ORIGINAL RESEARCH

# Risk Factors and Prognosis of Retropharyngeal Lymph Node Metastasis from Papillary Thyroid Carcinoma

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## ABSTRACT

**Objective** • Papillary thyroid carcinoma (PTC) metastasis to the retropharyngeal lymph node (RPLN) is rare but clinically significant due to its implications for patient prognosis and treatment strategies. This study aims to investigate the risk factors and prognosis associated with this uncommon metastasis.

**Methods** • We conducted a retrospective case-control study involving 34 PTC patients with RPLN metastasis treated between January 2007 and December 2017. These patients were compared with a control group of 68 PTC patients with lateral lymph node metastasis but no RPLN involvement, selected randomly from those treated between January 2010 and December 2012. Inclusion criteria included confirmed PTC diagnosis, documented RPLN metastasis, and comprehensive follow-up data. Data collection encompassed preoperative examinations, surgical treatments, and follow-up outcomes. Statistical analyses were performed using SPSS 19, with survival analysis conducted via the Kaplan-Meier method and the Log-rank test for single-factor analysis.

**Results** • Among the research group, only 7 patients were initially treated, while 27 had a history of thyroidectomy. The average time from initial thyroidectomy to RPLN metastasis was 93.1 months. Imaging methods such as CT scan, MRI, and 131I-SPECT/CT demonstrated high sensitivity in detecting RPLN metastasis. The 5-year survival rate was 77.5%. Patients with RPLN metastasis exhibited higher rates of tumor dedifferentiation, distant metastasis, and higher central lymph node density compared to the control group.

**Conclusions** • RPLN metastasis in PTC, though rare, should be considered during follow-up, particularly for patients with tumor dedifferentiation, glandular dissemination, and distant metastasis. Routine ultrasonography may miss these metastases; hence, periodic CT scans, MRI, or 131I-SPECT/CT are recommended. Despite the advanced disease stage at diagnosis, active treatment, including surgical resection via the transcervical approach, can result in a favorable prognosis. Metastasis to lymph nodes below the hyoid plane indicates a poorer prognosis. (*Altern Ther Health Med.* 2024;30(12):474-479).


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## INTRODUCTION

The incidence of papillary thyroid carcinoma (PTC) has increased in recent years, in spite of its favorable prognosis, it has a 20%-50% rate of lymph node metastasis.[1] Recurrence of PTC is always due to residual lymph node metastases not removed at initial surgery.[2] The usual sites of lymph node metastasis are para-tracheal or jugular lymph nodes (level VI, III, V).PTC is the most common type of differentiated thyroid cancer (DTC),[3] with a low occurrence rate of retropharyngeal lymph node (RPLN) metastasis ranging from 0.43% to 0.5%.[4] PTC metastases to RPLN are occult, and it is easy to miss diagnosis. Patients can be symptom-free. But the position of RPLN is deep and difficult to resect. The risk factors of this special metastasis are still not very clear. Although some case reports are describing RPLN metastasis from PTC, no large retrospective study has been reported.[2-7] In this study, we have retrospectively analyzed 34 PTC patients with RPLN metastasis to summarize preoperative examination, surgical treatment, prognosis data, and other clinical features and tried to find the risk factors and prognosis of this special metastasis. It is reported as follows:

## PATIENTS AND METHODS

### Patient Selection

From January 2006 to December 2017, 14341 patients with PTC were treated at the department of Head and neck surgery, Zhejiang Cancer Hospital. There were 34 PTC patients proved with RPLN metastasis (0.28%), as the research group. We use case-control study. During January 2010 to December 2012, there were 436 patients underwent thyroidectomy and lateral neck dissection, 68 PTC patients (1:2) with lateral lymph node metastasis were randomly selected as the control group, they were all proved without RPLN metastasis during the follow-up to March 2018.

### Patient Inclusion and Exclusion Criteria

**Inclusion Criteria.** Confirmed diagnosis of PTC metastases to the RPLN. (2) Have proven RPLN metastasis for the research group. (3) Have undergone thyroidectomy and lateral neck dissection between January 2010 and December 2012 for the control group. (4) Control group patients must have no RPLN metastasis confirmed during follow-up until March 2018. (5) Age range of 20-78 years for both research and control groups. (6) Comparable distribution of males and females between the research and control groups.

