Does Unilateral Thyroid Cancer Affect The Malignant Risk Of Contralateral Thyroid Nodules?-A Retrospective Cohort Study

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Research

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Abstract

Background

The incidence of thyroid nodules increased significantly, but the mortality rate of thyroid cancer remained stable or even decreased. However, surgical treatment of thyroid nodules is more aggressive, including the number and scope of surgery. the purpose of our study was to evaluate whether unilateral thyroid nodules affect the malignancy risk of contralateral thyroid nodules.

Methods

We conducted a retrospective study on all patients with thyroid nodules in a tertiary hospital within one year. Unilateral and bilateral thyroid nodules were the control group and the experimental group, respectively. Based on the TI-RADS grades, the experimental group and the control group were divided into two subgroups. We used chi-square test or Fisher's exact test to evaluate whether there were statistical differences in the incidence and pathological types of thyroid cancer between the experimental group and the control group.

Results

Our study showed that there was no significant difference in malignant risk between the experimental group 1 and the control group 1, and the experimental group 2 and the control group 2 (20%vs35%, p=0.724, 63.16%vs76.32%, p=0.297, respectively). Both the a-side thyroid of the experimental group and the control group were papillary thyroid carcinoma, including micropapillary thyroid carcinoma, and there was no difference in the proportion of micropapillary thyroid carcinoma (p = 0.200, 0.620, respectively).

Conclusions

There is no evidence that bilateral thyroid nodules affect each other in terms of malignant risk, that is, in bilateral thyroid nodules, unilateral thyroid cancer does not change the malignant risk of contralateral thyroid nodules.

This study has been registered with the Chinese Clinical Trial Registry, clinical trial registration number: ChiCTR2000038611, registration time: 2020-09-26.

1. Introduction

Thyroid nodules are defined as discrete lesions within the thyroid gland, radiologically distinct from surrounding thyroid parenchyma (1). Thyroid nodules are extremely common in the general population, and the study reports that it is 4%-7% and 30%-67% of the population by palpation and imaging examinations, respectively (2). At present, due to the popularity and application of high-resolution imaging examinations, we notice that compared with patients with thyroid nodules due to thyroid-related symptoms or thyroid palpation, more and more patients are accidentally discovered by imaging examinations. Most of these accidental thyroid nodules are usually asymptomatic and small (3). Research by Guth S et al. also shows that up to 68% of the general population have occult thyroid nodules (2). many imaging examinations can identify thyroid nodules. the incidence of thyroid nodules in ultrasound, computed tomography (CT) or magnetic resonance imaging (MRI), 18 fluorodeoxyglucose positron emission tomography (PET) is 65%, 15%, 1% to 2%, respectively (4). Among them, ultrasound is the most common imaging examination for the detection of thyroid nodules. Moreover, thyroid ultrasound is recommended by the British, American, and European Thyroid Association (BTA, ATA, and ETA, respectively) as the first-line examination to evaluate thyroid nodules (1.5.6). Thyroid ultrasound can accurately identify malignant thyroid nodules, and may even be better than the pathological results of thyroid fine-needle aspiration biopsy (FNAB) (7.8). Thyroid nodules include benign and malignant ones, and the proportion of malignant thyroid nodules varies from 4% to 12%, including thyroid nodules accidentally discovered by imaging examinations (7.9-16). Because of the high incidence of thyroid nodules in the population, the number of patients with thyroid cancer is huge. Thyroid cancer currently ranks fifth among female cancers. It is estimated that by 2030, thyroid cancer will rank second and ninth in female and male cancers, respectively (17). Not all thyroid nodules require biopsy or even surgical treatment. More than 90% of detected thyroid nodules are clinically insignificant because they have no ultrasound features that suggest malignancy or because they are cytologically benign (18). The emergence and application of the Thyroid Imaging Report and Data System (TI-RADS) (19), developed by the American College of Radiology (ACR), allows surgeons to stratify the risk of thyroid nodules and adopt appropriate management strategies for thyroid nodules. This has the benefits of timely treatment of clinically significant thyroid cancer, and also reduces the increased costs and risks due to biopsy and treatment of benign thyroid lesions and indolent thyroid cancer. The partial analysis shows that the malignant risk of TR1-5 thyroid nodules is significantly different. The malignant risks of TR1-5 thyroid nodules are < 2%, < 2%, 5%, 5%-20%, ≥ 20%, respectively.

