Original Article

Clinical preliminary study on the correlation between nodular goitre and papillary thyroid carcinoma

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Background: In clinical practice, we often encounter patients with concurrent papillary thyroid carcinoma (PTC) and nodular goitre (NG). What are the similarities and differences between these patients and patients with simple NG? Whether NG-related nodules can affect the occurrence and development of PTC still remains unknown.

Methods: We retrospectively analysed 650 patients undergoing surgery for a thyroid nodule in our hospital from January 1, 2015, to January 31, 2016. A total of 574 patients who met the inclusion criteria were divided into the NG, PTC and NG&PTC groups according to their postoperative pathological features. SPSS 22 software was used to compare the characteristics of patients between the three groups, the similarities and differences of potential risk factors (such as age, sex, residence location, BMI…) and thyroid function between the NG&PTC and NG groups, and the similarities and differences of tumour pathological features between the NG&PTC and PTC groups.

Results: There were significant differences in the composition ratios of age, gender and residence location between the NG, PTC and NG&PTC groups. There were significant differences in residence location and body mass index (BMI) between the NG group and the NG&PTC group. There were significant differences in the number of cancer nodules, lymph node metastasis, and central lymph node metastasis between the NG&PTC and PTC groups.

Conclusions: Overweight may affect the occurrence of PTC in patients with NG. NG may limit the intra- or extra-glandular metastasis of PTC but does not affect the growth and invasion of PTC.

Keywords: Papillary thyroid carcinoma (PTC); nodular goitre; body mass index

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Introduction

Thyroid cancer (TC) is one of the most common solid endocrine malignant tumours. It is more common in women, and its incidence has been increasing yearly. Papillary thyroid carcinoma (PTC) is the most common TC. Therefore, this study was performed to focus on PTC. According to research conducted in China, the incidence of TC increased by 1.93-fold in Tianjin from 1981 to 2006, while the incidence of PTC increased by 5.7-fold (1). The growth rate of PTC was ranked second among all female malignant tumours (1). In 2006, the incidence of TC was ranked eighth among female malignant tumours (1). By

2012, it was ranked third in incidence among all female malignancies (2). According to the National Comprehensive Cancer Network (NCCN) guidelines, the number of new-onset TC cases in the United States in 2017 was estimated as 56,870, ranking fifth among female malignancies (3). The increasing incidence of PTC is associated with the popularity of high-resolution ultrasound and the application of fine-needle biopsy, which have led to the early detection of micro papillary thyroid carcinoma (MPTC) (4). However, more importantly, the increase may be closely related to changes in people's living environment and eating habits (5). Accordingly, an in-depth study of PTC risk factors and clinical features is of great significance for the prevention and early detection of clinical PTC.

To date, mainstream studies have shown that nodular goitre (NG), a high body mass index (BMI), and Hashimoto thyroiditis (HT) are risk factors for TC and are closely related to the occurrence and development of TC (6-8). Among them, multinodular goiter is considered to be a strong risk factor for TC (9). Clinically, NG is a surgical indication if cancerization nodules are suspected (10). Although these studies have confirmed that individual factors such as BMI and HT are risk factors for PTC, whether these factors can increase the risk of NG development to PTC still remains unknown. There is no systematic study on the similarities or differences in the tumour biological characteristics between patients with NG&PTC and those with PTC.

Accordingly, this study retrospectively analysed the clinical data of 650 patients undergoing surgery for thyroid nodule from January 2015 to January 2016 in the Third Xiangya Hospital of Central South University to compare the clinical characteristics of patients with NG, PTC or NG&PTC, investigate the potential risk factors for NG cancerization to PTC, and study the similarities and differences in tumour biology between NG&PTC and PTC to provide a new research direction and theoretical basis for the clinical prevention and treatment of TC. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/tcr-19-2951).

Methods

Research subjects

Ethics Statement

The study was approved by the ethics committee of the Third Xiangya Hospital of Central South University (No.2015-S135), and each participant signed an informed consent. The whole research was conducted in accordance with the approved guidelines.

Patient inclusion and exclusion criteria

The following were the inclusion criteria: all patients undergoing thyroid nodule surgery at the Third Xiangya Hospital of Central South University from January 1, 2015, to January 31, 2016, and all patients with available data, such as height, weight, free triiodothyronine (FT3) level within 1 week before surgery, free thyroxine (FT4) level, thyroid stimulating hormone (TSH) level and postoperative pathology.

