the recurrent laryngeal nerve, and the capsule behind the gland should be maintained as much as possible. After complete hemostasis and catheter drainage, the incision was closed.

Every patient in the observation group (OG) underwent total thyroidectomy. The posture, incision, and exposure were the same as those in the CG.

After the thyroid was exposed, the thyroid suspensory ligament was separated and cut with the superior thyroid blood vessels disposed. The lower pole of the thyroid gland was revealed with ligation and incision of the middle and inferior thyroid veins and severing of the thyroid isthmus while protecting the recurrent laryngeal nerve. After being dissociated from the contralateral lobe, the entire thyroid gland including the thyroid isthmus was removed with the sternum thyroid muscle, and the sternohyoid muscle was severed horizontally at the level of the hyoid and thyroid cartilage. After sufficient hemostasis, suturing, and catheter drainage, the incision was closed.

Detection methods. Five milliliters of peripheral venous blood were collected and centrifuged. The levels of IL-17, IL-35, and SIL-2R were detected by an enzyme-linked immunosorbent assay. The detection kits were purchased from Shanghai Enzyme-linked Biotechnology Co., Ltd. (Shanghai, China).

2.3 Outcome Measurement

(1) The expression levels of serum IL-17, IL-35, and SIL-2R at four-time points (pre-operation and the third, fifth, and seventh days after operation) were compared between the two groups. (2) The incidence of complications and the relapse rate of DTC were determined in both groups during follow-up until March 2019. (3) Factors including gender, age, body mass index (BMI), lesion diameter, drinking history, smoking history, American Joint Committee on Cancer (AJCC) thyroid cancer stage, disease type, lesion side, comorbid diseases, and serum IL-17, IL-35, and SIL-2R expression levels were compared between DTC relapse and relapse-free patients. (4) The factors influencing DTC relapse were analyzed by a logistic regression.

2.4 Statistical Analysis

SPSS 23.0 statistical software was used to process the data. The measurement data were expressed as (± s) by the t test. The count data were expressed as n (%) with the χ^2 test. A multivariate analysis was performed using a logistic multiple regression equation. $P < 0.05$ was considered statistically significant.

3 Results

3.1 Comparison of Clinical Data

The clinical data of the two groups in terms of gender, age, BMI, lesion diameter, drinking history, smoking history, AJCC thyroid cancer stage, disease type, lesion side, and comorbid diseases were well balanced and comparable ($p > 0.05$) (Tab. 1).

Table 1: Comparison of clinical data between the two groups

Clinical data	Control group (n = 39)	Observation group (n = 39)	$t/\chi^2/u$	p
Age (year)	24–63 (41.16 ± 8.55)	26–65 (41.25 ± 7.59)	0.049	0.961
gender (male/female)	12/27	15/24	0.510	0.475
BMI (kg/m²)	20–24 (22.98 ± 0.45)	20–24 (23.02 ± 0.42)	0.406	0.686
lesion diameter (cm)	0.9–4.0 (2.74 ± 0.60)	0.8–4.0 (2.80 ± 0.56)	0.457	0.649
Drinking history	3 (7.69)	5 (12.82)	0.139	0.709
Smoking history	5 (12.82)	4 (10.26)	0.000	1.000
AJCC thyroid cancer stage				
Stage I	8 (20.51)	6 (15.38)	0.553	0.907
Stage II	14 (35.90)	16 (41.03)		
Stage III	12 (30.77)	11 (28.21)		
Stage IV	5 (12.82)	6 (15.38)		
Disease type				
Follicular thyroid carcinoma	6 (15.38)	8 (20.51)	0.348	0.555
Papillary thyroid carcinoma	33 (84.62)	31 (79.49)		
Lesion side				
Left side	16 (41.03)	19 (48.72)	0.466	0.495
Right side	23 (58.97)	20 (51.28)		

comorbid disease				
Hyperlipidemia	1 (2.56)	3 (7.69)	0.264	0.608
Diabetes	2 (5.13)	4 (10.26)	0.181	0.671
Heart disease	0 (0)	2 (5.13)	–	0.494
Hypertension	1 (2.56)	0 (0)	–	1.000

Note: "–" Indicates that the exact probability method is used for calculation, and there is no chi-square value.

3.2 Comparison of IL-17 Expression Levels

Compared with pre-operation data, the serum IL-17 levels in the two groups were significantly reduced after the operation ($p < 0.05$). The serum IL-17 levels in the OG were lower than those in the CG on the third, fifth, and seventh days after the operation ($p < 0.05$). The IL-17 levels in the two groups decreased after the operation, and the decrease of IL-17 levels was more significant in the OG (Fig. 1).

