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Advances in Research of Lateral Lymph Node Metastasis in Papillary Thyroid Carcinoma

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Abstract

Papillary thyroid carcinoma originates from thyroid follicular epithelial cells, which is one of the most common malignant tumors of the head and neck. It progresses slowly and has a good prognosis, but it is prone to cervical lymph node metastasis. At present, ultrasound is the first choice for clinical diagnosis, and qualitative diagnosis depends on the results of cytology or pathology. Surgery is the main treatment, supplemented by radioactive iodine therapy and TSH suppression therapy. In recent years, with the improvement of medical level, new research findings and new diagnostic perspectives are constantly proposed. This article reviews the current research progress of lateral lymph node metastasis in papillary thyroid cancer.

Keywords

Papillary Thyroid Cancer; Lymphatic Metastasis; Neck Dissection.

1. Introduction

The incidence of thyroid cancer has increased rapidly in recent years, and it has become the most common malignant tumor in the human endocrine system. Papillary thyroid carcinoma (PTC) is the most common type of thyroid cancer, accounting for more than 80% and ranking first in the incidence of all thyroid malignant tumors[1]. With the development of high-resolution ultrasound technology and the increase in health awareness, PTC (especially papillary thyroid microcarcinoma with tumor diameter < 1cm) has been frequently detected. Which is generally considered to be the main reason for the increase in the incidence of thyroid cancer. In addition, some studies have found that the incidence of thyroid cancer is related to obesity, increased radiation and environmental deterioration[2]. PTC originates from thyroid follicular epithelial cells with good differentiation and low invasiveness, but its cervical lymph node metastasis is not uncommon. Some patients even present with lateral lymph node enlargement as the first symptom, which not only increases the risk of local recurrence and distant metastasis, but also affects the specific survival rate of patients[3]. At present, experts and scholars at home and abroad have not reached a consensus on how to achieve the goal of accurate and individualized diagnosis and treatment for PTC patients with lateral lymph node metastasis[4][5]. With the improvement of medical level, new studies have continuously put forward new concepts of diagnosis and treatment. This article reviews the current research progress of lateral lymph node metastasis in PTC.

2. Pattern of Cervical Lymph Node Metastasis

Cervical lymph node metastasis is one of the main biological behaviors of PTC. About 30% to 80% of PTC patients already have cervical lymph node metastasis at the time of diagnosis, mainly involving deep cervical lymph nodes[5]. At present, the internationally recognized division of deep cervical lymph nodes is the zoning method proposed and revised by the Committee of the American

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Academy of Otorhinolaryngology-head and neck surgery and Oncology in 1991, which is divided into seven levels from I ~ VII[6][7]. Clinically, these seven levels are simply divided into central lymph nodes (level VI, VII) and lateral lymph nodes(level I ~ V). Lateral lymph nodes(level II ~ IV) are also called jugular chain lymph nodes because they are distributed along the internal jugular vein.

The pattern of cervical lymph node metastasis in PTC is closely related to the lymphatic drainage pattern of the thyroid gland, usually showing step-by-step metastasis along the lymphatic drainage pathway. Level VI is mostly the first station of lymph node metastasis, and then metastasize to lateral lymph nodes in level II ~ V after paratracheal lymph node drainage, or downwards to superior mediastinal lymph nodes (level VII), mostly ipsilateral metastasis, contralateral metastasis is rare[8]. However, sometimes "jumping metastasis" can be seen clinically (the central lymph node is negative, lateral lymph node is postive), which indicates that there is a deviation between PTC cervical lymph node metastasis and thyroid lymphatic drainage. Its incidence is low, ranging from 1.6% to 21.8%. It is more likely to occur when the cancer is located at the upper pole or isthmus of the thyroid[9]. Chen Rui et al. [10] found that the rate of lymph node metastasis in the central region of PTC was about 67.0%, and that in the lateral cervical region was about 54.7%. The lymph node metastasis rates in level II, III, IV and V of the lateral neck were 15.5%, 40.5%, 35.3% and 6.9% respectively. Thus it can be seen that lymph node metastasis in the central region is the most common, while lymph node metastasis in the lateral cervical region is followed by level III, IV, II and V, and level I, retropharyngeal and parapharyngeal lymph node metastasis is very rare. In addition, a large number of studies have shown that central lymph nodes metastasis is an independent risk factor for lateral lymph node metastasis (LLNM), and the positive number of central lymph nodes metastasis has important predictive value for LLNM[11][12]. A meta-analysis of 14 studies showed that PTC with central lymph node metastasis had a 6.84 times higher risk of LLNM than PTC without central lymph node metastasis[11]. Liu et al. [12]found that when the number of lymph node metastasis in the central region is more than three, the possibility of LLNM should be actively considered.

