

Application Progress in the Surgical Treatment of Differentiated Thyroid Cancer

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Abstract: Differentiated thyroid cancer accounts for more than 90% of thyroid cancer, including follicular and papillary carcinoma, and surgery is the main way to treat the disease. With the increasing incidence of thyroid cancer in recent years, the progress of its main treatment methods has attracted people's attention. In order to achieve good treatment results and promote the prognosis of patients, they should accurately evaluate their actual condition before surgery, and then choose the appropriate surgical method. This article mainly reviews the technology and application effect of DTC surgical treatment, in order to provide more basis and reference for the formulation of surgical treatment plans for DTC patients.

Keywords: Differentiated thyroid cancer, Surgical treatment, Application progress.

1. Introduction

Thyroid cancer is currently the fastest growing solid tumour in terms of incidence. According to the 2016 data released by the National Cancer Centre [1]: the overall incidence of thyroid cancer is located in the 7th place of malignant tumours in the country and the 3rd place of female malignant tumours. Subsequently, the survey data of our National Cancer Centre showed that compared with 2017, the incidence rank of thyroid cancer among malignant tumours in China remained unchanged in 2019, still ranked seventh and fourth among female malignant tumours, but the overall incidence rate showed a clear upward trend [2]. Thyroid cancer has become an important type of disease that affects the living standards of our people and requires active treatment. Among them, differentiated thyroid cancer (DTC) is the most common type of thyroid cancer in clinical practice, accounting for more than 90% of thyroid cancer cases. In recent years, with the changes in people's lifestyles and habits and the continuous improvement of clinical diagnostic technology, the incidence of DTC has been increasing year by year, which seriously affects people's quality of life and health, and needs to be actively treated [3]. For this disease, the clinic should adhere to the principle of "early detection and early treatment", but its early symptoms are not obvious, so it is necessary to use CT, colour Doppler ultrasound and other instruments to diagnose the patient, in order to accurately find the location of the thyroid gland swelling, its size and its relationship with the surrounding tissues, so as to be able to formulate personalised and targeted treatment plans for the patient [3]. and targeted treatment plans [4]. Surgery is the core treatment for this disease, and the effect of the first surgery will have a direct impact on the patient's prognosis and recurrence, so clinicians should formulate a treatment plan based on the patient's high-risk factors, pathological findings, etc., and choose the appropriate surgical method to improve the patient's therapeutic effect [5].

2. Clinical Diagnosis of DTC

A scientific and reasonable surgical plan cannot be formulated

without accurate preoperative diagnosis and evaluation of the disease. Clinical diagnosis of DTC is mainly made through colour Doppler ultrasound, puncture biopsy, CT, magnetic resonance imaging (MRI) and other methods to clarify the number, location, size, relationship with surrounding tissues, and the nature of the mass. At the same time, the presence or absence of lymph node metastasis is determined, and the patient's medical history and the results of ancillary investigations are analysed in order to make a final treatment plan. The Guidelines for Adult Thyroid Nodules and Differentiated Thyroid Cancer [6] recommend ultrasound as the first choice for thyroid disease, but ultrasound has a subjective influence, and can only be used as a preliminary judgement of the nature of thyroid nodules, with poor sensitivity, and cannot be used as a criterion for confirming the diagnosis. However, preoperative and postoperative ultrasonography is valuable for clinical diagnosis and postoperative prognosis. Fine needle aspiration biopsy (FNAB) is currently the most accurate method for the differential diagnosis of the nature of thyroid nodules, and the specificity and sensitivity of FNAB for the diagnosis of the nature of thyroid nodules are >90%. The specificity and sensitivity of FNAB for the diagnosis of thyroid nodules are both >90%, and its sensitivity and accuracy can be close to 100% if combined with the examination of gene mutations [7]. In clinical practice, it is found that the proportion of FNAB technology in the diagnosis of thyroid diseases is not high, and the main reason for this is that the technology has been used for a relatively short period of time, and at present, some medical institutions do not have the conditions (equipment and technicians) to carry out this examination. Therefore, the training of high-quality pathologists is a major prerequisite for the promotion and application of this technique. In addition to the above examination means, in the Thyroid Cancer Diagnostic and Treatment Guidelines (2018 Edition) [8], the assisting role of CT, positron emission tomography CT (PETCT), MRI, and functional metabolic imaging in the diagnosis of thyroid disease has also been affirmed; CT can better clarify the presence of lymph node metastasis and diseased tissue. Lymph node metastasis and the relationship between the diseased tissue and the surrounding tissues,

PET-CT and MRI are not commonly used in the diagnosis of thyroid diseases, but only as supplementary examinations.