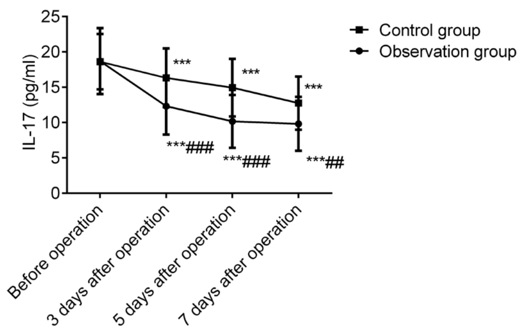

Figure 1: Comparison of expression levels of serum IL-17 in the two groups between pre-operation and post-operation. Note: Compared with preoperative, *** $p< 0.001$; Compared with the control group at the same time, $^{###}p < 0.01$, $^{###}p< 0.001$

3.3 Comparison of IL-35 Expression Levels

Compared with pre-operation data, the serum IL-35 levels in the two groups of patients increased significantly after the operation ($p < 0.05$). The OG showed increased serum IL-35 levels compared with the CG on the third, fifth, and seventh days after the operation ($p < 0.05$). Thus, the postoperative IL-35 levels increased in both groups, and the increase of IL-35 levels was more significant in the OG (Fig. 2).

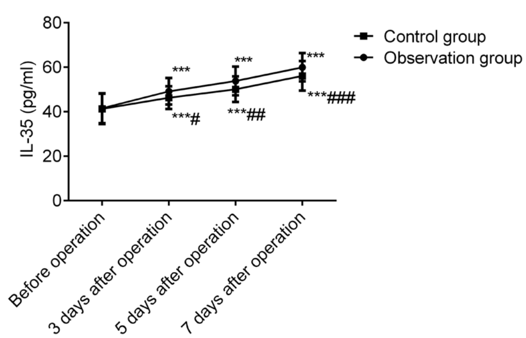

Figure 2: Comparison of the expression levels of serum IL-35 in the two groups between pre-operation and post-operation. Note: Compared with preoperative, $^{***}p < 0.001$; Compared with the control group at the same time, $^{##}p < 0.05$, $^{###}p < 0.01$, $^{###}p < 0.001$

3.4 Comparison of IL-2R Expression Levels

Compared with pre-operation data, the postoperative serum SIL-2R levels in the two groups were significantly reduced ($p < 0.05$). The OG showed decreased serum SIL-2R levels compared with the CG on the third, fifth, and seventh days after the operation. The SIL-2R levels in the two groups decreased after the operation, and the decrease of IL-2R levels was more significant in the OG (Fig. 3).

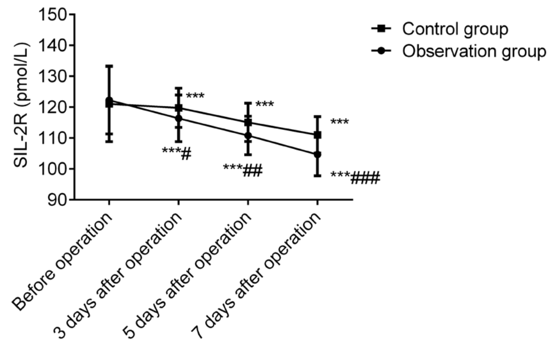

Figure 3: Comparison of expression levels of serum SIL-2R in the two groups between pre-operation and post-operation. Note: Compared with preoperative, $^{***}p < 0.001$; Compared with the control group at the same time, $^{\#\#}p < 0.05$, $^{\#\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$

3.5 Incidence of Complications and DTC Relapse Rate

No patients were lost to follow-up until March 2019. During this period, there was no relapse in the OG whereas the DTC relapse rate was 15.38% in the CG ($p < 0.05$) (Tab. 2).

Table 2: Comparison of the incidence of complications and DTC relapse rate between the two groups, n (%)

Group	Case	Incidence of complications					DTC relapse rate
		Recurrent laryngeal nerve injury	Superior laryngeal nerve injury	Laryngeal edema	Postoperative bleeding	Incidence of complications	
Control group	39	0 (0)	1 (2.56)	1 (2.56)	0 (0)	2 (5.13)	0 (0)
observation group	39	1 (2.56)	0 (0)	1 (2.56)	1 (2.56)	3 (7.69)	6 (15.38)
χ^2						0.000	4.514
P						1.000	0.034

3.6 Univariate Analysis

The differences in age; lesion diameter; serum IL-17, IL-35, and SIL-2R expression levels; AJCC thyroid cancer stage; and disease type were statistically significant ($p < 0.05$) (Tab. 3).