3. Diagnosis of Lateral Lymph Node Metastasis

3.1 Ultrasonography

At present, ultrasonography is still the first choice for preoperative imaging evaluation of PTC with lateral lymph node metastasis. It has incomparable advantages over other examination methods, such as simple operation, low cost, real-time, non-invasive and so on. Occult lymph node metastasis with a diameter of several millimeters can also be found, which is valuable for clinical staging and treatment plan optimization. Both the National Comprehensive Cancer Network and the ATA guidelines recommend preoperative ultrasound assessment of cervical lymph node metastasis in patients with thyroid cancer, especially lateral lymph nodes[4][13]. However, ultrasonic examination also has some limitations. The study shows that the sensitivity of ultrasound in the diagnosis of central lymph node metastasis (CLNM) is 33%, and the specificity is 93%. The high rate of missed diagnosis may be due to the deep location of central lymph nodes and the complexity of their anatomy, which makes ultrasound difficult to detect and lead to difficulties in diagnosis. While the sensitivity of ultrasound in diagnosing LLNM is 70%, and the specificity is 84%, which indicates that ultrasound can provide better diagnostic information for the evaluation of LLNM than CLNM[14]. In addition, there is still no unified criterion for ultrasound assessment of cervical lymph node metastasis, which relies more on the experience of the ultrasonographer, a certain bias in preoperative staging is inevitable.

3.2 Fine Needle Aspiration Biopsy and Thyroglobulin Measurement

Fine needle aspiration biopsy (FNAB) is considered to be the "gold standard" for preoperative evaluation of suspected lymph node metastasis. Combined with ultrasound, the safety and accuracy of FNAB can be greatly improved, and the accuracy can reach more than 95% [4]. However, the ATA guidelines recommend ultrasound-guided FNAB only for suspicious lymph nodes with short diameter ≥ 8~10mm and with abnormal ultrasound findings, which may be due to the concealed

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location of lymph nodes with diameter < 8mm and adjacent to the important structures of the neck, making FNAB easy to misdiagnose and the safety is low[4]. In addition, for some cases of cystic lymph nodes, lymph nodes micrometastases or insufficient number of sampled cells resulting in false negative of FNAB, unable to diagnose or inconsistent with ultrasonic diagnosis, it is often necessary to measure the level of thyroglobulin (FNA-Tg) in needle-washout fluid to assist diagnosis and reduce the rate of missed diagnosis of lymph nodes metastasis. At present, the research on FNA-Tg is limited, and there is no unified diagnostic threshold. Whether patients retain thyroid, serum Tg values, Tg-Ab values, and serum TSH levels may affect FNA-Tg[15][16][17]. Some scholars believe that lymph node Tg eluate 1.0ng/ml is the best critical value for the diagnosis of lymph node metastasis in PTC, which can obtain the highest diagnosis rate (sensitivity 93.2%; specificity 95.9%), and they found that FNA-Tg combined with FNAB can obtain better diagnostic results (sensitivity 98.4%; specificity 94.4%)[18]. However, some studies take into account the serum Tg values of patients, and suggest that different serum Tg values should adopt different lymph node eluate Tg cut-off values. 1.0ng/ml should be used as the best cut-off value in patients with low serum Tg values, while in patients with high serum Tg levels, the ratio of lymph node eluate to serum Tg greater than 0.5 has better diagnostic value[19].

3.3 Molecular Detection

With the in-depth study in the field of molecular biology of thyroid cancer, more and more molecular markers have been used in the preoperative diagnosis and prognosis of thyroid cancer. At present, the commonly used molecular detection methods include immunocytochemistry, mRNA and miRNA expression analysis, gene mutation or fusion. Among them, the combined detection of multiple genes can greatly improve the sensitivity and specificity of diagnosis, and greatly improve the diagnosis rate for thyroid nodules or suspicious lymph nodes that cannot be clearly diagnosed by FNAB[20]. BRAF gene is the focus of clinical research and application. BRAFV600E is the most common mutation site of PTC, which mostly occurs in classical and high-cell PTC, while is rare in follicular subtype PTC. It has a high specificity (100%) in the diagnosis of benign and malignant thyroid uncertain nodules, but the sensitivity is only about 40%. Therefore, it is often used in combination with ultrasound, FNAB and other diagnostic methods[21]. In addition, BRAF gene mutation is also associated with high invasiveness of PTC, such as extracapsular invasion, lymph node metastasis, tumor recurrence and distant metastasis[22]. Therefore, FNAB combined with BRAF gene detection can further improve the diagnosis rate of PTC with lateral lymph node metastasis, and help in preoperative risk assessment and clinical prognosis prediction to develop personalized diagnosis and treatment plan.

