

## Analysis of Causes of Pathologically Negative Findings in Reoperation for Differentiated Thyroid Cancer: Postprint

**Authors:** Wu Xin, Li Binglu, Zheng Chaoji, He Xiaodong

**Date:** 2019-03-11T00:00:00+00:00

### Abstract

**Objective:** To analyze the potential causes of negative pathology in reoperation for differentiated thyroid cancer. **Methods:** Clinical data of 218 patients who underwent reoperation for differentiated thyroid cancer at Peking Union Medical College Hospital between January 2013 and December 2017 were retrospectively analyzed. Differences in general characteristics, surgical information, pathological results, and ultrasound findings between patients with negative and positive reoperation pathology were compared. **Results:** The cohort included 70 male and 148 female patients, with a male-to-female ratio of 1:2.11. Ages ranged from 7 to 70 years, with a mean age of  $(43.7 \pm 12.7)$  years. The interval between the current and previous surgery ranged from 6 to 307 months, with a median of 15 months. All 218 patients were preoperatively diagnosed with tumor recurrence/metastasis; 27 cases had negative postoperative pathology, while 191 cases were positive. No significant differences were observed between the two groups regarding surgical approach or ultrasound findings; however, statistically significant differences were identified in age and the presence of multicentric lesions in thyroid pathology from the initial surgery ( $p < 0.05$ ). **Conclusion:** Differentiated thyroid cancer is associated with long survival, and reoperation is common. Patient age and unicentric lesions in thyroid pathology from the initial surgery may be risk factors for negative pathology in reoperation.

### Full Text

#### Preamble

#### Clinical Analysis of Pathologically Negative Reoperation for Differentiated Thyroid Cancer

Wu Xin, Li Bing-lu, Zheng Chao-ji, He Xiao-dong

Department of General Surgery, Peking Union Medical College Hospital, Chi-

nese Academy of Medical Sciences and Peking Union Medical College, Beijing 100730, China

Corresponding author: Li Bing-lu

Tel: 010-69152610, E-mail: libinglu@pumch.cn

## Abstract

**Objective:** To analyze potential causes of pathologically negative reoperation in differentiated thyroid cancer patients.

**Methods:** Clinical data from 218 patients who underwent reoperation for differentiated thyroid cancer at Peking Union Medical College Hospital between January 2013 and December 2017 were retrospectively analyzed. Patients with negative and positive pathological results were compared in terms of demographics, surgical information, pathological findings, and ultrasonography outcomes.

**Results:** The cohort included 70 male and 148 female patients, with a male-to-female ratio of 1:2.11. Patient ages ranged from 7 to 70 years, with a mean age of  $(43.7 \pm 12.7)$  years. The interval between the initial surgery and reoperation ranged from 6 to 307 months, with a median of 15 months. All 218 patients were preoperatively diagnosed with tumor recurrence or metastasis; however, 27 cases yielded negative postoperative pathology, while 191 cases were positive. No significant differences were observed between the two groups in surgical approach or ultrasonography findings, but significant differences were found in age and whether the primary thyroid pathology showed multicentric lesions ( $p < 0.05$ ).

**Conclusion:** Differentiated thyroid cancer is associated with long survival and frequent reoperations. Patient age and monocentric primary thyroid lesions may be risk factors for pathologically negative reoperation.

**Keywords:** differentiated thyroid cancer; thyroid neoplasms; reoperation; negative

## Introduction

The incidence of thyroid cancer has been gradually increasing worldwide due to advances in imaging diagnostics and the widespread availability of health screenings. Differentiated thyroid carcinoma accounts for over 90% of all thyroid cancers [1]. These tumors exhibit slow growth, low malignancy, high resectability, and favorable prognosis. Many patients with differentiated thyroid cancer undergo reoperation due to clinically diagnosed recurrence or metastasis during follow-up, with some cases yielding negative pathology upon reoperation. Surgeons must carefully weigh the benefits and risks to avoid both overtreatment and delayed diagnosis [2].

Between January 2013 and December 2017, Peking Union Medical College Hospital treated 218 patients undergoing reoperation for differentiated thyroid can-

cer, including 27 cases with negative pathology. We analyzed the underlying causes to provide evidence for improving preoperative diagnostic accuracy in reoperation candidates.