3. Advances in Surgical Treatment Modalities

3.1 Traditional Thyroid Surgery

Traditional thyroid surgery was proposed by Professor Kocher, a Swiss medical doctor, in 1872, and the first thyroid surgery in the history of mankind was carried out through practice, and at present, some hospitals are still treating patients with differentiated thyroid cancer with this classical surgery [9]. A curved incision is made in the patient's neck, which has the advantages of clear exposure, precise haemostasis, and simple operation, but also has the disadvantages, such as a large postoperative scar, which has a large impact on the human body's aesthetics. With the continuous improvement of people's requirements for surgical treatment, this procedure can no longer meet the needs of patients, especially female patients, the large postoperative scar will cause psychological discomfort [10].

(1) Thyroidectomy: The effect of the first surgery will have a direct impact on the patient's postoperative adjuvant treatment plan, prognosis, postoperative quality of life, and the possibility of recurrence, etc. Subtotal thyroidectomy, subtotal thyroidectomy, and total excision have their own advantages as the main surgical procedures in the treatment of thyroid cancer. Subtotal and subtotal excision retains a portion of the thyroid tissues, but there is a high risk of recurrence and metastasis in the postoperative period. Total resection is more difficult to perform, may cause damage to peripheral tissues and nerves, and has a higher rate of postoperative complications, but the wide scope of the operation can significantly reduce the risk of postoperative recurrence and improve the long-term prognosis after surgery [11]. The guidelines clearly state that unilateral total lobectomy + isthmus resection and total/proximal total thyroidectomy are the current standard of care for patients with DTC.

A) Unilateral total resection of the affected lobe + isthmus resection is the minimal procedure for the treatment of DTC, and this procedure is mainly suitable for patients with low-risk, solitary or unilateral lesions, small diameters, no lymph node metastasis, and no combination of high-risk factors. Kang Wanyu et al [12] showed that unilateral lobectomy with isthmus resection and bilateral lobectomy could effectively resect the cancer foci in patients with micropapillary thyroid cancer, but compared with bilateral lobectomy, unilateral lobectomy with isthmus resection had a lower incidence of postoperative complications and higher surgical satisfaction, suggesting that unilateral lobectomy with isthmus resection could be used for patients with some indications to reduce the trauma to the patient. This suggests that unilateral lobectomy with isthmus resection can be used in patients with some indications to reduce the trauma to the patient, but whether the long-term efficacy of this procedure is comparable to that of total lobectomy requires further research to confirm.

B) The current clinical scope of total/proximal total thyroidectomy is: high-risk, bilateral or multiple cancer foci,

large diameter of the primary lesion (>4 cm), has invaded the surrounding tissues, combined with lymph node metastasis, combined with distal metastasis, and the patient himself/herself combined with high-risk factors. It has also been suggested that the elderly (age >55 years) DTC population should also be an applicable group for total/near-total thyroidectomy. Tan Yuewen et al [13] found that compared with near-total thyroidectomy, the clinical effect of treating DTC through total thyroidectomy is more satisfactory, and it is worthwhile to promote its use in the clinic. Zhang Wanyong et al [14] showed that compared with traditional open surgery, patients treated with total thyroidectomy had more significant improvement in perioperative indicators, less pain, better quality of life, fewer complications, and their overall treatment results were better. Total/proximal total thyroidectomy can effectively prevent and treat small lesions on the contralateral side from being missed, and is also conducive to postoperative radiological and other follow-up treatments and investigations, thus reducing the risk of recurrence. However, it should be noted that total/proximal total thyroidectomy may cause damage to the parathyroid glands and the laryngeal recurrent nerve, and so on.