4. Treatment of Lateral Lymph Node Metastasis

4.1 Surgery

Surgical treatment is the first choice for PTC with lateral lymph node metastasis, and it is also the best treatment at present. Once the suspected lateral lymph nodes are diagnosed by preoperative FNAB or intraoperative frozen pathology, standardized therapeutic lateral neck dissection (LND) should be performed. With the continuous summary and analysis of the pattern of PTC with lateral lymph node metastasis, the concept of LND has changed now, and the mode of operation has been constantly optimized. Traditional simple lymphadenectomy is no longer used because of the high recurrence rate, and radical neck dissection is gradually transformed into functional LND due to excessive trauma and postoperative complications, which seriously reduce the quality of life of patients. The latter retains some important functional structures of the neck (such as internal jugular vein, sternocleidomastoid muscle, accessory nerve, etc.). Selective lateral neck dissection is a kind of functional lateral neck dissection, which has become the mainstream surgical method at present. Some scholars even proposed that super-selective lateral neck dissection (level III and IV) is safe and feasible for PTC that preoperative evaluation of level II lymph node is negative (cN1b stage), which greatly improve the quality of life of patients after operation[23]. However, when preoperative and

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intraoperative evaluation of extensive cervical lymph node metastasis, complicated with large lymph node metastasis (diameter ≥ 3cm) or obvious invasion of surrounding tissue, radical neck dissection should still be selected. Blindly pursuing functional preservation and reducing the scope of operation is inadvisable.

PTC with lateral cervical lymph node metastasis is mainly multi-regional metastasis, in which level IIa, III, IV lymph nodes are most often involved. All therapeutic LND should include level IIa, III, IV at least[5][24]. The possibility of lymph node metastasis in level I is very low, and routine dissection is not needed. Level I lymph node dissection should be performed when radical neck dissection is satisfied or the presence of lymph node metastasis is confirmed by preoperative evaluation[25]. Lymph node metastasis in level IIb and V is relatively rare, moreover, complex local anatomy, long operation time, high risk of operation and many postoperative complications (postoperative bleeding, chylous leakage, cervical plexus injury, accessory nerve injury, etc.). And it is found that there was no significant difference in the risk of postoperative recurrence whether to lymph node dissection in level IIb and V[26]. Therefore, there is still no consensus on whether routine LND in level IIb and V should be performed. A meta analysis of the clinicopathological data of 1145 patients of PTC who underwent LND showed that the lymph node metastasis rate in level IIb was as high as 15.5%, which could not be ignored[27]. In addition, it was found that the incidence of lymph node metastasis in level IIb increased significantly when there was lymph node metastasis in level IIa or multi-level lymph node metastasis in lateral neck, and level IIa and IIb should be dissected at the same time[28]. Strajina et al. [29]summarized 467 patients of PTC who underwent LND with a mean follow-up of 64 months. It was found that the recurrence rate was 12% in patients who underwent comprehensive LND (level II ~ Vb) for the first time, while 23% in patients who underwent selective LND (level II ~ IV), indicating that it was necessary to dissect lymph nodes in level V. In addition, the sternocleidomastoid muscle-banded intermuscular lymph nodes are often ignored in LND. A multicenter study found that intermuscular lymph nodes have a high metastasis rate of approximately 23.48%, and more attention should be paid when the tumor is located in the lower pole of the thyroid[30].

4.2 Radioactive Iodine Therapy

Radioactive iodine (RAI) therapy is an important part of adjuvant therapy for PTC after surgery. The treatment objectives include ablation of residual thyroid, adjuvant therapy and treatment of known residual or recurrent diseases, which can effectively reduce the risk of tumor recurrence and metastasis, while facilitate highly sensitive follow-up examination by monitoring serum Tg levels and radioactive iodine whole-body imaging after surgery. At present, there is still controversy about the selection of indications for postoperative RAI therapy in patients with PTC and the optimal dose of RAI therapy in patients with intermediate-risk and low-risk PTC. The 2015 ATA guidelines provide detailed RAI therapy recommendations for patients with different risk of recurrence, in which RAI therapy is not recommended for low-risk patients, strongly recommended for high-risk patients, and only general recommended for patients with intermediate-risk of recurrence[4]. However, the results of a recent meta-analysis showed that the overall success rate of ablation after RAI therapy was 71%, and that of intermediate-risk patients (72%) was higher than that of high-risk patients (52%). In addition, only 2% of intermediate-risk patients with successful ablation were combined with recurrence, while the recurrence rate of intermediate-risk patients without successful ablation was 14%. This indicates that recurrent intermediate-risk patients still need aggressive RAI therapy after surgery[31]. It has also been reported that in patients with intermediate-risk and low-risk PTC, there is no difference in ablation success rate and tumor recurrence rate between low-dose or high-dose RAI therapy, but low-dose RAI therapy has a lower incidence of side effects (including salivary gland injury, second tumor, myelosuppression, etc.), so low-dose RAI therapy is more recommended[32]. Therefore, the indications should be strictly controlled before choosing RAI therapy, taking into account individual recurrence risk stratification, postoperative Tg level and diagnostic whole-body imaging results. Active monitoring and protection should be taken during treatment, as well as real-

