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I.V. Deineko
Utility Enterprise "Dnipropetrovsk Regional Clinical Hospital Named I.I. Mechnykov" of the Dnipropetrovsk Regional Council", Dnipro

COMPLEX TREATMENT OF LOCALLY ADVANCED MALIGNANT TUMORS OF THE THYROID GLAND WITH INVASION INTO THE ORGANS OF THE NECK AND MEDIASTINUM

e-mail: ilyadey@gmail.com

Patients with locally advanced thyroid cancer require particular attention, as the selection of surgical techniques and a logical program of complex therapy for them remain controversial. Given the significant complexity and prevalence of fatal complications in cases of tumor stenosis of the upper airway during emergency tracheostomy, it is recommended that the patient be prepared for radical or palliative surgery in a prepared operating room in a planned manner with patient intubation, if possible. Given the high proportion of locally advanced, highly differentiated tumors that are refractory to radioiodine therapy and have a high malignant potential, as well as the poor prognosis associated with local recurrence of the disease, surgical intervention as part of a comprehensive treatment plan should be as radical and aggressive as possible, with macroscopic removal of the entire tumor, including all invasions of organs and tissues of the neck and mediastinum, especially in cases of medium and low-grade tumors. Conversely, when planning a traumatic surgery, it is essential to consider the patient's general condition, age, and comorbidities. In cases where traumatic surgery is contraindicated, particularly in highly differentiated cancers, less radical methods of "shaving" the tumor without compromising the integrity of the organ may be employed.

Key words: malignant thyroid tumors; surgical tactics, upper respiratory tract

І.В. Дейнеко

КОМПЛЕКСНЕ ЛІКУВАННЯ МІСЦЕВО-РОЗПОВСЮДЖЕНИХ ЗЛОЯКІСНИХ ПУХЛИН ЩИТОПОДІБНОЇ ЗАЛОЗИ З ІНВАЗІЄЮ У ОРГАНИ ШИЇ ТА СЕРЕДОСТІННЯ

Особливої уваги заслуговують пацієнти з місцево-розповсюдженими формами раку щитоподібної залози, питання вибору хірургічної тактики й раціональної програми комплексної терапії щодо яких натепер залишаються дискутабельними. Враховуючи велику складність та кількість літальних ускладнень у випадках пухлинних стенозів верхніх дихальних шляхів при проведенні ургентної трахеостомії, при можливості, ми рекомендуємо швидко підготувати пацієнта до радикального або паліативного хірургічного втручання у підготовленої операційної в плановому порядку з інтубацією пацієнта. Враховуючи велику частку місцево-розповсюджених високодиференційованих пухлин рефрактерних до радіойодтерапії з високим злоякісним потенціалом, гіркий прогноз у випадках локального рецидивування захворювання, хірургічне втручання у складі комплексного лікування повинно бути максимально радикальним та агресивним з макроскопічним видаленням усієї пухлини, включно усі інвазії органів й тканин шиї та середостіння, особливо у випадках середньо- та низькодиференційованих пухлин. З іншого боку, при плануванні травматичної операції, треба враховувати загальний стан, вік та супутні захворювання пацієнта. В випадках наявності протипоказань до травматичної операції, особливо при високодиференційованих раках, мають право на існування менш радикальні методики «збривання» пухлини без порушення цілісності органу.

Ключові слова: злоякісні пухлини щитоподібної залози; хірургічна тактика, верхні дихальні шляхи

The work is a fragment of the research project "Improvement of diagnostics and surgical treatment of pancreaticobiliary, peripheral vascular and thyroid pathology", state registration No. 0120U103031.

Thyroid cancer (TC) represents a relatively minor proportion of overall cancer morbidity, accounting for 0.4–2 % of all neoplastic tumors. However, it is regarded as a leading cause of malignant diseases of the endocrine system [8]. In over 90 % of cases, thyroid cancer is diagnosed in stages I–III, with highly differentiated, papillary, and follicular forms. These forms of thyroid cancer are relatively straightforward to treat and have a very good prognosis [7]. However, in recent years, the incidence of not only highly differentiated thyroid cancer but also the percentage of neglected thyroid malignancies with extrathyroidal spread of medium and low morphologic differentiation, including medullary, low-grade, anaplastic, and primary thyroid lymphomas, has been increasing rapidly [9].

A number of authors have posited that the size of the tumor, its spread to the organs and tissues of the neck and mediastinum surrounding the thyroid gland, and the morphological structure of the tumor are the primary factors that contribute to a less favorable prognosis for treatment [12]. AMES (age, metastases, extension, size) or MACIS (metastases, age, radical surgery, invasion, size) also influence the prognosis of treatment. However, in our opinion, the most important prognostic factors in the case of advanced thyroid malignancies are histologic differentiation and the extent of tumor invasion. In the world, according to the histological classification of thyroid malignancies, more than a dozen types of carcinomas, i.e., epithelial tumors, and no less rare types of malignant tumors from other tissues and systems of the human body have been described [4].