**Exclusion Criteria.** Patients treated outside the specified time frames. (2) Control group patients who did not undergo thyroidectomy and lateral neck dissection. (3) Patients without proven RPLN metastasis for the research group, and patients without confirmed absence of RPLN metastasis during follow-up for the control group.

### Randomization Process

The randomization of the control group was performed to ensure unbiased selection and comparability with the research group. We employed a computerized random number generator to select 68 patients from the 436 eligible patients. This method ensured that each patient had an equal chance of being included in the control group, thereby minimizing selection bias and ensuring that the control group was representative of the larger population of patients who underwent thyroidectomy and lateral neck dissection. The randomization process also accounted for matching the control group with the research group in terms of age and sex, ensuring that these demographic variables did not confound the study results.

### Methods

Comprehensive examinations were performed before the operation, including thyroid function, serum Thyroglobulin (Tg), thyroid ultrasound, enhanced CT or MRI, nasofibroscopy/laryngoscope, CT-guided fine needle aspiration cytology (FNAC), and PET-CT. These tests were critical in the diagnostic and treatment planning process. Thyroid function tests measured hormone levels to determine thyroid gland function and influenced the surgical approach. Serum Thyroglobulin (Tg) levels served as a marker for thyroid cancer, especially for monitoring recurrence or metastasis. Thyroid ultrasound used sound waves to create images of the thyroid gland, assisting in the assessment of nodule size and characteristics and in guiding FNAC procedures. Enhanced CT or MRI provided detailed cross-sectional images, identifying tumor size, extent, and involvement of adjacent tissues, which was essential for surgical planning and determining disease extent. Nasofibroscopy/laryngoscopy examined the nasopharynx and larynx to ensure vocal cords and nearby structures were unaffected by the tumor, which was crucial for preserving vocal function during surgery. CT-guided FNAC, a minimally invasive procedure, extracted cells from a nodule or lymph node with high accuracy, providing cytological evidence to confirm malignancy and guide treatment decisions. PET-CT provided both metabolic and anatomical information, useful in detecting distant metastasis and in cases where other imaging results were inconclusive, revealing metabolic activity indicative of cancer spread not visible on other imaging tests.

Surgery was performed on all patients. The clinicopathologic findings from these patients were studied. Clinical features like tumor location, tumor bilaterality, tumor size, multifocality, extracapsular invasion, tumor dedifferentiation, lymphovascular invasion, central lymph node density, lateral lymph node density, level II lymph node density, distant metastasis were collected.

### Follow-up

All the patients were followed up by telephone and outpatient review. They were followed up for 12~130 months by March 2018 (median time: 57 months).Patients were monitored at regular intervals, with follow-up visits typically scheduled at 3 months, 6 months, 1 year, and annually thereafter. During these follow-ups, a variety of clinical data were collected to assess the patients' health status and treatment outcomes. This included monitoring for any postoperative complications, such as infection, bleeding, or hypocalcemia. Additionally, the presence of recurrent disease or metastasis was evaluated through physical examinations, serum Thyroglobulin (Tg) levels, and imaging studies such as ultrasound, CT, or PET-CT scans. Treatment outcomes, including the effectiveness of the initial surgery and any adjuvant therapies, were recorded, as well as the overall survival times and disease-free survival rates.

### Statistical analyses

SPSS 19 statistical software was used to establish a database, with the Kaplan-Meier method employed for survival analysis and the Log-rank test for single-factor analysis. $P < .05$ indicated statistical significance. Survival time was calculated from the operation time after diagnosis of retropharyngeal lymph node metastasis. The Kaplan-Meier method was chosen for its ability to estimate survival probabilities over time, accommodating censored data typical in long-term follow-up studies. The Log-rank test was used to compare survival curves between patient groups, identifying statistically significant differences in survival times, thus fitting the study's objectives of evaluating long-

term survival outcomes and prognostic factors. Survival time was calculated from the operation time after the diagnosis of retropharyngeal lymph node metastasis.