## Methods

### 1.1 Subjects

From January 2013 to December 2017, the Department of General Surgery at Peking Union Medical College Hospital performed 13,102 thyroid cancer surgeries. Clinical data were retrospectively analyzed according to the following inclusion criteria: (1) pathologically confirmed diagnosis of differentiated thyroid cancer at initial surgery; (2) clinically diagnosed tumor recurrence or metastasis during follow-up with subsequent reoperation at our institution; and (3) complete clinical data. Exclusion criteria included: (1) history of previous thyroid surgery other than the index procedure; and (2) history of head and neck radiation. Based on these criteria, 218 patients (1.66%) were enrolled.

### 1.2 Data Collection and Diagnostic Criteria

All patient demographics, surgical details, and pathological information were obtained from inpatient and outpatient medical records provided by the hospital's Medical Records Department, with supplementary data collected through telephone follow-up. The diagnosis of differentiated thyroid cancer at initial surgery was established based on: (1) formal postoperative paraffin pathology reports for patients who underwent initial surgery at our hospital; or (2) both external hospital paraffin pathology reports and pathology consultation at our institution for patients initially treated elsewhere. The surgical extent of the initial procedure was determined by reviewing the operative notes and pre-reoperative ultrasound findings. Clinical diagnosis of tumor recurrence or metastasis was defined as: no residual tumor or lymph node metastasis on ultrasound examination at 3-6 months after initial surgery, with newly detected recurrence or lymphatic metastasis on follow-up ultrasound at 6 months or later.

### 1.3 Statistical Analysis

Data were analyzed using SPSS 19.0 statistical software. Categorical data were described as absolute numbers and percentages, with intergroup comparisons performed using chi-square tests or Fisher's exact tests as appropriate. Continuous data were expressed as mean  $\pm$  standard deviation or median according to statistical principles, with intergroup comparisons conducted using t-tests. The significance level was set at  $\alpha=0.05$ .

## Results

Among all 218 enrolled patients, 70 were male and 148 were female, with a male-to-female ratio of 1:2.11. Ages ranged from 7 to 70 years, with a mean

age of  $(43.7 \pm 12.7)$  years. Based on reoperative pathology results, patients were divided into two groups: negative ( $n=27$ ) and positive (tumor recurrence or lymph node metastasis) ( $n=191$ ).

## 2.1 Initial Surgery Characteristics

Ninety-five patients underwent their initial surgery at our hospital, while 123 were treated at external institutions. All initial surgical pathology specimens confirmed differentiated thyroid cancer, including 212 cases of papillary carcinoma and 6 cases of follicular carcinoma. Tumor size ranged from 0.1 to 4.0 cm, with a mean of  $(1.3 \pm 0.8)$  cm. One hundred forty-seven patients underwent lymph node dissection at initial surgery; among these, 43 had metastases in both central and lateral neck compartments, 46 had central compartment metastasis only, 3 had lateral compartment metastasis only, and 55 had no lymph node metastasis. The number of metastatic lymph nodes ranged from 1 to 39, with a median of 1. Comparisons between patients with negative and positive reoperative pathology regarding demographics and initial surgery information are detailed in Table 1. Significant differences were observed between the two groups in age and whether the primary thyroid pathology demonstrated multicentric lesions ( $p < 0.05$ ).

## 2.2 Reoperation Characteristics

All patients received thyroid hormone replacement therapy after initial surgery to maintain thyroid-stimulating hormone (TSH) levels below 0.1 mU/L. All patients were confirmed to have no residual tumor on ultrasound examination at 3-6 months postoperatively. Patients who underwent bilateral lobectomy had no clinically detectable thyroglobulin under TSH stimulation. The interval between initial surgery and reoperation ranged from 6 to 307 months, with a median of 15 months, and all reoperations were completed successfully. The extent of lymph node dissection in reoperations was determined preoperatively based on ultrasound findings. Differences in reoperative extent between the two groups are detailed in Table 2. Thirty-two patients underwent intraoperative parathyroid autotransplantation, 2 underwent concurrent internal jugular vein resection, and 1 underwent simultaneous tracheostomy. No cases of unplanned postoperative tracheostomy, permanent recurrent laryngeal nerve paralysis, or permanent hypoparathyroidism occurred. All patients were discharged uneventfully, demonstrating favorable perioperative safety. Ultrasound examination was a critical tool for determining reoperation indications. Comparisons of preoperative ultrasound findings between the two groups are detailed in Table 3. Only 11 patients underwent preoperative lymph node fine-needle aspiration biopsy, with all cytology results being positive.