The incidence of thyroid nodules is increasing, however, the attributable mortality of thyroid cancer remains stable or even decreases. At present, a more aggressive strategy for thyroid nodules is adopted in clinical practice, which is not only reflected in the significant increase in the number of surgery for thyroid nodules but also in the scope of surgery (preferably total thyroidectomy or subtotal thyroidectomy), even if the patient is

Low-medium risk of thyroid cancer. Because most thyroid cancers are characterized by indolence, these thyroid cancers may not cause any symptoms in the patient's life or have no impact on the lifespan of the patient. Therefore, not all thyroid cancer are required surgery immediately. This more aggressive treatment strategy not only leads to an increase in the number of patients with thyroid postoperative complications but also increases the risk of postoperative complications, especially long-term and serious postoperative complications. Therefore, from the perspective of patients and society, it may not be beneficial. The thyroid is usually characterized by bilateral nodules. According to the anatomical characteristics of the thyroid, the study regarded the bilateral thyroid gland as two separate parts to investigate whether the two affect each other in terms of malignant risk.

2. Materials And Methods

2.1 Study design and population

This study was a single-center retrospective cohort study. All patients with thyroid nodules were enrolled in the Department of General surgery of a tertiary hospital from December 2018 to December 2019. According to the inclusion criteria and exclusion criteria, the subjects were screened and grouped. Then, statistical analysis was performed on the experimental group and the control group.

2.2 data collection

The data of this study were obtained through the hospital electronic case system. The research data included demographic characteristics (including age and gender), chief complaint, medical history, thyroid ultrasound results, surgical procedures, and postoperative pathology. Among them, thyroid ultrasound results included TI-RADS classification of thyroid nodules, thyroid nodule size, and cervical lymph nodes.

2.3 Research objects and groups

Excluding patients with incomplete data or other interfering factors, other patients were divided into the experimental group and the control group according to the results of thyroid ultrasound. First of all, to facilitate the subsequent statistical analysis, we had a special definition for bilateral thyroid cancer. For bilateral thyroid cancer, the side with higher TI-RADS grade or more malignant pathology was b-side thyroid, while the contralateral side was a-side thyroid. For example, bilateral thyroid cancer, in which one side was papillary carcinoma (a-side), the other side was undifferentiated carcinoma or medullary carcinoma (b-side).In this study, statistical analysis was performed on the a-side thyroid nodules in the experimental group and the thyroid nodules in the control group.

The inclusion criteria of the experimental group: (1) Bilateral thyroid nodules; (2) Bilateral thyroid nodules were surgically removed; (3) Bilateral thyroid nodules had postoperative pathology; Exclusion criteria of the experimental group：(1) Bilateral benign thyroid nodules ; (2) History of malignant tumors in other tissues or organs (except thyroid); (3) History of thyroid surgery due to thyroid nodules or other thyroid diseases. Those who met the above conditions were the experimental group, which were divided into two subgroups based on the TI-RADS classification of a-side thyroid nodules. TI-RADS 3 and 4 were the experimental groups 1 and 2, respectively. The inclusion criteria of the control group: (1) Unilateral thyroid nodules; (2) Unilateral thyroid nodules were surgically removed; (3) Unilateral thyroid nodules had postoperative pathology; Exclusion criteria of the control group：(1) History of malignant tumors in other tissues or organs (except thyroid); (2) History of thyroid surgery due to thyroid nodules or other thyroid diseases. Those who met the above conditions were the control group, which were divided into two subgroups based on the TI-RADS classification of unilateral thyroid nodules. TI-RADS 3 and 4 were the control group 1 and 2, respectively.

2.4. statistics

In statistical analysis, we used absolute frequencies and percentages to describe categorical variables, and mean and 95% confidence intervals to describe continuous variables. Student’s t-tests were used to determine the difference in age between the experimental groups and the control groups. In terms of gender, postoperative pathological results, and surgical procedures between the experimental groups and the control groups, we used the chi-square test or Fisher's exact test to determine the difference. All analyses were performed using IBM SPSS Statistics version 25; $p<0.05$(bilateral) was statistically significant.