## RESULT

In the research group, there are 9 males and 25 females. The average age of retropharyngeal lymph node metastasis is 54.5 (range 20-78) years old. Of these patients, 7 patients were initial treatment (without thyroidectomy before), and 27 patients had thyroidectomy history before retropharyngeal lymph node metastasis; the median time from initial treatment to retropharyngeal lymph node metastasis was 93.1 months (range from 1 to 312 months); 3 cases had a history of radiotherapy (dose range: 48 ~ 70 Gy); 12 cases had I131 isotope treatment history before (total dose range: 100 ~ 400 mCi). Four patients combined with pulmonary metastasis, and one patient combined with pulmonary and mediastinal metastasis. Patient data are presented in Table 1.

Preoperative Examination: In the research group, 27 patients had a history of thyroidectomy. Upon detection of retropharyngeal lymph node (RPLN) metastasis, 24 patients underwent total thyroidectomy, and preoperative thyroglobulin (Tg) was elevated in 20 of these patients (83.3%). Routine physical examinations or ultrasonography could not detect RPLN, making ultrasonography-guided fine-needle aspiration cytology impractical. However, if the metastatic RPLN is large enough under the hyoid bone, ultrasonography can detect the inferior part of the RPLN. Enhanced CT, with a sensitivity of 94% and specificity of 100%, was used for its detailed cross-sectional images that allow precise identification of abnormal lymph nodes. MRI, with a sensitivity of 97%, offers excellent soft tissue contrast, helping distinguish metastatic lymph nodes from surrounding structures. PET-CT and SPECT were also utilized for their ability to highlight metabolically active or functionally abnormal lymph nodes. Additionally, 11 patients were pathologically confirmed as having RPLN metastasis through CT-guided fine-needle aspiration cytology (FNAC), which involves using a thin needle to extract tissue or fluid samples for microscopic examination. Image features are provided in Figures 1-3.

### Surgical treatment

**Surgical Treatment of Retropharyngeal Lymph Node (RPLN) Metastasis**:The RPLNs are not routinely resected in PTC neck dissections. However, all patients in this study underwent radical resection via a neck incision. For 16 cases with metastatic lymph nodes located at the nasopharyngeal or oropharyngeal level (above the level of the hyoid bone), a cervical incision was made, the submandibular gland was either upturned or resected, and the deep part of the digastric muscle was freed to access the retropharyngeal space. The internal and external carotid arteries were then freed, pulled, and protected to facilitate the extraction of the retropharyngeal lymph nodes.

For 10 cases with metastatic lymph nodes located below the level of the hyoid bone, careful separation of the pharyngeal and laryngeal mucosa was necessary to maintain

**Table 1.** Characteristics of 34 PTC patients with retropharyngeal lymph node metastasis

| Characteristics | Research Group (n=34) |
|---|---|
| Gender | 9 males, 25 females |
| Age (years) | Average: 54.5 (Range: 20-78) |
| **Treatment history** | |
| Initial treatment | 7 patients without prior thyroidectomy |
| Thyroidectomy History | 27 patients with prior thyroidectomy |
| Time to RPLN Metastasis | Median: 93.1 months (Range: 1-312 months) |
| **Previous Therapies** | |
| Radiotherapy | 3 cases (dose range: 48-70 Gy) |
| I131 Isotope Treatment | 12 cases (total dose range: 100-400 mCi) |
| **Metastatic Status** | |
| Pulmonary Metastasis | 4 patients |
| Pulmonary and Mediastinal Metastasis | 1 patient |