(2) Lymph node dissection: patients with clear lymph node metastasis should undergo lymph node dissection; whether and what kind of cervical lymph node dissection should be performed in patients without lymph node metastasis needs to be determined. The current consensus is that patients with DTC should undergo ipsilateral central lymph node dissection; for patients with combined high-risk factors, bilateral cancers, and patients with significant local invasion, cervical lymph node dissection should be performed at the same time as total excision; for patients with clear cervical lymph node metastasis, it is generally recommended to carry out lateral cervical lymph node dissection; and for patients with a high proportion of central lymph node metastasis, clinical practice should be based on their specific conditions, while ensuring that lymph node metastasis can be treated in the same way as the central lymph node metastasis. For patients with a high percentage of central lymph node metastasis, the clinic should consider performing lateral cervical lymph node dissection according to their specific conditions while ensuring that the surrounding tissues and nerves are adequately protected; cervical lymph node dissection is mainly therapeutic, and preventive should be implemented or not depending on the specific conditions [15].

3.2 Lumpectomy-assisted Thyroidectomy

Thyroidectomy with the aid of laparoscopy was first performed by an Italian scholar, Professor Miccoli, in 1997, and is now widely used in the world, and is known as 'Miccoli's surgery' in the medical community. The procedure involves making a 1.5 cm incision in the patient's neck and then removing the lesion with the aid of laparoscopy [16]. Compared with conventional thyroid surgery, this procedure involves a smaller incision, relatively less intraoperative bleeding, and less postoperative scarring. However, there is a risk of instability of artificial pulling to build the cavity during the operation, and there are still a lot of shortcomings. Professor Gao Li's team invented a special instrument for building the cavity on the basis of Professor Miccoli's surgical

operation, and improved the operation method and process of this operation to form the 'modified Miccoli's operation' [17]. In the early stage, medical researchers generally believed that this procedure was of good clinical value for patients with tumours <3 cm in diameter and a thyroid volume <20 ml by colour Doppler ultrasound, especially for patients with benign diseases suggested by cytological and clinical tests, such as follicular tumours or low-grade malignant papillary carcinomas, and patients with no enlarged lymph nodes in the neck on examination. With the continuous development and improvement of laparoscopic technology and related instruments, the guidelines at home and abroad do not clearly stipulate that thyroid surgery cannot be assisted by laparoscopy, so the indications for this procedure have been relaxed, which also provides a platform for surgeons to develop innovatively, and many medical practitioners have improved the Miccoli procedure by applying it to cervical lymph node dissection and removal of thyroid cancer. The Miccoli procedure has been modified by many surgeons for neck lymph node dissection and thyroid cancer removal. However, the small exposure range of lymph node dissection using this procedure leads to incomplete exposure, and the operation space is small, making it difficult to remove the whole lymph node, which increases the probability of lymphatic fistula to a certain extent [18].

3.3 Totally Lumpectomy Thyroidectomy

In 1997, Professor Huscher's team completed the world's first case of complete laparoscopic thyroidectomy, and in 2001, Professor Qiu Ming's team completed the first case of complete laparoscopic thyroidectomy in China [19]. There are many routes for this surgery, such as subclavian route, combined sternomastoid route, oral route, retroauricular route, axillary route, areolar route, anterior sternal route, combined axillary areolar route, etc. Currently, the majority of operators prefer the sternomastoid route. This procedure is suitable for patients with T1 stage papillary thyroid cancer with cervical lymph node metastasis, secondary surgery, and cervical lymph node dissection in elective area. Compared with previous surgeries, complete laparoscopic thyroidectomy can really make the patient's neck scarless, which is very suitable for patients with high cosmetic requirements, and the use of a laparoscope during the operation can magnify the site of the lesion, which is more conducive to the operator to carry out fine operation, avoiding intraoperative damage to the surrounding tissues or blood vessels, which further improves the accuracy and effectiveness of the treatment [20]. However, this procedure is more traumatic, as it requires the creation of a subcutaneous gap, so the risk of postoperative complications is increased, and the damage caused to the patient's organism is greater than that of both traditional thyroid surgery and laparoscopic-assisted thyroidectomy. In recent years, 3D laparoscopy has been gradually promoted in thyroid surgery. Under the guidance of 3D laparoscopic technology, the operator is able to present a three-dimensional structure during the operation, which makes the field of the operation clearer, and promotes a more accurate and detailed dissection, and is able to effectively protect the function of the parathyroid glands, the laryngeal reentry nerve, and other structures, but the only disadvantage is that the operator is very susceptible to visual fatigue during the operation, and is therefore a more demanding surgeon.