The exclusion criteria were as follows: patients with a history of oral antithyroid drugs or thyroid hormone within 3 months before surgery; patients with a history of radioactive iodine treatment; patients pathologically diagnosed with non-PTC or non-NG; patients with a previous history of head and neck irradiation or thyroid disease surgery; patients with a history of other cancers; patients with a family history of TC; and patients aged <18 or >80 years.

This study was approved by the Ethics Committee of the Third Xiangya Hospital.

Patient data

General data

The general data include age, gender, height, weight and residence location. The formula for BMI is: BMI = weight (kg)/height^2 (m^2), and the BMI was classified based on Chinese standards (BMI <18.5, 18.5–23.9, ≥24, corresponding to underweight, normal weight and overweight, respectively; in the overweight category, BMI 24–27.9 is considered as overweight, and BMI ≥28 is considered as obese) (11). The body surface area (BSA) was calculated using the DU.bois formula, namely, BSA =0.007184 × [weight (kg)]$^{0.425}$ × [height (cm)]$^{0.725}$ (12).

Laboratory studies

Serum FT3, FT4 and TSH concentrations were measured within one week before surgery. The test results of 420 patients were obtained from the Nuclear Medicine Laboratory of the Third Xiangya Hospital of Central South University by using the ADVIA Centaur® XP immunoassay analyser from Siemens Inc. The normal ranges are as follows: FT3: 1.8–4.2 pg/mL; FT4: 0.8–1.76 ng/mL; and

Table 1 Characteristics of patients with nodular goitre, nodular goitre & papillary thyroid carcinoma and papillary thyroid carcinoma

Variable	NG (n=317)	PTC (n=183)	NG&PTC (n=74)	P
Age (years)	47.19±12.03	40.38±10.40	45.54±12.06	<0.001
<55, n (%)	235 (74.1)	172 (94.0)	59 (79.7)	
≥55, n (%)	82 (25.9)	11 (6.0)	15 (20.3)	<0.001
Sex, n (%)				
Male	70 (22.1)	64 (35.0)	16 (21.6)	
Female	247 (77.9)	119 (65.0)	58 (78.4)	0.004
Residence location, n (%)				
Rural	201 (63.4)	97 (53.0)	36 (48.6)	
Urban	116 (36.6)	86 (47.0)	38 (51.4)	0.015

TSH: 0.35–5.5 μIU/mL. The data of the remaining 153 patients were obtained from the Endocrine Laboratory of the Third Xiangya Hospital of Central South University by using Roche's Cobas e601 electrochemiluminescence detection immunoassay system. The normal ranges are as follows: FT3: 3.1–6.8 pmol/L; FT4: 10.3–22.65 pmol/L; and TSH: 0.27–4.2 μIU/mL.

Pathological data

The pathological data included the pathological type of nodules, the number of cancer nodules, the size of cancer nodules, the degrees of lymph node metastasis and degree of inflammation. The pathology reports were obtained from the Department of Pathology of the Third Xiangya Hospital of Central South University.

Statistical analysis

IBM SPSS 22.0 statistical software was used for the statistical analysis. Quantitative data with a normal distribution are expressed as $\bar{x}$±s. A *t*-test was used to compare the difference in the mean between the two groups. One-way analysis of variance (ANOVA) was used to compare the differences in the mean between the multiple groups. The categorical variables are expressed as the number of patients and percentages, and the chi-square test was used to compare the difference between the rates or composition ratio of the groups. The risk factors for PTC in NG patients were analysed by logistic regression analysis, with α_{in}=0.05 and α_{out}=0.10. The relative risk was assessed by the odds ratio (OR), and the 95% confidence interval (CI) was calculated. P<0.05 was considered statistically significant.