**Figure 1.** Contrast-enhanced CT (axial view) showing a well-defined right RPLN.

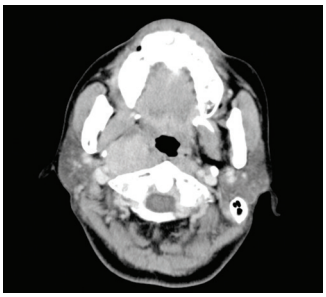


**Figure 2.** MRI (coronal view) showing left RPLN with infiltration of the nasopharyngeal mucosa.

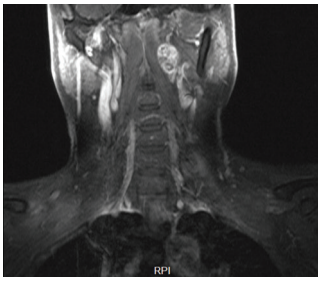



**Figure 3.** (a) 'Inverse grey' axial CT, (b) 'hot iron' SPE scan-CT coregistration images of left RPLN metastasis.

**Table 2.** Compare of clinicopathologic features between the two group

| | Research group (n=34) | Control group (n=68) | Statistical value | *P* value |
|---|---|---|---|---|
| Tumor size(mm) | 36.8±17.6 | 15.0±10.4 | $t$ =7.841 | <.001 |
| Tumor bilaterality(m/n,%) | 11/34,32.4 | 14/68,20.6 | $\chi^2$=1.696 | .193 |
| Multifocality(m/n,%) | 16/34,47.1 | 22/68,32.4 | $\chi^2$=2.097 | .148 |
| Extracapsular invasion(m/n,%) | 19/34,55.9 | 29/68,42.6 | $\chi^2$=1.594 | .207 |
| Tumor disseminated in the gland(m/n,%) | 9/34,26.5 | 13/68,19.1 | $\chi^2$=0.724 | .395 |
| Tumor dedifferentiation(m/n,%) | 7/34,20.6 | 3/68,4.4 | $\chi^2$=6.708 | .010 |
| Lymphovascular invasion(m/n,%) | 5/34,14.7 | 9/68,13.2 | $\chi^2$=0.041 | .839 |
| Central lymph node density | 0.83±0.27 | 0.38±0.21 | $t$ =9.068 | <.001 |
| Lateral lymph node density | 0.41±0.21 | 0.43±0.27 | $t$=0.414 | .680 |
| Level II lymph node density | 0.59±0.18 | 0.38±0.22 | $t$ =4.871 | <.001 |
| Distant metastasis(m/n,%) | 8/34, 23.5 | 0/68,0 | $\chi^2$=17.362 | <.001 |

**Figure 4.** The survival rate of RPLN(+) patients.

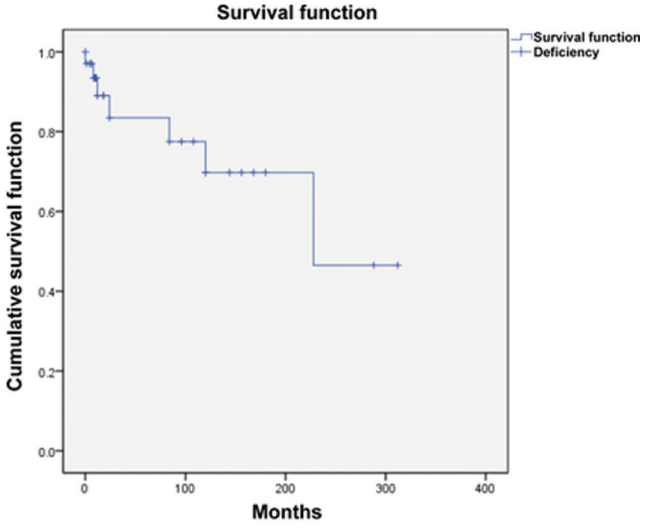
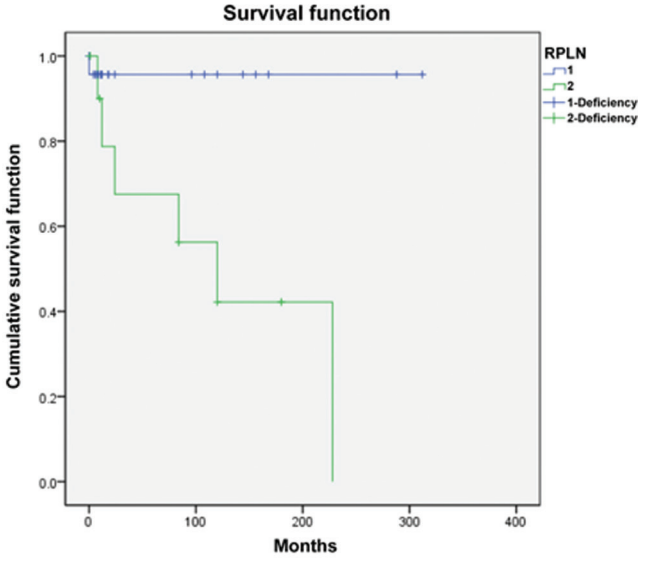