3. Results

The collection and grouping process of cases was shown in Fig 1.

Our results on demographic characteristics were shown in Table 1. The average age of the experimental group and the control group were 50.82±10.98 and 47.72±9.58, respectively ($P=0.093>0.05$). The average age of the experimental group 1 and the control group 1 were 50.11±10.244, 50.13±9.848($P=0.993>0.05$), respectively. The average age of the experimental group 2 and the control group 2 were 53.26±9.48 and 46.76±9.43, respectively (P=0.037＜0.05). In terms of gender, there were $P=0.680$ (> 0.05) and $P=0.016$ (< 0.05) in the experimental group 1 and the control group 1, and the experimental group 2 and the control group 2, respectively.

We used the chi-square test to statistically analyze the postoperative pathological distribution of the two groups. The statistical results were shown in Table 2. We saw that there were no significant differences in the two subgroups, and their p-value was 0.724 (>0.05) and 0.297 (>0.05), respectively. In our collection of case data, we saw that thyroid cancer in the a-side thyroid of the experimental group and the control group were thyroid papillary carcinoma (including thyroid micropapillary carcinoma), and there were no other types of thyroid cancer. Moreover, there were no significant differences in the two subgroups, and the P-value was 0.200 (>0.05) and 0.620(>0.05), respectively. Because there were fewer cases in the control group 1, we can not compare the proportion of thyroid micropapillary carcinoma in thyroid papillary carcinoma, but in the experimental group 1, 2, and the control group 2, we saw that the proportion of thyroid micropapillary carcinoma was relatively high. We found that the proportion of thyroid micropapillary carcinoma was relatively high, reaching 61.54%, 83.3%, and 89.66%, respectively. We saw that when the thyroid nodules on the a-side of the experimental group and the control group were benign, the statistical analysis of the surgical procedures of the two subgroups was shown in Table 2.There was no significant statistical difference between the experimental group 1 and the control group 1 (p=0.131>0.05). However, there were significant statistical differences between the experimental group 2 and the control group 2(p=0.001<0.05). We saw that when the thyroid nodules in the experimental group and the control group were malignant, the results were shown in Table 3. Although statistical results cannot be obtained in the two subgroups due to the small number of cases, we can still see that more patients in the experimental group and the control group undergo thyroid lobectomy.

We saw the distribution of pathological types of b-side thyroid carcinoma in the experimental group, as shown in Table 4. In the experimental group 1, the pathological types of thyroid carcinoma were 64 (98.46%) thyroid papillary carcinoma, including 31 (47.69%) thyroid micropapillary carcinoma, and 1 (1.54%) medullary thyroid carcinoma. Similarly, in the experimental group 2, 18 (94.74%) thyroid papillary carcinoma, including 7 (36.84%) thyroid micropapillary carcinoma, 1 (5.26%) thyroid undifferentiated carcinoma.

4. Discussion

Thyroid nodules are an extremely common disease and have a high incidence in the general population. First, we compared the demographic characteristics of the experimental group and the control group. We saw that there was no significant statistical difference in age and gender between the experimental group 1 and the control group 1. However, there were statistical differences in age and gender between the experimental group 2 and the control group 2. We saw that compared with the experimental group 2, the average age in the control group 2 was younger(46.76vs.53.21 p=0.037) and there were more male patients(19/42vs.0/15 p=0.016). This is consistent with the fact that men with thyroid cancer are usually younger.

A systematic review including 14 studies at a moderate risk of bias found the odds ratio for thyroid cancer to be lower in patients with a multinodular goiter than in those with single nodules (20). Moreover, thyroid nodules are usually bilateral nodules. Because of the anatomical characteristics of the thyroid, we regarded the bilateral thyroid gland as two independent units to evaluate whether bilateral thyroid nodules interact with each other in terms of malignant risk. Our study showed that there was no significant difference in malignant risk between the experimental group 1 and the control group 1, and the experimental group 2 and the control group 2 (20%vs. 35%, p=0.724, 63.16% vs. 76.32%, p=0.297, respectively).