Results

Characteristics of patients with NG, NG&PTC and PTC

In terms of age composition, there were significant differences between the NG patients (47.19±12.03), NG&PTC patients (40.38±10.40) and PTC patients (45.54±12.06) (F=20.359, P<0.001), as shown in *Table 1*. Considering that age is important for PTC staging and prognosis, the tumour-node-metastasis (TNM) staging system of the American Joint Committee on Cancer (AJCC) uses age (over 55) as a reference to determine the mortality risk in patients with differentiated thyroid carcinoma (DTC) (13). We converted the data to nominal variables based on the age of 55 years for the stratified analysis, which showed that there were significant differences between NG patients (82 patients aged over 55 years, 25.9%), NG&PTC patients (15 patients aged over 55 years, 20.3%) and PTC patients (11 patients aged over 55 years, 6.0%) (χ^2=30.065, P<0.001), as shown in *Table 1*.

In terms of gender composition, there were significant differences between NG patients (247 female patients, 77.9%), NG&PTC patients (58 female patients, 78.4%) and PTC patients (119 female patients, 65.0%) (χ^2=10.883, P=0.004), as shown in *Table 1*.

In terms of residence composition, there were significant differences between NG patients (116 patients in urban areas, 36.6%), NG&PTC patients (38 female patients, 51.4%) and PTC patients (86 female patients, 47.0%) (χ^2=8.337, P=0.015), as shown in *Table 1*.

Table 2 Potential risk factors for papillary thyroid carcinoma occurrence in nodular goitre patients

Risk factors	NG (n=317)	NG&PTC (n=74)	P value
Age (years)	47.19±12.03	45.54±12.06	0.290
<55	235 (74.1%)	59 (79.7%)	
≥55	82 (25.9%)	15 (20.3%)	0.315
Sex			
Male	70 (22.1%)	16 (21.6%)	
Female	247 (77.9%)	58 (78.4%)	0.931
Residence location			
Rural	201 (63.4%)	36 (48.6%)	
Urban	116 (36.6%)	38 (51.4%)	0.019
BMI	23.17±3.23	23.89±3.53	0.094
<24	204 (64.4%)	35 (47.3%)	
≥24	113 (35.6%)	39 (52.7%)	0.007
BMI_F			
<24	172 (69.6%)	32 (55.2%)	
≥24	75 (30.4%)	26 (44.8%)	0.035
BMI_M			
<24	32 (45.7%)	3 (18.8%)	
≥24	38 (54.3%)	13 (81.3%)	0.048
BSA	1.61±0.16	1.63±0.14	0.353
BSA_F	1.57±0.11	1.59±0.10	0.159
BSA_M	1.80±0.16	1.80±0.13	0.862
Hashimoto thyroiditis (HT)			
Y	5 (1.6%)	4 (5.4%)	
N	312 (98.4%)	70 (94.6%)	0.122

Comparison of risk factors between the NG and NG&PTC patients

Although the composition characteristics of the three types of patients (NG, NG&PTC or PTC) were significantly different, we still suspected that a relationship may exist between the three types of patients. First, we conducted an analysis comparing patients with NG and those with NG&PTC. In terms of age, there was no significant difference (F=0.049, P=0.290) between the NG patients (47.19±12.03) and NG&PTC patients (45.54±12.06). We converted the data to a nominal variable based on the age of 55 years for the stratified analysis, which showed no significant differences between the NG patients (82patients aged over 55 years, 25.9%) and NG&PTC patients (15 patients aged over 55 years, 20.3%) (χ^2=1.008, P=0.315; *Table 2*).

In terms of gender composition, there were no significant differences between NG patients (247 female patients, 77.9%) and NG&PTC patients (58 female patients, 78.4%) (χ^2=0.007, P=0.931), as shown in *Table 2*.

Regarding residence composition, there were significant differences between the NG patients (116 patients in urban areas, 36.6%) and NG&PTC patients (38 female patients, 51.4%) (χ^2=5.474, P=0.019; *Table 2*).

In terms of BMI, there was no significant difference

Table 3 Comparison of thyroid function measured by the Centaur® XP immunoassay system between the nodular goitre patients and nodular goitre & papillary thyroid carcinoma patients