**Figure 5.** Compare of survival rate between the two group: RPLN above hyoid plane; RPLN under hyoid plane




the integrity of the pharyngeal mucosa. If the tumor had invaded the mucous layer or hypopharyngeal cavity, the hypopharyngeal mucosa was removed, resulting in a mucosal defect that was repaired using a flap if needed. In these patients, 6 cases required hypopharyngeal mucosa resection, with 3 patients having direct suturing post-resection and the other 3 patients requiring repair using an antebrachial flap due to larger defects. The number of metastatic retropharyngeal lymph nodes ranged from 1 to 2, with an average diameter of 2.5 cm (range 1.5 - 5.5 cm).

All patients also had lateral cervical lymph node metastasis (N1b), with 4 cases presenting pulmonary metastasis and 1 case with both pulmonary and mediastinal metastasis. Detailed clinical data are shown in Table 1. Postoperative complications: Following surgery, two patients experienced postoperative bleeding, which was successfully managed through redebridement and hemostasis procedures. Additionally, one patient developed a postoperative pharyngocutaneous fistula, which resolved with conservative management involving local dressing changes.

### Compared to the control group

**Tumor Size**: Research Group: Larger tumor sizes observed. Control Group: Smaller tumor sizes reported.

**Central and Level II Lymph Node Density**: Research Group: Higher density of central and Level II lymph node involvement. Control Group: Lower density of central and Level II lymph node involvement.

**Tumor Dedifferentiation Rate**: Research Group: Higher incidence of tumor dedifferentiation. Control Group: Lower incidence of tumor dedifferentiation.

**Distant Metastasis Rate**: Research Group: Elevated rate of distant metastasis. Control Group: Lower rate of distant metastasis.

### Prognosis

Among the 34 patients in this study, recurrence patterns included parapharyngeal lymph node recurrence in 2 patients, focal or cervical lymph node recurrence in 5 patients, and distant metastasis in 8 cases (5 of which were detected before surgery). Causes of death included lung metastasis in 1 case, progression of neck cancer in 5 cases, and cachexia in 1 case.

Survival analysis revealed a 5-year survival rate of 77.5% (Figure 4). Univariate analysis highlighted a significant impact of retropharyngeal lymph node (RPLN) metastasis location on survival rates, with cases located under the hyoid plane showing a relatively poorer prognosis ($P$ = .009) (Figure 5).

## DISCUSSION

RPLNs are located in the retropharyngeal space, surrounded by pharyngeal constrictor muscles anteriorly, the pre-vertebral fascia posteriorly, the carotid sheath laterally, the skull base superiorly, and the level of vertebra C3 inferiorly. These nodes are divided into two groups: lateral and medial (Figure 1). In cases of PTC metastasis, the affected RPLNs are typically in the lateral group, which can be further classified into lateral nasopharyngeal and lateral oropharyngeal nodes based on their specific locations. There is some variation in the terminology used in the literature,

with some papers referring to these nodes as parapharyngeal lymph nodes (PLNs). However, RPLNs and PLNs actually describe the same anatomical structures.[8] This terminology difference can be attributed to the nodes' location within the parapharyngeal space, which overlaps with the retropharyngeal space.

**Metastasis Patterns to RPLN**

(1) Nasopharyngeal Carcinoma: Most likely cancer type to metastasize to RPLNs.
(2) Oropharyngeal Cancer: Shows moderate likelihood of metastasis to RPLNs.
(3) Hypopharyngeal Carcinoma and Esophageal Cancer: Less common, but observed to metastasize to RPLNs.
(4) Thyroid Cancer: Rarely metastasizes to RPLNs, with reported rates between 0.43% to 2.5%.[6]

**Lymphatic Pathways to RPLN**

(1) Jugular Chain: One of the pathways for metastasis to RPLNs.
(2)Direct Thyroid Lymphatic Pathway: Involves the posterosuperior lymphatic chain originating from the upper pole of the thyroid.