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time dynamic evaluation of patients' curative effect and timely adjustment of RAI therapy decision and follow-up plan, so that RAI therapy can reduce side effects as much as possible while ensuring the effect of treatment.

4.3 TSH Suppression Therapy

Thyroid-stimulating hormone (TSH), as a growth factor of thyroid follicular cells, may affect the occurrence and development of thyroid carcinoma derived from follicular cells. Therefore, TSH supppression therapy is considered to be an important intervention after surgery. Patients can control the level of serum TSH at or below the low limit by exogenous supplement of supraphysiologic dose of thyroid hormone, so as to inhibit the growth of thyroid follicular cells and reduce the recurrence and metastasis of TSH-dependent thyroid carcinoma, at the same time, thyroid hormone supplementation can also help patients restore normal thyroid function and play an alternative role[33]. A meta-analysis of 4174 patients with PTC showed that TSH suppression therapy effectively reduced the risk of tumor recurrence, metastasis and mortality in patients with intermediate-risk and high-risk PTC[34]; whereas, for patients with low-risk PTC, suppression of TSH to a very low level (< 0.1mU/L) did not improve overall survival rate[35]. In addition, long-term overdose of thyroid hormone can lead to arrhythmia, angina pectoris, decreased bone mineral density, mental abnormalities and other side effects, seriously affecting the quality of life of patients. Therefore, it is necessary to take into account the risk of postoperative tumor recurrence and the risk of side effects associated with TSH suppression therapy in patients with PTC, establish individual TSH control objectives, continuously and dynamically evaluate the efficacy and adjust the dose in real time during the follow-up period to suppress tumor recurrence while reducing adverse cardiovascular and skeletal risk events and improve the quality of life of patients[36].

4.4 Molecular Targeted Therapy

Most patients with PTC can achieve long-term tumor-free survival through traditional surgery combined with postoperative TSH suppression therapy and RAI therapy, but for advanced and iodine-refractory PTC, the effect of traditional treatment is not good, so molecular targeted therapy has become an important treatment. Its mechanism is mainly to inhibit the molecular pathway and related signal transduction pathways of the occurrence and development of PTC, so as to inhibit the progression of advanced metastatic lesions or restore the ability of tumor cells to recover radioactive iodine uptake. According to the different targets, the targeted drugs can be divided into anti-angiogenic tyrosine kinase inhibitors, selective V-raf mouse sarcoma virus oncogene homologue B1 inhibitors, selective MAPK kinase inhibitors and mTOR inhibitors. Among them, multi-target tyrosine kinase inhibitors sorafenib and levatinib have been approved for clinical use in many countries. Studies have shown that the objective effective rate of sorafenib is 12.2%, while that of Levatinib is 64.8%. Both of them can prolong the median progression-free survival time of iodine-refractory PTC and reduce the tumor size in some patients[37][38][39]. Molecular targeted therapy is specific and effective, but it is often limited by its side effects, so it is necessary to develop new targeted drugs with high efficiency and low adverse reactions in the future to achieve individual and accurate treatment of advanced and iodine-refractory PTC.

5. Conclusion

With the continuous development of medical level, the diagnostic methods of lateral lymph node metastasis of PTC are gradually diversified with their own advantages and characteristics, but there is still a lack of a diagnostic method with high sensitivity, specificity and accuracy. Reasonable combined application of mutiple diagnostic techniques will further improve the diagnosis rate. At present, the management of lateral lymph node metastasis of PTC is still controversial, mainly focused on the scope of cervical lymph node dissection. Therefore, constantly summarize the pattern of cervical lymph node metastasis in PTC, combined with the clinicopathological features and auxiliary examination of patients to obtain reliable clinical stages, and make the scope of surgical dissection accurate, individualized has become a trend. In addition, for high-risk stratified and iodine-

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refractory PTC, in addition to more active surgical treatment, reasonable RAI treatment, radiotherapy and chemotherapy, molecular targeted therapy and other comprehensive therapy are needed. New research results continue to promote the development of diagnosis and treatment technology of PTC, but in order to obtain universal recognition, it still needs to be verified by large samples and multicenter prospective research.

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