Risk factor	NG (n=224)	NG&PTC (n=58)	P value
FT3	3.18±0.48	3.16±0.57	0.758
FT4	1.27±0.67	1.48±1.81	0.400
TSH	1.75±2.69	2.08±2.44	0.397

between NG patients (23.17±3.23) and NG&PTC patients (23.89±3.53) (F=2.458, P=0.094). Considering the difference between the Chinese population and the world population(11), according to Chinese standards, we converted "overweight" into a nominal variable based on BMI≥24 for further analysis, which showed that NG patients (113 overweight patients, 35.6%) and NG&PTC patients (39 overweight patients, 52.7%) had significantly different BMIs (χ^2=7.345, P=0.007). Given the sexual dimorphism of obesity (14,15), patients were compared separately according to gender. Among the female patients, BMI was significantly different (χ^2=4.436, P=0.035) between the NG patients (75 overweight patients, 30.4%) and NG&PTC patients (26 overweight patients, 44.8%). Among the male patients, BMI was still significantly different (χ^2=3.923, P=0.048) between the NG patients (38 overweight, 54.3%) and NG&PTC patients (13 overweight patients, 81.3%), as shown in *Table 2*.

In terms of BSA, there was no significant difference between the NG (1.61±0.16) and NG&PTC (1.63±0.14) patients (F=1.354, P=0.353). Given the sexual dimorphism of obesity (14,15), patients were compared separately according to gender. Among the female patients, BSA was not significantly different between the NG (1.57±0.11) and NG&PTC (1.59±0.10) patients (F=0.226, P=0.159). Among the male patients, there was no significant difference between the NG patients (1.80±0.16) and NG&PTC (1.80±0.13) patients (F=0.747, P=0.862), as shown in *Table 2*.

In terms of HT, there was no significant difference (χ^2=2.393, P=0.122) between the NG patients (5 patients with HT, 1.6%) and NG&PTC patients (4 patients with HT, 5.4%; *Table 2*).

Therefore, we speculated that the NG&PTC patients may be a subset of the NG patients.

Differences in thyroid function between the NG and NG&PTC patients

To test this speculation, we further studied the thyroid function of both NG and NG&PTC patients. Two types of serum thyroid-related hormone testing equipment were available in our hospital and were used randomly for the patients included in this study. This resulted in a reduced sample size for each piece of equipment. Thus, we compared the results separately according to the equipment used.

The samples of 420 patients were assessed using a Siemens ADVIA Centaur® XP immunoassay device, including samples from 224 NG patients and 58 NG&PTC patients. The FT3 level was not significantly different between the NG patients (3.18±0.48) and NG&PTC patients (3.16±0.57) (F=0.355, P=0.758). The FT4 level was not significantly different between the NG patients (1.27±0.67) and the NG&PTC patients (1.48±1.81) (F=4.459, P=0.400). The TSH level was not significantly different between the NG patients (1.75±2.69) and NG&PTC patients (2.08±2.44) (F=0.497, P=0.397), as shown in *Table 3*.

The samples from 154 patients were measured using a Roche Cobas e601 electrochemiluminescence detection immunoassay system, including samples from 93 NG patients and 16 NG&PTC patients. The FT3 level was not significantly different between the NG patients (5.12±1.01) and NG&PTC patients (4.97±0.84) (F=0.838, P=0.565). The FT4 level was not significantly different between the NG patients (16.24±3.00) and NG&PTC patients (15.31±5.18) (F=4.551, P=0.494). The TSH level was not significantly different between the NG patients (1.89±1.51) and NG&PTC patients (2.61±1.73) (F=0.759, P=0.090), as shown in *Table 4*.

These data further confirm the speculation that the NG&PTC patients may be a subset of the NG patients.

Univariate and multivariate logistic regression analysis of risk factors for patients with NG or NG&PTC

Since the NG&PTC patients may be a subset of the NG patients, what risk factors can trigger this progression? Univariate logistic regression analysis showed that residence

Table 4 Comparison of thyroid function measured by the Cobas e601 test immunoassay analyser between the nodular goitre patients and nodular goitre & papillary thyroid carcinoma patients

Risk factor	NG (n=93)	NG&PTC (n=16)	P value
FT3	5.12±1.01	4.97±0.84	0.565
FT4	16.24±3.00	15.31±5.18	0.494
TSH	1.89±1.51	2.61±1.73	0.090

Table 5 Univariate logistic regression analysis of risk factors for papillary thyroid carcinoma in the nodular goitre patients

Selected variable	b	S_b	P	OR	95% CI
Female	–0.027	0.313	0.931	0.973	0.527–1.798
Age ≥55 years	0.317	0.316	0.371	1.372	0.738–2.551
Residence in an urban area	–0.604	0.260	0.020	0.547	0.328–0.910
BSA	0.762	0.819	0.352	2.142	0.430–10.654
Presence of HT	–1.271	0.684	0.062	0.280	0.073–1.071
BMI ≥24	–0.699	0.261	0.007	0.497	0.298–0.829