**Imaging characteristics and diagnosis retropharyngeal lymph node metastasis in PTC**

RPLNs are located in the retropharyngeal space above the level of the hyoid bone, with their normal size ranging between 2 to 5 mm. The diagnostic value of ultrasound for RPLNs is limited, making it insufficient as the sole criterion for differential diagnosis. Preoperative evaluation primarily relies on CT or MRI imaging due to their ability to provide detailed images of lymph nodes. Enhanced imaging helps in identifying the increased vascularity of metastatic lymph nodes, liquefaction refers to the breakdown of tissue within the lymph node, and calcification indicates the presence of metastatic deposits, particularly in thyroid cancer. These characteristics highlight abnormal features that contribute significantly to the diagnostic process. When imaging results are inconclusive, a definitive diagnosis can be achieved through fine needle aspiration (FNA). In our research, 10 RPLN metastases were discovered incidentally through follow-up imaging, underscoring the importance of these techniques.[9] For patients with lateral neck lymph node metastasis, CT scanning should extend from the base of the skull to the chest to fully assess the status of retropharyngeal and lung metastasis. Additionally, for those with RPLN metastasis, coronal CT and MRI should be included to thoroughly evaluate the site, scope, and surrounding infiltration of metastatic lymph nodes. Advanced imaging techniques like PET-CT and SPECT are also used to detect RPLN metastasis, offering additional insights into metabolic activity and aiding in comprehensive assessment. In conclusion, imaging plays a critical role in the diagnosis and management of RPLN metastasis in PTC, and strengthening the use of CT, MRI, and other advanced imaging techniques during preoperative evaluation and postoperative follow-up can enhance detection and treatment planning for patients with this condition.

**Clinical characteristics of retropharyngeal lymph node metastasis in PTC**

Patients with RPLN metastasis in the research group often had a long history of cervical lymph node metastasis, with an average duration of 93.1 months from the initial thyroidectomy to the detection of retropharyngeal lymph node metastasis. Compared to the control group, risk factors for RPLN metastasis included tumor dedifferentiation, cancer dissemination within the gland, distant metastasis, and higher central lymph node density. Patients with metastasis at the oropharyngeal level often presented with symptoms such as difficulty swallowing or breathing due to the tumor's proximity to the pharynx and larynx. In contrast, metastasis at the nasopharyngeal level frequently did not exhibit specific clinical symptoms, making it more challenging to detect based on symptoms alone. Elevated thyroglobulin (Tg) levels were a significant indicator of metastasis. Tg is a glycoprotein secreted by thyroid follicular epithelial cells, with normal levels typically ranging from 5-40 μg/L. In the research group, elevated Tg levels signaled potential RPLN metastasis. In the study, 32 patients were classified as stage T4, with all exhibiting lateral neck lymph node metastasis. Seven cases had distant metastasis at the time of treatment, and three developed distant metastasis during follow-up. The study explored whether the primary thyroid tumor's location (upper, middle, or lower third of the thyroid lobe) affected RPLN metastasis. Although no clear association was established, cancer dissemination within the gland was confirmed as a risk factor for RPLN metastasis. Primary thyroid tumors in the research group were generally larger and more prone to dedifferentiation, increasing the likelihood of distant metastasis.

**Treatment of RPLN metastasis in PTC**: The removal of RPLNs can be challenging due to their deep location and high upper border. RPLNs are typically situated medial to the carotid artery and deep to the mandible, making surgical access difficult without significant trauma. Mandibulotomy, which involves the removal of the mandible, can cause substantial surgical trauma and is generally avoided. Instead, we opt for a lateral cervical approach, which allows safe and complete resection of the RPLN without the need for mandibulotomy. This approach involves retracting the stylohyoid muscles and the posterior belly of the digastric muscle to expose the RPLN. In our study, all patients had their RPLNs removed via this lateral cervical approach, which proved to be safe and effective.[10-14] However, different pathological types may require different approaches. For instance, in one patient with medullary papillary thyroid carcinoma and pharyngeal lymph node metastasis, a mandibulotomy was necessary to access the RPLN. In recent years, endoscopic transoral or robotic surgeries have been reported as safe and effective alternatives for RPLN resection. Despite these advancements, most studies have small sample sizes or are limited to case reports. Therefore, further exploration