## Discussion

Thyroid cancer is one of the most common malignancies in the Asia-Pacific region and represents the most frequent head and neck malignant tumor [3,4]. Among Chinese women under 30 years of age, thyroid cancer ranks first in cancer incidence [5]. Differentiated thyroid cancer exhibits favorable biological behavior with low invasiveness, satisfactory surgical outcomes, long patient survival, and a tumor-related mortality risk of only 0.5 per 100,000 [6]. Therefore, the risk of recurrence and metastasis warrants greater attention from researchers than mortality risk. Common indications for reoperation include not only clinically diagnosed tumor recurrence or metastasis but also residual disease after initial surgery, remnant ablation before radioiodine therapy, and intraoperative frozen section failure to diagnose thyroid cancer [7-9]. Among these, clinically diagnosed recurrence or metastasis demands particularly high preoperative diagnostic accuracy and is more likely to result in negative postoperative pathology.

Common complications after thyroid surgery include recurrent laryngeal nerve injury, parathyroid gland dysfunction, and major neck vessel injury [10], with the former two being more prevalent. Literature reports indicate that permanent and temporary vocal cord paralysis after central compartment lymph node dissection in reoperative thyroid cancer can reach 17.8% and 22.2%, respectively, while permanent and temporary hypocalcemia can occur in 4.9% and 46.3% of cases [11]. Improving preoperative diagnostic accuracy and understanding risk factors for negative reoperative pathology can help avoid overtreatment and reduce serious complications.

Ultrasonography is the preferred preoperative imaging modality for thyroid disease. Its diagnostic capabilities have improved annually, playing an increasingly important role in surgical decision-making [12]. Typical ultrasound features of thyroid cancer nodules include hypoechoic solid nodules with irregular shape, ill-defined borders, absence of a clear capsule, microcalcifications, and abundant blood flow [13]. Characteristic imaging findings of metastatic cervical lymph nodes include rounded shape, loss of corticomedullary differentiation, calcifications or hyperechoic foci within the cortex, and peripheral blood flow [14]. Disorganized blood flow signals within lymph nodes represent a highly specific indicator for identifying metastatic lymph nodes on ultrasound [15]. All patients with suspected tumor recurrence or metastasis should be evaluated by experienced sonographers. Accurate recognition of ultrasound features can improve diagnostic accuracy and reduce unnecessary surgery [16]. However, the presence of fibrous scar tissue significantly increases the difficulty of ultrasound examination. This is particularly evident when evaluating enlarged cervical lymph nodes, as inflammatory and malignant enlargement can be challenging to differentiate completely. In this study, all reoperative patients underwent ultrasound examination by experienced sonographers, yet no significant differences were observed in any preoperative ultrasound parameters between patients with negative and positive pathology. The preoperative ultrasound misdiagnosis rate reached 12.4%. Nevertheless, ultrasonography remains the most important tool

for detecting thyroid cancer recurrence and metastasis. For challenging cases, independent assessments by multiple sonographers may help improve preoperative diagnostic accuracy. Additionally, contrast-enhanced CT and MRI can be valuable adjuncts to ultrasound for evaluating lymph node metastasis, extrathyroidal invasion, and anatomic localization [17].

Analysis of patient demographics and initial surgery characteristics can also contribute to improved preoperative diagnostic accuracy. In this study, no significant difference in gender distribution was observed between patients with negative and positive reoperative pathology, but age showed a significant difference. Patients with negative pathology were significantly older than those with positive pathology. Age 45 represents a threshold in differentiated thyroid cancer staging systems, with patients younger than 45 having better prognosis [2,18]. Consequently, surgeons may adopt a more aggressive treatment approach for patients over 45 when clinical suspicion of recurrence or metastasis arises, which may explain the significant age difference between the two groups. However, recent studies [19-21] have demonstrated that papillary thyroid cancer prognosis exhibits a linear relationship with patient age, with no specific age serving as a definitive staging cutoff. This suggests that surgeons need not adopt a uniformly more aggressive attitude toward patients over 45 when evaluating reoperation indications.