Table 3: Univariate analysis

Clinical data	DTC relapse patients (n = 6)	DTC relapse-free patients (n = 72)	$t/\chi^2/u$	*p*
Age (year)	24–65 (53.26 ± 5.82)	25–64 (41.86 ± 8.35)	3.269	0.002
gender (male/female)	1/5	26/46	0.266	0.606
BMI (kg/m²)	20–24 (22.25 ± 0.82)	20–24 (22.30 ± 0.81)	0.145	0.885
lesion diameter (cm)	0.9–4.0 (3.36 ± 0.28)	0.8–4.0 (2.14 ± 0.62)	4.757	0.000
expression levels of IL-17 (pg/ml)	14–18 (16.34 ± 0.79)	10–15 (13.25 ± 0.82)	8.889	0.000
expression levels of IL-35 (pg/ml)	34–58 (40.09 ± 3.01)	40–65 (51.11 ± 5.51)	4.819	0.000
expression levels of SIL-2R (pmol/L)	120–130 (125.34 ± 2.28)	110–128 (118.16 ± 1.01)	14.849	0.000
Drinking history	1 (16.67)	7 (9.72)	–	1.000
Smoking history	1 (16.67)	8 (11.11)	–	1.000

AJCC thyroid cancer stage				
Stage I	0 (0)	14 (19.44)	26.120	0.000
Stage II	0 (0)	30 (41.67)		
Stage III	1 (16.67)	22 (30.56)		
Stage IV	5 (83.33)	6 (8.33)		
Disease type				
Follicular thyroid carcinoma	6 (100.00)	8 (11.11)	23.985	0.000
Papillary thyroid carcinoma	0 (0)	64 (88.89)		
Lesion side				
Left side	3 (50.00)	32 (44.44)	0.027	0.870
Right side	3 (50.00)	40 (55.56)		
comorbid disease				
Hyperlipidemia	0 (0)	4 (5.56)	0.137	0.711
Diabetes	1 (16.67)	5 (6.94)	–	0.392
Heart disease	0 (0)	2 (2.78)	0.866	0.352
Hypertension	1 (16.67)	0 (0)	–	0.077

Note: "–" Indicates that the exact probability method is used for calculation, and there is no chi-square value.

3.7 Multivariate Analysis

Every statistically significant single factor was included in the logistic analysis. The results showed that lesion diameter was not significantly correlated with DTC relapse ($p > 0.05$). However, older age; higher IL-17, lower IL-35, and higher SIL-2R expression levels; higher AJCC thyroid cancer stage; and disease type were positively correlated with DTC relapse ($p < 0.05$) (Tab. 4).

Table 4: Analysis of influencing factors of DTC relapse

Influencing factors	β	SE	Wald	OR	*p*	95%CI
Older age	0.391	0.362	1.167	1.932	0.042	1.925–1.946
Larger lesion diameter	0.686	0.559	1.506	1.125	0.714	1.078–3.206
Higher IL-17	0.317	0.205	2.391	1.993	0.018	1.886–2.995
Lower IL-35	0.326	0.322	1.025	1.946	0.036	1.904–1.969
Higher SIL-2R	0.539	0.225	5.739	1.996	0.015	1.925–4.998
Higher AJCC thyroid cancer stage	0.358	0.219	2.672	1.989	0.026	1.874–3.999
Disease type	0.527	0.489	1.161	1.929	0.046	1.894–2.935

4 Discussion

At present, surgical treatment for DTC is generally recommended by clinicians, but there are no specific criteria regarding the selection of total thyroidectomy and subtotal thyroidectomy. Because the thyroid is an important endocrine organ in the human body, patients undergoing total thyroidectomy must take medication for a long time to maintain normal hormone levels, and the incidence of hypocalcemia complications after total thyroidectomy increases. A previous study indicated that excessive treatment should be avoided [8]. Some critics suggest that total thyroidectomy should be used to reduce DTC relapse [9]. It follows that the postoperative relapse rate is a key factor affecting the selection of surgical procedures, and clinical theoretical reference is expected to clear the lesion to the greatest extent and avoid excessive treatment. In this study, there were no cases of relapse in the OG whereas the DTC relapse rate was 15.38% in the CG ($p < 0.05$). Similar to other reports, our findings suggest that total thyroidectomy has advantages in reducing DTC relapse.