is needed, especially since most patients require concurrent resection of primary thyroid lesions and lateral neck lymph nodes. Transoral surgery can be considered for isolated RPLN metastasis after thorough evaluation, and endoscopic-assisted surgery may be beneficial in cases with difficult exposure, improving vision and space and enhancing safety.

**Prognosis analysis of RPLN metastasis in PTC:**

The prognosis of PTC is generally good, but patients with RPLN metastasis typically have a long history of the disease, are diagnosed at a later stage, and have a high rate of distant metastasis. In this study, the lung metastasis rate was 28.6% (8/28), with one patient succumbing to lung metastasis. However, lung metastasis was not the primary prognostic factor. Despite the advanced stage of RPLN metastasis in PTC, the postoperative 5-year survival rate was 82.5% following treatment. Univariate analysis indicated that the location of RPLN metastasis significantly impacted prognosis. Metastatic lymph nodes located below the level of the hyoid bone often invade the larynx and hypopharynx, affecting breathing, eating, and speech functions. These cases involve more extensive surgeries and challenging treatments, resulting in a worse overall prognosis compared to patients with RPLN located above the level of the hyoid bone. All patients who died with RPLN metastasis in this study were over 50 years old, suggesting that age may be a factor in poorer prognosis. However, statistical analysis did not show a significant difference, indicating the need for more extensive research with a larger sample size.

PTC metastasis to RPLN is rare but should be considered during follow-up, particularly for patients with tumor dedifferentiation, tumor dissemination within the gland, and distant metastasis. These patients often have elevated serum Tg levels. Routine ultrasonography may miss these metastases, so periodic CT scans, MRI, or 131I-SPECT/CT are recommended for follow-up. Patients with retropharyngeal lymph node metastasis generally have more advanced disease and may require multiple treatments, yet the prognosis remains favorable with active treatment.

Surgical resection via the lateral cervical approach is the main treatment method, with metastasis to lymph nodes below the level of the hyoid bone indicating a poorer prognosis.

While the lateral cervical approach for RPLN removal is commonly used due to its effectiveness, alternative approaches such as transoral or robotic surgery offer potential advantages and disadvantages. Transoral surgery provides a less invasive option with potentially reduced recovery times and minimal scarring, but it may offer limited access and visualization, especially for deeper or more complex cases. Robotic surgery enhances precision and access through minimally invasive techniques, improving visualization and maneuverability in confined spaces, but it involves higher costs and requires specialized training and equipment. Each approach should be considered based on the patient's specific condition, the surgeon's expertise, and the available resources.

Future research should focus on several key areas to improve the management and outcomes of RPLN metastasis in PTC patients. There is a need for further exploration of treatment strategies, especially when patients require simultaneous resection of primary thyroid lesions and lateral neck lymph nodes. Developing guidelines for the use of alternative surgical approaches, such as transoral or robotic surgery, in different clinical scenarios could enhance patient outcomes. Additionally, more extensive studies are needed to understand the impact of age, tumor stage, and metastasis location on prognosis, with larger sample sizes to achieve statistical significance. Ongoing research should also investigate the effectiveness of various imaging modalities in early detection and monitoring of RPLN metastasis, aiming to establish standardized protocols for follow-up care. Overall, these efforts will contribute to more personalized and effective treatment plans for patients with PTC and RPLN metastasis.

## CONFLICT OF INTEREST

The authors have no potential conflicts of interest to report relevant to this article.

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## AUTHOR CONTRIBUTIONS

JZ and LG designed the study, WZ collected the data, MZ analyzed the data, JZ and LG prepared the manuscript. All authors read and approved the final manuscript.

## ETHICAL COMPLIANCE

The ethics committee of Zhejiang Cancer Hospital approved this study.

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