Regarding initial surgery characteristics, no significant impact on reoperative pathology results was observed for surgical extent, tumor size, capsular invasion, presence of lymph node metastasis, or number of metastatic lymph nodes. Only multicentricity of the primary thyroid lesion showed a significant difference between groups. Patients with monocentric lesions at initial surgery were more likely to have negative pathology at reoperation. Previous studies have confirmed that multicentric lesions exhibit more aggressive behavior, with higher recurrence rates compared to monocentric lesions regardless of tumor size [22-24]. This suggests that greater caution is warranted when diagnosing postoperative recurrence or metastasis in patients with monocentric lesions. Furthermore, tumor size and capsular invasion affect cancer staging, with the latter also influencing recurrence risk stratification [25]. Patients with lymph node metastasis exceeding 3 nodes show significantly decreased recurrence-free survival [26,27]. These factors can aid in determining reoperation indications. The lack of significant differences in tumor size, capsular invasion, and lymph node metastasis parameters between groups in this study may be related to sample size.

Only 11 patients in this cohort underwent preoperative lymph node fine-needle aspiration biopsy, with all cytology results being positive. Biopsy represents the gold standard for preoperative diagnosis and should be advocated to reduce the likelihood of negative reoperative pathology. The low biopsy rate in this study may be attributed to factors such as scheduling delays and patient preferences. The 2015 American Thyroid Association guidelines explicitly state that when imaging surveillance detects suspicious lymph nodes measuring 8 mm in the central compartment or 10 mm in the lateral compartment, therapeutic

lymph node dissection should be performed after biopsy-confirmed recurrence [28]. These recommendations specify size thresholds for suspicious lymph nodes and emphasize the importance of biopsy, which plays a crucial role in achieving accurate preoperative diagnosis and avoiding negative reoperative pathology.

In summary, differentiated thyroid cancer is associated with favorable prognosis and long survival, making reoperation for clinically diagnosed recurrence or metastasis relatively common. Even with effective ultrasound evaluation, negative postoperative pathology cannot be completely avoided. Patient age and multicentricity of the primary thyroid lesion may influence reoperative pathology outcomes. This study has several limitations: first, the retrospective design precluded predetermined sample size and study parameters; second, using ultrasound as the standard for diagnosing recurrence may have affected preoperative diagnostic accuracy; and third, heterogeneity in initial surgical approaches across different institutions may have influenced reoperation outcomes. Multi-center, prospective studies are needed to further clarify risk factors for negative reoperative pathology and better guide clinical practice.

## References

- [1] Sherman SI. Thyroid carcinoma [J]. *Lancet*, 2003,361:501-511.
- [2] Cabanillas ME, McFadden DG, Durante C. Thyroid cancer [J]. *Lancet*, 2016,388:2783-2795.
- [3] Sundram F, Robinson BG, Kung A, et al. Well-differentiated epithelial thyroid cancer management in the Asia Pacific region: a report and clinical practice guideline [J]. *Thyroid*, 2006,16:461-469.
- [4] Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2009 [J]. *CA Cancer J Clin*, 2009,59:225-249.
- [5] Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015 [J]. *CA Cancer J Clin*, 2016,66:115-132.
- [6] Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States, 1973-2002 [J]. *JAMA*, 2006,295:2164-2167.
- [7] Shi L, Cheng B, Qu XC, et al. Clinical analysis of 72 reoperations for thyroid cancer [J]. *Chinese Journal of Surgery*, 2007,45:871-873.
- [8] Wang ZY, Li F, Zhang WJ. Clinical analysis of reoperation for differentiated thyroid cancer [J]. *Chinese Journal of Otorhinolaryngology Head and Neck Surgery*, 2010,45:951-953.
- [9] Wu X, Xu XQ, Zheng CJ, et al. Clinical analysis of reoperation for differentiated thyroid cancer [J]. *Chinese Journal of Bases and Clinics in General Surgery*, 2017,24:813-818.
- [10] Li CH, Wang ZH, Chen J, et al. Prevention of complications in reoperation for differentiated thyroid cancer [J]. *Journal of Endocrine Surgery*, 2017,11:294-295.
- [11] Roh JL, Kim JM, Park CI. Central compartment reoperation for recurrent/persistent differentiated thyroid cancer: patterns of recurrence, morbidity, and prediction of postoperative hypocalcemia [J]. *Ann Surg Oncol*, 2011,18:1312-

1318.