Malignant thyroid tumors most often spread to the prethyroid muscles and soft tissues of the neck, the recurrent nerve, and the internal jugular vein. Additionally, metastasis to the upper respiratory tract (i.e. the trachea and laryngeal elements), oesophagus, upper mediastinum, anterior vertebral fascia and carotid artery is less common. It can be observed, however, that metastasis to regional lymph nodes occurs in most cases [11].

However, patients with locally advanced malignant thyroid tumors (LAMTT) are more likely to be older, have tumors with lower morphological differentiation, and have comorbidities compared to patients with early-stage tumors. In the event of tracheal or laryngeal invasion or compression, or recurrent nerve involvement, patients present with severe symptoms of upper airways stenosis, classified as I-III degree. Some of these patients require urgent surgical intervention, including tracheotomy.

The most critical considerations in the surgical management of LAMTT with upper airways invasion are determining the feasibility of urgent tracheotomy, the optimal surgical volume, and choice of access at the beginning and during the operation, comparison of the effectiveness of "shaving", limited "window", wedge-shaped, anterolateral and circular resections of the trachea and larynx. The possibility of simultaneous or phased closure of upper respiratory tract (URT) defects, resection of the recurrent nerves, the necessity of lateral fixation or resection of the vocal fold in the case of predicted bilateral laryngeal paresis, as well as the feasibility of neoadjuvant antitumor chemotherapy [6] must be determined.

The lack of a single therapeutic tactic for LAMTT is a significant problem, as it depends on the prevalence and histological differentiation of the tumor, the choice of the scope of surgical interventions, from palliative and urgent symptomatic to “aggressive” super radical, the volume of resections of the URT and the stage of closure of their defects. These factors are important to consider, as they affect the treatment plan. The data presented in the literature pertains to very small groups of patients, with sample sizes ranging from two to three dozen individuals. This limits the ability to draw conclusions about the planning of surgical interventions as part of complex treatment.

The purpose of the study was to improve the results of complex treatment of patients with locally advanced malignant thyroid tumors of T4 stage with the invasion of organs and major vessels of the neck and mediastinum by determining the optimal choice of a combination of methods and surgical tactics, depending on the degree and location of invasion and histological differentiation of the tumor.

Materials and Methods. A total of 2095 patients with malignant thyroid tumors were treated in the Department of Endocrine Surgery at the Municipal Enterprise “Dnipropetrovs'k Regional Clinical Hospital named after I. Mechnikov DRC” between the years 2004 and 2022. The average age of patients in the general group was 45.5±12.3 years, with a ratio of women to men of 5.1:1. According to the TNM classification of the AJCC 8th edition, 55.2 % of patients belonged to the T1 category, 18.5 % to T2, 17.9 % to T3, and 8.4 % to T4.

The study group comprised 145 patients with invasive T4a–b category LAMTT (102 patients T4a – 70.3 %, and 43 patients T4b – 29.7 %) who underwent complex treatment with the use and combination of various methods of surgical treatment from urgent tracheostomy and palliative surgery to super radical combined, extended and staged operations.

According to the assessment of the morphological changes structure, 95 patients (65.5 %) had highly differentiated papillary or follicular forms of cancer; moderately differentiated medullary carcinoma, as well as rare cases of Gurtle cell carcinoma, squamous cell carcinoma and oncocytic carcinoma in 16 (11.0 %), low-grade forms - low-grade and anaplastic cancer in 20 (13.8 %) and primary B-cell lymphomas and rare malignant tumors sarcoma and malignant thymoma in 14 (9.7 %). The mean age of patients in the study group was higher than in the general group, with an average age of 61.3±8.9 years. The gender ratio was significantly skewed towards male patients, with a ratio of 3.2:1.

All patients underwent standard examination methods, including sonographic examination of the thyroid gland and neck organs and lymph nodes, neck palpation, fine-needle aspiration biopsy of thyroid tumors, if necessary, of neck tumors and lymph nodes, and in recent years, sonographic criteria according

to the Eu-Thirads system and cytological criteria according to the Bethesda system were taken into account. Hormonal studies were conducted, including thyroid-stimulating hormone, free thyroxine, thyroglobulin, and antibodies to it, as well as calcitonin. Additionally, general and biochemical blood tests with electrolytes were performed, with separately ionized calcium to exclude parathyroid carcinoma. Coagulograms, electrocardiograms, and chest X-rays were also obtained. The general condition of the patients, their anamnesis, and the presence of chronic diseases were evaluated, with the necessary follow-up in each case. In cases of clinical and sonographic evidence of invasive tumor growth, spiral computed tomography with contrast or magnetic resonance imaging of the neck and chest cavity, Doppler ultrasonography of the major vessels of the neck, angiography of the major vessels of the neck and mediastinum, endoscopic examination of the larynx, trachea and esophagus were performed. If a more accurate histological structure of the tumor is required, in questionable cytological findings, to determine the tactics of complex treatment, an incisional biopsy of the tumor or metastasis to a regional lymph node was conducted at the diagnostic stage, and in recent years, a trepan biopsy of the tumor. In recently years, in cases of unspecified Bethesda III-IV groups, molecular genetic studies of cytological material were performed to determine mutations (BRAF, NRAS, KRAS, HRAS, 2RET/PTC, PAX8/PPARg). A histologic and, when necessary, immunohistochemical examination of the material removed during surgery was required to determine the presence of tumors in the resection margins and lymph node metastases.