Because the types of thyroid carcinoma in the a-side of the experimental group and the control group were all papillary thyroid cancer, including micropapillary thyroid carcinoma, we saw no significant difference in the proportion of micropapillary carcinoma between the two subgroups (p=0.200,p=0.620, respectively). Moreover, we also noticed that it was extremely high, especially in the experimental group 2 and the control group 2, reaching 83.33% and 89.66%, respectively. We saw that in the b-side of the experimental group, except for 1 medullary thyroid carcinoma in the experimental group 1 and 1 Anaplastic thyroid carcinoma in the experimental group 2, all other cases were thyroid papillary carcinoma.

Although thyroid nodules are prevalent in the general population, more than 90% of thyroid nodules have no clinical significance, because most of them are benign or even malignant thyroid nodules, especially those smaller than 1 cm, which usually show indolent or non-invasive behavior. Therefore, not all thyroid nodules require surgery(18.21-26). For benign thyroid nodules only need regular ultrasound examination, Surgery may be considered for growing solid nodules that are benign on repeat cytology if they are large (>4 cm), causing compressive or structural symptoms, or based upon clinical concern (21.27). There are four pathological types of thyroid carcinoma, and their treatment and prognosis are different based on the pathological types of thyroid cancer. Papillary and follicular thyroid cancers have a favorable prognosis, with mortality rates of 1% to 2% at 20 years for Papillary thyroid cancer (PTC)(28) and 10% to 20% at 20 years for follicular thyroid cancer(29). However, patients with medullary thyroid carcinoma have a mortality rate of 25% to 50% at 10 years, and most patients with poorly differentiated and Anaplastic thyroid cancer die within one year after diagnosis (5-year mortality, 90%)(29.30). Papillary thyroid cancer is generally perceived as low-risk thyroid cancer(29) and is not associated with well-recognized predictors of mortality(31.32). With the popularity of high-resolution thyroid ultrasound, the incidence of thyroid nodules has gradually increased(18.29), which is attributed to the increase in papillary thyroid cancer or micropapillary thyroid cancer, and more than 50% of them are labeled as low-risk thyroid cancer, It may not have any symptoms or affect the life span of the patient (33-35). For micropapillary thyroid cancer, we can consider active surveillance regularly(1.36.37). Generally speaking, the scope of surgery for thyroid cancer was determined by the initial clinical characteristics of thyroid nodules, the experience and preference of the surgeon, and the preference of the patient. The American Thyroid Association (ATA) guidelines recommended thyroid lobectomy for low-risk thyroid nodules, and bilateral thyroidectomy (including total thyroidectomy and subtotal thyroidectomy) or thyroid lobectomy for intermediate-risk thyroid nodules(1). many studies have demonstrated that overall survival and disease-free survival are not negatively impacted by lobectomy compared with thyroidectomy (38-44).

The increase in the incidence of thyroid nodules can be seen worldwide(45). In the US, a retrospective population-based evaluation of patients with thyroid cancer found that the incidence increased from 3.6/100000 in 1973 to 8.7/100000 in 2002, a 2.4-fold increase(46); Similarly, we saw that in South Korea between 1993 and 2011, thyroid cancer increased 15 times (47.48). However, the mortality rate of thyroid cancer remained stable or even declined(46-51). At the same time, we have also noticed that the number of thyroid surgeries increased dramatically. Two studies have shown a 2-4 times increase in the number of thyroid surgeries(49.50). Another study showed that between 2006 and 2011, the number of thyroid surgeries in the United States increased from 99,613 to 130,216 per year, with an average annual growth rate of 12% (52). This evidence also indirectly indicated that more aggressive treatment strategies were adopted for thyroid nodules in clinical practice. Because all the b-side thyroid glands were thyroid cancers in the experimental group, unilateral lobectomy was performed in all the b-side thyroid glands in the experimental group. In the pathological types of b-side thyroid nodules in the experimental group 1 and 2, the proportion of papillary thyroid carcinoma was 98.46% and 94.74%, respectively. Moreover, micropapillary thyroid carcinoma reached 47.69% and 36.84% respectively. We have known that papillary thyroid cancer, especially Papillary thyroid microcarcinoma, is an indolent tumor, most of which may not have an impact on the lifespan of patients. In our study, we found that almost all the b-side thyroid nodules in the experimental group were thyroid papillary carcinoma, and the a-side thyroid nodules in the experimental group were benign, but there were 46.15% and 85.71% lobectomy in the a-side of the experimental group 1 and 2, respectively. The a-side thyroid nodules were malignant, we saw a higher proportion, up to 84.62% and 96.55% in the experimental group 1 and 2, respectively. There were not many cases in our study, however, it reflected the current status of more aggressive treatment strategies for thyroid nodules to some extent. This was reflected not only in the substantial increase in the number of thyroid nodule surgeries but also in more thorough surgical procedures, which tend to subtotal thyroidectomy or total thyroidectomy. Many studies have confirmed that more resources were used for the diagnosis, treatment, and follow-up of those thyroid cancers, which may not affect the life of the patient or even have no symptoms(33.34). A large observational study based on the SEER database found that after controlling tumor size, for those patients with low-risk tumors, aggressive surgical treatment has no benefit in survival(41). Several studies have indirectly demonstrated the current status of overtreatment of thyroid nodules(20.33.34.50.52.53).