3.4 Robotic Thyroidectomy

In 2009, Kang et al. used the da Vinci Surgical System for the first time to treat thyroid cancer patients via the axillary pathway, and then other pathways of robotic thyroid surgery gradually began to be applied [21]. The da Vinci Surgical System is a robotic arm that is adjusted and controlled by the surgeon via remote control at the console for the purpose of completing surgical operations. This procedure can avoid the operator's hand tremor during surgery and operation errors, and can also relieve the operator's fatigue to a certain extent, which is especially suitable for narrow space operation, complex reconstructive surgery and perivascular dissection. Currently, there are three main paths chosen for surgery using the da Vinci Surgical System, namely, unilateral transaxillary, bilateral transaxillary, and via the retroauricular fold along the occipital hairline. According to the research analysis, robotic thyroidectomy has high safety and effectiveness, and is very suitable for lymph node clearance in patients with highly differentiated thyroid cancer, which can meet the patients' requirements for overall aesthetics. Some scholars compared the effects of traditional thyroid surgery and robotic thyroidectomy and found that patients treated with the latter were significantly more satisfied with the cosmetic effect than the former [22]. At present, the da Vinci surgical system is the most advanced surgical system, which can enlarge the three-dimensional three-dimensional field of view, while the robotic arm can carry out multi-directional free movement, which can achieve consistency with the direction of the hand control, and is more convenient for the operator to operate.

3.5 Postoperative Adjuvant Therapy

Endocrine therapy: the endocrine therapy of DTC mainly refers to the postoperative thyroid-stimulating hormone (TSH) suppression therapy, the physiological function of TSH is to promote the growth and function of the thyroid gland, but the high level of TSH is a high-risk factor that leads to the occurrence and development of thyroid cancer, so, for most of the patients, the postoperative treatment through the TSH suppression therapy has an important significance in preventing the disease recurrence and metastasis. Zhu Hui et al [23] found that in the process of postoperative TSH suppression therapy for thyroid cancer, levothyroxine sodium tablets combined with thyroid tablets can help to improve the patient's thyroid function and enhance the immune function, and it has a high degree of safety. Wang Xin et al [24] showed that TSH suppression therapy for DTC can effectively improve thyroid function and enhance immune function, and has no significant effect on bone metabolism. For the selection of the dosage of TSH inhibition therapy after surgery, patients should be evaluated and then choose the appropriate drugs and dosage based on the principles of timely, adequate and long-term treatment; pregnant women and other special groups should be monitored regularly for bone density, heart, etc., in order to formulate a reasonable endocrine treatment plan [25]. (2) Radiation therapy ^{131}I therapy is a commonly used postoperative radiation therapy for thyroid cancer, and the principle of its treatment is the affinity of thyroid cells for iodine, so the use of radioactive iodine element ^{131}I can assist in the removal of malignant tumour cells and thyroid tissues in the postoperative period, effectively preventing the recurrence and metastasis of the

cancer cells [26]. Xu Weihong et al [27] showed that for DTC patients treated with TOETVA surgery, postoperative combined ¹³¹I treatment can significantly improve the patients' near-term efficacy and inhibit the metastasis of tumour cells compared with postoperative treatment with eugenol. In addition to this, radiation therapy is not a conventional treatment for DTC, but as a kind of local treatment for tumours, its application in patients with advanced thyroid cancer is more effective. Currently, it is believed that local radiotherapy is used for thyroid cancer patients who are unable to receive ¹³¹I or surgical treatment, those who are found to have residual lesions (visible to the naked eye) but are unable to undergo surgical treatment or ¹³¹I, and those who are treated for palliative purposes, and its applicability and necessity for DTC is still controversial.