- [12] Zhang B, Jiang YX, Li JC, et al. Role of ultrasound in surgical decision-making for thyroid nodules: an 11-year review at Peking Union Medical College Hospital [J]. *Medical Journal of PUMCH*, 2015,6:124-127.
- [13] Cappelli C, Castellano M, Pirola I, et al. The predictive value of ultrasound findings in the management of thyroid nodules [J]. *QJM*, 2007,100:29-35.
- [14] Xu JZ, Liang ZY, Wang XH, et al. Comparison of ultrasound features between primary and recurrent/persistent metastatic cervical lymph nodes in papillary thyroid carcinoma [J]. *Acta Academiae Medicinae Sinicae*, 2017,39:675-681.
- [15] Wu Q, Fang SB, Li XY, et al. Role of preoperative ultrasound localization in lymph node dissection for thyroid cancer [J]. *Medical Journal of PUMCH*, 2015,6:338-342.
- [16] Sharengao W, Tan L, Wang ZJ. Ultrasonographic features of misdiagnosed benign thyroid nodules [J]. *Medical Journal of PUMCH*, 2016,7:115-118.
- [17] Zhang H. Management strategies for postoperative recurrence of differentiated thyroid cancer [J]. *Chinese Journal of General Surgery (Electronic Edition)*, 2016,10:573-575.
- [18] Greene FL, Page DL, Fleming ID, et al, eds. *AJCC cancer staging manual* [M]. 6th edition. New York: Springer, 2002:77-87.
- [19] Adam MA, Thomas S, Hyslop T, et al. Exploring the relationship between patient age and cancer-specific survival in papillary thyroid cancer: rethinking current staging systems [J]. *J Clin Oncol*, 2016,34:4415-4420.
- [20] Bischoff LA, Curry J, Ahmed I, et al. Is above age 45 appropriate for upstaging well-differentiated papillary thyroid cancer? [J] *Endocr Pract*, 2013,19:995-997.
- [21] Ganly I, Nixon IJ, Wang LY, et al. Survival from differentiated thyroid cancer: what has age got to do with it? [J] *Thyroid*, 2015,25:1106-1114.
- [22] Mazzaferri EL. Management of low-risk differentiated thyroid cancer [J]. *Endocr Pract*, 2007,13:498-512.
- [23] Roti E, degli Uberti EC, Bondanelli M, et al. Thyroid papillary microcarcinoma: a descriptive and meta-analysis study [J]. *Eur J Endocrinol*, 2008,159:659-673.
- [24] Ito Y, Kudo T, Kihara M, et al. Prognosis of low-risk papillary thyroid carcinoma patients: its relationship with the size of primary tumors [J]. *Endocr J*, 2012,59:119-125.
- [25] Chinese Society of Endocrinology, Endocrine Surgery Group of Chinese Society of Surgery, Head and Neck Cancer Committee of China Anti-Cancer Association, Chinese Society of Nuclear Medicine. Guidelines for diagnosis and treatment of thyroid nodules and differentiated thyroid cancer [J]. *Chinese Journal of Endocrinology and Metabolism*, 2012,28:779-797.
- [26] Wu MH, Shen WT, Gosnell J, et al. Prognostic significance of extranodal extension of regional lymph node metastasis in papillary thyroid cancer [J]. *Head Neck*, 2015,37:1336-1343.
- [27] Park YM, Wang SG, Lee JC, et al. Metastatic lymph node status in the central compartment of papillary thyroid carcinoma: a prognostic factor of lo-

coregional recurrence [J]. Head Neck, 2016,38 Suppl 1:E1172-1176.

[28] Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer [J]. Thyroid, 2016,26:1-133.

*Note: Figure translations are in progress. See original paper for figures.*

*Source: ChinaXiv –Machine translation. Verify with original.*