When it comes to thyroid surgery, postoperative complications are an inevitable issue. Common complications after thyroid surgery include dyspnea, nerve damage (including superior laryngeal nerve injury, and recurrent laryngeal nerve injury), hypoparathyroidism(54.55). One study showed that the risk of total thyroidectomy included recurrent laryngeal nerve injury (2.5%, rarely on both sides), hypocalcemia (8.1%), and bleeding (56). Does more aggressive surgery for thyroid nodules increase the risk of postoperative complications? A study showed that different thyroid surgical procedures and the incidence of postoperative hypocalcemia were not statistically significant(57). However, Another study showed that there was a significant difference in postoperative complications between total thyroidectomy and partial thyroidectomy. The incidence of permanent nerve injury was 7.0% vs 1.3% ($p < 0.005$), temporary nerve injury 8.6% vs 2.2% ($p < 0.005$), and postoperative transient hypoparathyroidism 18.0%vs 2.1% ($p < 0.005$) (38). moreover, Thyroid lobectomy can provide histological diagnosis and tumor removal with a lower risk of complications(18). Therefore, the current more aggressive treatment strategy for thyroid nodules may not be a good choice for patients and society.

we can take a more conservative treatment for the low-to medium-risk thyroid gland, which can retain enough thyroid tissue to meet normal physiological needs without affecting the prognosis of the patient while reducing the possibility of postoperative complications. Moreover, at present, patients with low-to medium-risk thyroid nodules are the most common patients in clinical practice, accounting for the vast majority of all patients. Nowadays, the increasing burden of health care in various countries, especially in the face of coronavirus this year, makes their medical funds tighter. For thyroid nodules, we should do more research on the treatment and benefits (including patients and society) to reduce the waste of medical resources and the risk of complications after thyroid surgery.

Although preliminary conclusions are drawn based on our trial data, there are still many limitations to be improved. Our study is a retrospective cohort study and has its limitations. There may be selective errors in the experimental group and the control group cases. But this also reflected the current status of surgical treatment of thyroid nodules. The study is a single-center case study with insufficient evidence and needs to be conducted in a multi-center and larger population. Our study almost only studied the effect of papillary thyroid carcinoma on the malignant risk of contralateral thyroid nodules, and other types of thyroid pathology can also be considered in the future. Our study did not conduct prospective studies on postoperative complications of thyroid surgery. We hope that there will be more studies on the correlation between different thyroid surgical procedures and complications in the future. Although many studies have indirectly confirmed that the current more aggressive thyroid treatment strategy leads to a large waste of medical resources, direct evidence are still lacking. Therefore, the treatment strategy of thyroid nodules still needs further research, so that it can find a balance point in terms of treatment effect, risk of postoperative complications, and economy, so that clinically significant thyroid nodules can be treated timely and appropriately, and It will not increase the burden on patients, including physical, mental, and economic aspects, and cause waste of medical resources.