The pathogenesis of DTC is complicated; it involves multiple factors such as genetic factors, radiation, sex hormones, and benign thyroid disease [10–12]. Studies have pointed out that the occurrence, invasion, and metastasis of DTC are the result of the interaction of multiple molecules and cytokines [13]. IL-17 is a type of cytokine with abundant biological effects secreted by macrophages, natural killer cells, and dendritic cells. It participates in the activation process of T cells and can stimulate epithelial cells, endothelial cells, neutrophils, and fibroblasts to release many inflammatory cytokines [14–17]. IL-35 is an immune inflammatory mediator, and recent studies have found that it has a unique immunosuppressive effect [18–21]. SIL-2R is regarded as a marker in various malignant tumors because it is formed by the shedding of cancer cells and entering the circulating blood. It plays an important role in the activation and proliferation of immune cells and can reflect the severity of the patient's condition [22–25]. IL-17, IL-35, and SIL-2R have been extensively studied in the thyroid field. Liu et al. [26] reported that IL-17 and SIL-2R increased with the clinical stage of thyroid cancer, and there was a significant difference in different clinical stages. Kang et al. [27] compared the serum IL-17 and IL-35 levels in patients with thyroid cancer with those in patients with thyroid adenoma and found that patients with thyroid cancer had significantly higher IL-17 and IL-35 levels. Wang et al. [28] pointed out that serum IL-17 and SIL-2R levels were significantly positively correlated with the pathological stage of thyroid cancer whereas L-35 levels were significantly negatively correlated with the pathological stage of thyroid cancer. Therefore, IL-17, IL-35, and SIL-2R are closely related to the onset, invasion, and metastasis of DTC. This study found that the serum IL-17 and SIL-2R levels in the OG were lower than those in the CG on the third, fifth, and seventh days after operation, and the IL-35 level was higher than that in the CG ($p < 0.05$), which suggests that total thyroidectomy can improve the body's immune and inflammatory responses compared with subtotal thyroidectomy.

The purpose of DTC surgical treatment is to remove cancerous tissue, prevent disease relapse, and improve patient prognosis [29,30]. Although the scope of DTC surgical resection remains controversial, the selection of surgical procedures is often based on the comprehensive estimates of disease stage and cervical lymph node metastasis. Generally, the scope of lesion resection in low-risk patients can be conservative, and the range of resection in patients with high-risk factors should be expanded. There is no unified standard for low-risk and high-risk factors. Kang et al. [31] reported that advanced age, clinical stage Ⅲ to Ⅳ, and lymph node metastasis are the influencing factors of multifocal thyroid cancer surgery. Zhang [32] showed that the prognosis of thyroid cancer is related to indexes including patient gender, age, pathological type, and tumor stage. In this study, a univariate analysis was performed on the general data of relapsed and non-relapsed patients. Every statistically significant single factor was included in the logistic analysis. The results showed that older age; higher IL-17, lower IL-35, and higher SIL-2R expression levels; higher AJCC thyroid cancer stage; and disease type were positively correlated with DTC relapse ($p < 0.05$). This illustrates that influencing factors including older age; higher IL-17, lower IL-35, and higher SIL-2R expression levels; higher AJCC thyroid cancer stage; and disease type are independent risk factors that affect the relapse of thyroid cancer after surgery. These findings can provide a reference for the selection of clinical surgery procedures in the treatment of thyroid cancer. If a DTC patient without lymph node metastasis meets the following conditions (older age; higher IL-17, lower IL-35, and higher SIL-2R expression levels; higher AJCC thyroid cancer stage; and characteristics of follicular thyroid cancer), a total thyroidectomy is suggested. A subtotal thyroidectomy can be performed in patients without the above risk factors under close monitoring to achieve maximum removal of the lesion and avoid overtreatment. Because of grouping by surgical procedures, this study is a non-prospective study, which may lead to biased results. This limitation must be further improved and verified in the future.

In summary, compared with subtotal thyroidectomy, total thyroidectomy has more advantages in improving immune inflammation and reducing the relapse rate. Older age; higher IL-17, lower IL-35, and higher SIL-2R expression levels; higher AJCC thyroid cancer stage; and disease type are independent risk factors that affect the relapse of thyroid cancer after surgery. These findings can provide a reference for the selection of clinical surgery procedures in the treatment of thyroid cancer.

5 Conclusion

This study confirms that total thyroidectomy has more advantages in clinical application. Considering the importance of the thyroid, it innovatively analyzes the risk factors that affect postoperative relapse. This study has practical value in ensuring the maximum removal of the lesion and avoiding excessive treatment.

Funding Statement: The author(s) received no specific funding for this study.

Conflicts of Interest: The authors declare that they have no conflicts of interest to report regarding the present study.

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