Table 6 Multivariate logistic regression analysis of risk factors for papillary thyroid carcinoma in the nodular goitre patients

Selected variable	b	S_b	P	OR	95% CI
Female	–0.112	0.427	0.794	0.894	0.387–2.066
Age ≥55 years	0.385	0.329	0.243	1.469	0.770–2.802
Residence in an urban area	–0.719	0.271	0.008	0.487	0.287–0.829
BSA	–0.767	1.386	0.580	0.464	0.031–7.020
Presence of Hashimoto thyroiditis (HT)	–1.353	0.715	0.058	0.258	0.064–1.049
BMI ≥24	–0.865	0.346	0.012	0.421	0.214–0.829

in an urban area (P=0.020) and BMI ≥24 (P=0.007) were risk factors for PTC occurrence in patients with NG. Female sex (P=0.931), age ≥55 years (P=0.371), large BSA (P=0.352), and concurrent HT (P=0.062) were not risk factors for PTC occurrence in patients with NG, as shown in *Table 5*. Multivariate logistic regression analysis showed that residence in an urban area (P=0.008) and BMI ≥24 (P=0.012) were independent risk factors for PTC occurrence in patients with NG, as shown in *Table 6*.

Therefore, the NG patients may become NG&PTC patients due to NG cancerization facilitated by a high BMI.

Effects of NG on the tumour biological characteristics of PTC

What is the difference in the biological characteristics of tumours between the NG&PTC and PTC patients? We further compared and analysed the tumour biological characteristics between the NG&PTC and PTC patients.

Regarding number of cancer nodules, NG&PTC patients (64 patients with single cancer nodules, 86.5%) and PTC patients (128 patients with single cancer nodules, 69.9%) had significantly different numbers (χ^2=7.630, P=0.006), as shown in *Table 7*.

Regarding the size of cancer nodules, that in NG&PTC patients (25 patients with cancer nodules >1 cm, 33.8%) and PTC patients (72 patients with cancer nodules >1 cm, 39.3%) was not significantly different (χ^2=0.693, P=0.405), as shown in *Table 7*.

Regarding extra-glandular invasion, the results in NG&PTC patients (7 positive patients, 9.5%) and PTC

Table 7 Impact of nodular goitre on papillary thyroid carcinoma progression

Factors	PTC	NG&PTC	P value
Number of cancer nodules			
Single	128 (69.9%)	64 (86.5%)	
Multiple	55 (30.1%)	10 (13.5%)	0.006
Cancer nodule size			
≤1 cm	111 (60.7%)	49 (66.2%)	
>1 cm	72 (39.3%)	25 (33.8%)	0.405
Extra-glandular invasion			
N	166 (90.7%)	67 (90.5%)	
Y	17 (9.3%)	7 (9.5%)	0.966
Lymph node metastasis			
N	123 (67.2%)	63 (85.1%)	
Y	60 (32.8%)	11 (14.9%)	0.004
Central lymph node metastasis			
N	131 (71.6%)	65 (87.8%)	
Y	52 (28.4%)	9 (12.2%)	0.006
Lateral lymph node metastasis			
N	166 (90.7%)	71 (95.9%)	
Y	17 (9.3%)	3 (4.1%)	0.156

patients (17 positive patients, 9.3%) were not significantly different (χ^2=0.002, P=0.966), as shown in *Table* 7.

In terms of lymph node metastasis, the results in the NG&PTC patients (11 patients with metastases, 14.9%) and PTC patients (60 patients with metastases, 32.8%) were significantly different (χ^2=8.465, P=0.004). Furthermore, central lymph node metastasis was significantly different (χ^2=7.690, P=0.006) between the NG&PTC patients (9 patients with metastasis, 12.3%) and PTC patients (52 patients with metastasis, 28.4%). Lateral cervical lymph node metastasis was not significantly different between the NG&PTC patients (3 patients with metastases, 4.1%) and PTC patients (17 patients with metastases, 9.3%) (χ^2=2.013, P=0.156), as shown in *Table* 7.

Thus, NG may influence intra- and extra-glandular metastasis of PTC but has no effect on its growth and invasion.