Finally, the issue of fine-needle aspiration biopsy(FNAB) of thyroid nodules is specifically explained. Many thyroid treatment guidelines recommend FNAB before surgery, but FNAB has a high proportion of insufficient biopsy specimens and indeterminate pathological results. For those patients with insufficient biopsy specimens or indeterminate pathological results, FNAB may need to be performed again. However, some patients may not have clear pathological results after repeated FNAB. In our study, surgeons advised all patients with thyroid nodules to perform FNAB, but fully informed them of the pros and cons, and almost all patients refused to perform FNAB. Because of the improvement of surgical techniques, anesthesia, and nursing care, the length of hospital stay has been shortened, which is another reason.

5. Conclusions

According to our current data, there is no evidence that bilateral thyroid nodules affect each other in terms of malignant risk, that is, in bilateral thyroid nodules, unilateral thyroid cancer does not change the malignant risk of contralateral thyroid nodules.

Declarations

Ethics approval and consent to participate:

The study was approved by the Ethics Committee of the Fourth Affiliated Hospital of China Medical University, and its number is EC-2020-KS-021. The informed consent of patients was obtained in this study.

Consent for publication: Not applicable

Availability of data and materials：the data used during the current research are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions

HL participated in research design, literature review, data collection and statistical analysis, discussion, and article writing. JJ and QC participated in data collection, analysis and discussion. ZL participated in research design, analysis, discussion, and review. All authors read and approved the final manuscript.

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Tables

Table 1
Statistical analysis of demographic characteristics of the experimental group and the control group

	Gender		P-value	Age		P-value
	Male	Female		Mean	95%CI	
Experimental group 1	10(15.38%)	55(84.62%)	0.680	50.11	(39.87,60.36)	0.993
Control group 1	1(7.14%)	14(92.86%)		50.13	(40.65,60.08)	
Experimental group 2	0(0.00%)	15(100%)	0.016	53.21	(39.98,66.44)	0.037
Control group 2	19(45.24%)	23(54.76%)		46.76	(37.33,56.19)	

Table 2
statistical results of pathology and surgical procedures of thyroid nodules

	Thyroid nodules Pathology		**P-value**	**Pathological types of thyroid cancer**		**P-value**	**Thyroid surgical procedure***		**P-value**
	Benign	**Malignant**		**Micropapillary thyroid cancer**	**Papillary Thyroid Cancer**		**Lobectomy**	**Unilateral partial thyroidectomy**	
Experimental group 1(%)	**52(80%)**	**13(20%)**	**0.724**	**8(61.54%)**	**5(38.46%)**	**0.200**	**24(46.15%)**	**28(53.85%)**	**0.131**
Control group 1(%)	**13(65%)**	**2(35%)**		**0(0.00%)**	**2(100.00%)**		**3(23.08%)**	**10(77.92%)**	
Experimental group 2(%)	**7(36.84%)**	**12(63.16%)**	**0.297**	**10(83.33%)**	**2(16.67%)**	**0.620**	**6(85.71%)**	**1(14.29%)**	**0.001**
Control group 2(%)	**9(23.68%)**	**29(76.32%)**		**26(89.66%)**	**3(10.34%)**		**0(0.00%)**	**9(100.00%)**	

*For thyroid nodules in the experimental groups, unilateral lobectomy was performed on the b-side thyroid, and the a-side thyroid surgical procedures were discussed here.For the control group, the surgical procedures with one side of thyroid nodules were discussed here.(The above discussion was the surgical procedures of benign thyroid nodules on the a-side of the experimental group and the control group.)