4. Targeted Therapy

With the continuous development of basic medicine, not only has there been a further understanding of the mechanism of cancer development, at the same time, targeted molecular therapeutic drugs have also been developed based on the already defined oncogenic sites. Feng Zhiping et al [28] showed that miR-143-3p could inhibit the proliferation, invasion and migration of DTC cells, and its main mechanism of action is to block the signalling pathway PI3K/Akt. Bianfang et al [29] found that peptide P11 could inhibit the expression of miR-126 in DTC cells and then play an anti-cancer role. Feng Kaixiang [30] found that solute carrier family 27 member 2 (SLC27A2) is a potential diagnostic marker and therapeutic target for DTC. Wang Ning et al [31] showed that levatinib was effective in the treatment of advanced DTC by modulating the VEGFR-targeting pathway to inhibit the PI3K/AKT signalling pathway, thereby inducing apoptosis of thyroid cancer cells to achieve anti-cancer effects. Targeted therapeutic drugs act on specific cancer-causing sites, targeting the tumour cells without affecting the surrounding normal tissues, which is relatively safe.

5. Development and Application of Multidisciplinary Diagnosis and Treatment Model

In recent years, with the promotion and application of MDT mode, the demand for cancer prevention and fight against cancer has risen from single-dimensional diagnosis and treatment to multidimensional and full-process health management of thyroid cancer, and MDT diagnosis mode is mainly applied to complex and difficult thyroid cancers, such as locally advanced thyroid cancers, giant thyroid cancers, relapsed and metastatic thyroid cancers as well as special thyroid cancers, etc. Through continuous, standardised and individualized precise treatment, a relatively fixed multidisciplinary expert team (including thyroid surgery, ear, nose and throat, thoracic surgery and chest surgery) is organised for specific patients. Through continuous, standardised and individualised precision treatment, and organising a relatively fixed multidisciplinary team of experts (including thyroid surgery, otorhinolaryngology, thoracic surgery, nuclear medicine, endocrinology, ultrasonography, imaging, anaesthesia, radiotherapy, intensive care unit, pathology, etc.) for a specific patient, multidisciplinary

collaboration is needed to formulate a scientific, reasonable and effective diagnostic and therapeutic strategy, and to enhance the comprehensive therapeutic efficacy. Surgery for locally advanced thyroid cancer is extensive and traumatic, involving resection and reconstruction of major organs, and radical surgery is a key means to improve patient prognosis. In the past 10 years, a multidisciplinary team of experts has cooperated with each other and jointly issued the Chinese Expert Consensus on Surgical Treatment of Locally Advanced Thyroid Cancer (2020 Edition) [32] to standardise the diagnostic and treatment process, so that neoadjuvant therapy can be used to reduce the stage of thyroid cancer for patients who are unsuitable for surgical treatment, thus creating the conditions for the performance of a protective radical surgery. Neoadjuvant therapy for thyroid cancer mainly includes external radiotherapy, chemotherapy and targeted therapy. Neoadjuvant chemotherapy and neoadjuvant radiotherapy, as a kind of local treatment, theoretically have the effect that can reduce the size of the tumour and so on. In the treatment of advanced thyroid cancer, targeted therapy plays an important role in prolonging the survival time of patients and improving the quality of survival, and it has better clinical effects on iodine-refractory DTC or thyroid cancer that is ineffective in conventional treatment. In addition, tumour immunotherapy is rapidly developing and gradually entering into the clinical practice of tumour treatment, which may become a method of treating advanced thyroid tumours.

6. Summary

With the continuous progress and development of science and technology and medical care, there will be more and more techniques and means that can be applied to the treatment of DTC in the clinic, and the formulation of DTC treatment protocols is moving in the direction of more standardisation. Clinical practice should be based on accurate preoperative examination and diagnostic results, combined with patient assessment results, to choose appropriate and scientific surgical plans to improve patient prognosis and quality of life.

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