Discussion

Current studies indicate that the occurrence and development of PTC may be related to multiple factors (16,17). The presence of NG is one of the high-risk factors. In addition, the possible risk factors for TC include gender, geographic location, radiation, inflammation, obesity, abnormal iodine intake, TSH, thyroid hormone, Ras gene activation, BARV V600E gene mutation and P53 gene inactivation (18,19). These risk factors may also cause the progression of NG to TC. Therefore, we conducted the above retrospective analysis based on the clinical facts.

From the perspective of patient characteristics, the three groups differed in age, gender, and residence location. Previous studies have confirmed that the mean age of NG patients is greater than that of PTC patients, and the incidence of NG is greater among women (19). Our study further found that the difference in age and sex composition ratios between the NG&PTC group and the NG group was relatively smaller than that between the NG&PTC group and PTC group. In the residence location composition, the difference between the NG&PTC group and the PTC group was relatively smaller than that between the NG&PTC and NG groups. In summary, the NG&PTC

patients and NG patients may be from the same general population, and the NG&PTC patients may have originally been NG patients who progressed to NG&PTC patients under the impact of certain factors. The distribution of residence location was similar between the NG&PTC patients and the PTC patients, but it should be noted that patients living in an urban area have convenient access to medical service (e.g., frequent physical examination), which is helpful for early detection of PTC.

In a further comparison between NG patients and NG&PTC patients, chi-square and univariate logistic regression analyses showed that residence in an urban area and BMI ≥24 were risk factors for PTC occurrence in patients with NG. Multivariate logistic regression analysis indicated that residence in an urban area and BMI ≥24 are independent risk factors for PTC occurrence in patients with NG. The analysis of the differences in residence composition has been described above. Some studies have shown a relationship between obesity and cancer. Some researchers have suggested that adipose cells are one of the main components of the matrix surrounding the tumour and can secrete some signalling molecules and provide nutritional support for the cancer cells they surround. Adipose cells act as an endocrine organ and "granary" in the proliferation and metastasis of tumours (20-22). However, the mechanism by which high body fat percentage affects cancer remains unclear. In clinical practice, overweight patients with thyroid nodules may need to receive more frequent follow-up with active examinations. However, whether weight control can prevent the progression of NG to PTC remains to be further studied.

The NG&PTC patients had similar age and gender composition ratios to those of the NG patients. Other studies have shown that age and gender are not risk factors for PTC occurrence in NG patients. The study by Kim *et al.* (23). revealed that BSA is associated with multifocality of PTC. In the present study, BSA was not a risk factor for the development of PTC in patients with NG. Some researchers have found that the preoperative elevated serum TSH level is associated with an increased incidence of PTC (24,25). The data we obtained by two methods showed that there were no significant differences in serum FT3, FT4 and TSH levels between NG patients and NG&PTC patients. This result suggests that thyroid hormone or thyroid stimulating hormone may not cause the occurrence of PTC in NG patients.

Moreover, we also compared the difference in tumour status between the NG&PTC patients and the PTC patients and attempted to analyse the effect of NG on PTC progression. In the study, we found that more NG&PTC patients presented with single-focal carcinoma and were less prone to the occurrence of central lymph node metastasis. The growth of NG nodules may limit intra- and extra-glandular metastasis of PTC. Although there was no significant difference in lateral lymph node metastasis between the two groups, this may be due to the low rate of lateral lymph node metastasis and the insufficient sample size. In terms of tumour diameter and extra-glandular invasion, there were no significant differences between the NG&PTC patients and PTC patients. This result may indicate that NG may not affect the growth and invasion of PTC.

In conclusion, NG&PTC patients and NG patients may come from the same general population. Overweight may trigger the occurrence of PTC in NG patients. NG may limit intra- and extra-glandular metastasis of PTC but does not affect the growth and invasion of PTC. Based on the above conclusions, we may need to be more careful in the identification and follow-up of patients with thyroid nodules in clinical practice. Furthermore, because intra- and extra-glandular metastases are not common in NG&PTC patients, aggressive treatments, such as lymph node dissection or postoperative ^{131}I radiation therapy, may not be suitable.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The scheme was authorized by ethics committee of the Third Xiangya Hospital of Central South University (No: 2015-S135).

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