Table 3
distribution of surgical procedures for malignant thyroid nodules*

	Thyroid surgical procedure*	
	Lobectomy	Unilateral partial thyroidectomy
Experimental group 1(%)	11(84.62%)	2(15.38%)
Control group 1(%)	2(100.00%)	0(0.00%)
Experimental group 2(%)	12(100%)	0(0.00%)
Control group 2(%)	28(96.55%)	1(3.45%)

*The above discussion was the surgical procedures of malignant thyroid nodules on the a-side of the experimental group and the control group

Table 4
Pathological types of b-side thyroid cancer in the experimental group

	Papillary Thyroid Cancer		**Medullary Thyroid Cancer**	**Follicular thyroid carcinoma**	**Anaplastic thyroid carcinoma**
	Yes*	no			
Experimental group 1(%)	31(47.69%)	33(50.77%)	1(1.54%)	0(0%)	0(0%)
Experimental group 2(%)	7(36.84%)	11(57.90%)	0(0%)	0(0%)	1(5.26%)
*Thyroid micropapillary carcinoma					

Figures

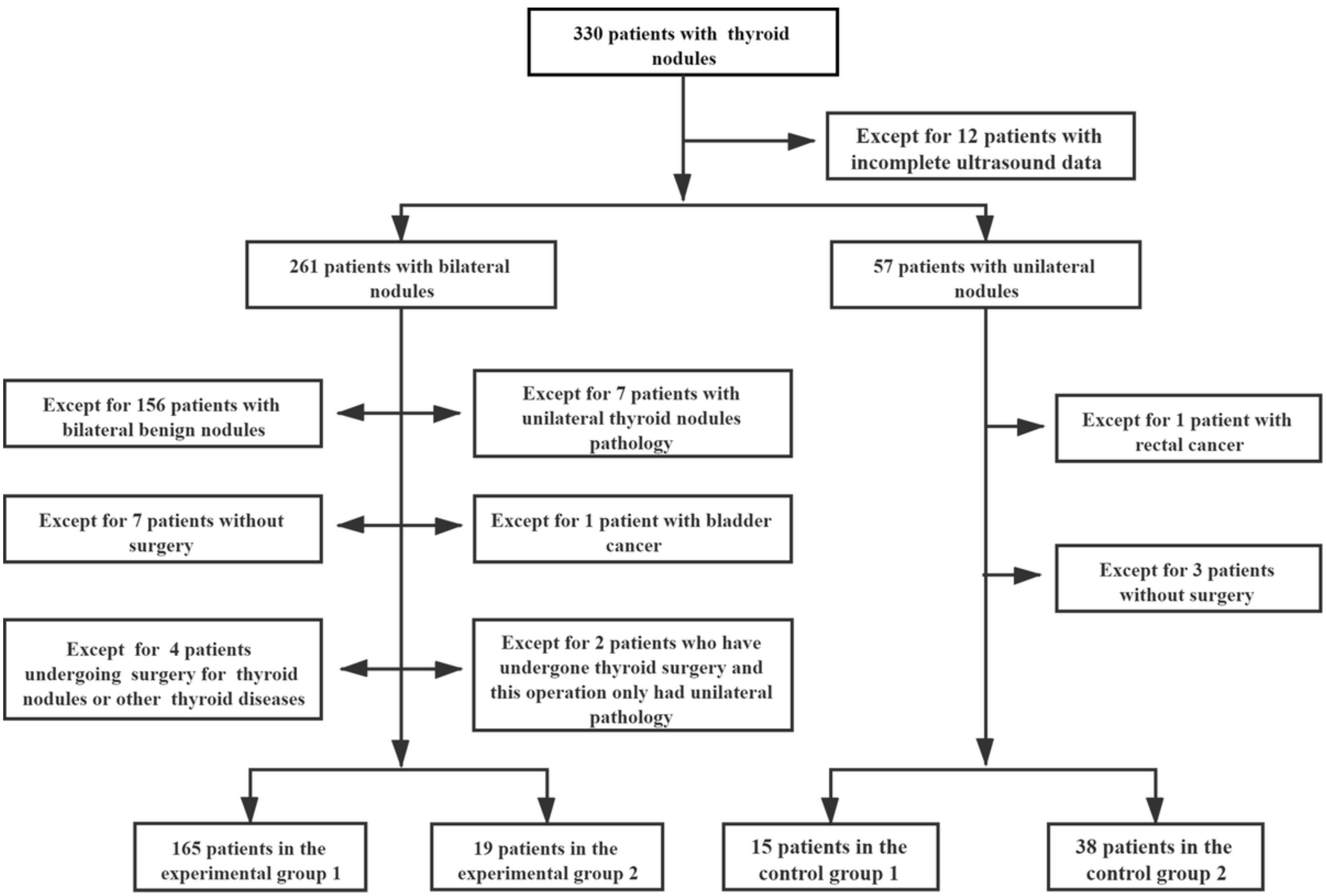

Figure 1

Process of cases collection and grouping

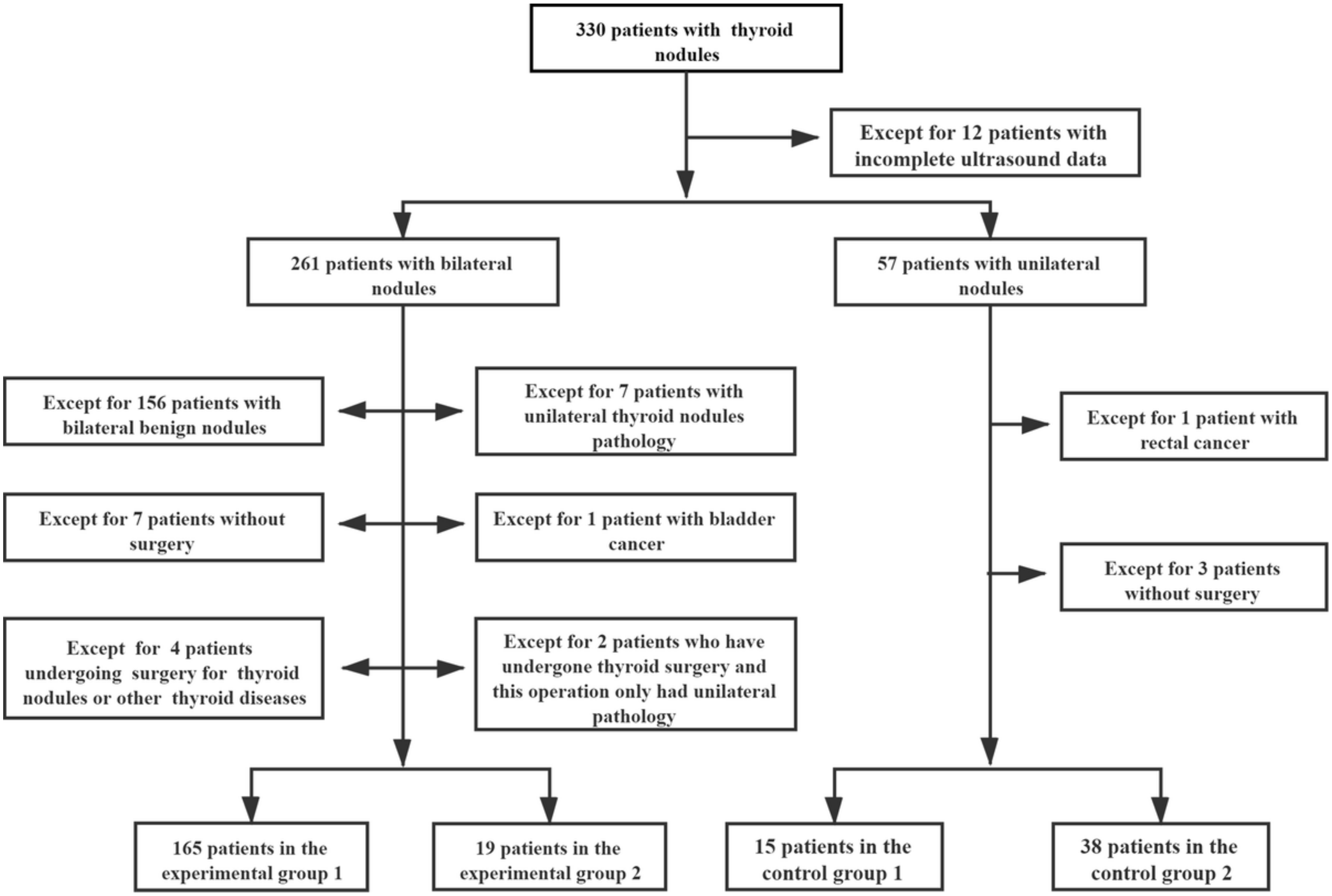

Figure 1

Process of cases collection and grouping