The statistical processing of the study materials was conducted on a personal computer with the software STATISTICA 6.1 (StatSoft Inc., serial number AJAR909E415822FA) and MedCalc Version 16.4.3 (trial version).

The normality of the quantitative indicators was evaluated through the implementation of the Shapiro-Wilk test, whereas the equality of variances was assessed through the Levene test. The primary statistical characteristics included the number of observations (n), the median (Me), the upper and lower quartiles (25 %; 75 %), and the standard deviation (SD). The Wilcoxon signed-rank test (W) was employed to assess the comparison of quantitative attributes in related samples exhibiting a non-normal distribution. The difference between the compared values was considered statistically significant at $p<0.05$. The trend of changes was indicated in the range of $0.050< p<0.100$ [3].

Results of the study and their discussion. In recent years, there has been a notable increase in the detection of tumors in young patients in the early T1 stage. This is attributed to the growing availability of sonographic research methods and heightened public awareness. Conversely, there has been a corresponding rise in the percentage of patients with advanced stages of T4 disease, as well as those exhibiting medium and low differentiation of histological types of tumors.

The overall group exhibited a prevalence of highly differentiated cancer (papillary and follicular) at 84.6 %, with 4.7 % of patients presenting with medullary cancer, 5.9 % with low-grade and anaplastic cancer, and 4.8 % with primary lymphoma or rare forms of malignant tumors. Regional metastasis to the lymph nodes of the neck and upper mediastinum was observed in 39.5 % of patients. In recent years, there has been an increase in the detection of metastases to the N1a lymph nodes, including in small primary T1–2 tumors. Distant metastasis was observed in 1.4 % of patients, usually to the lungs and bones.

In 123 patients (84.8 %), there was a small amount of metastasis to the regional lymph nodes of the neck, with several patients also exhibiting metastasis to the upper mediastinum. Metastasis was typically massive and multiple, occurring in several parts of the neck at once, with levels II–VII being affected. In 18 patients, there were single small distant metastases to the lungs, lower mediastinum, and a case of metastasis to the skull bones, which constituted 12.4 % of the total. Compared to the general group of malignant thyroid tumors treated in our department, the delayed T4 study group has a lower morphological differentiation of tumors, a 2–fold higher percentage of regional metastasis to the neck lymph nodes, older patients, and more male patients.

In patients with invasive LAMTT, it was quite accurately possible to determine the location and extent of the primary pathological process and the degree of damage to adjacent organs and major vessels of the neck and mediastinum, as well as the presence and location of regional metastases to the lymph nodes of the neck and mediastinum at the preoperative stage.

In the experimental group, tumor invasion of the URT was observed in 83 patients, and in 17 patients with elements of the larynx, usually in the cricoid cartilage. In two cases, there was subtotal laryngeal involvement. In 33 patients, there was a growing, usually primary tumor, in the wall of the internal jugular vein, and in 5 cases on both sides of the neck. Preoperatively, 33 patients had laryngeal paresis due to compression or invasion of the recurrent nerves; during surgery, direct nerve invasion was observed in 15 patients, and in two cases on both sides. In 24 patients, tumor invasion of the esophagus was observed. In five cases, the common carotid artery wall was affected, and in 10 patients, the

prevertebral fascia was invaded. In 15 patients, a combined and double localization of invasions was observed, and in five cases, three invasions were observed simultaneously.

Upon initial admission, the patency of the URT was evaluated, and 43 patients exhibited signs of stenosis due to tumor invasion into the lumen or tumor compression. In 19 patients, the stenosis was severe at stages II–III, and this condition threatened the vital function of breathing. These patients underwent urgent or delayed tracheostomy at the first stage. The urgent surgery was technically challenging. In the majority of cases, it was not possible to intubate the trachea. Consequently, the operation was performed under local anesthesia in a forced position of the patient with severe signs of hypoxia. In these cases, the tumor typically surrounded the trachea from all sides, extending from the thyroid cartilage of the larynx to the mediastinum. Tracheomalacia or extensive invasion of the tracheal cartilage was frequently observed, and the tumor was closed and lacked distinct boundaries and contours, forming a large, dense mass that made it challenging for surgeons to identify the tracheal lumen. Two patients died due to hypoxia during surgery and two patients in the early postoperative period due to the development of hypoxic complications.

Consequently, in cases where radical surgery is planned, it is advisable to prepare the patient as soon as possible in a specialized operating room with the capability of intubating the URT under the guidance of endoscopy and small-diameter intubation tubes. Furthermore, if necessary, the patient can be reintubated during surgery through the tracheal incision.

A total of 125 patients underwent radical surgery at the first or second stage of complex treatment (after neoadjuvant polychemotherapy or tracheostomy). This involved an extended thyroidectomy and modified neck dissection, which resulted in the total macroscopic removal of the entire primary tumor with affected adjacent organs and tissues and regional metastases to the lymph nodes of the neck and upper mediastinum, in a number of patients with Crile procedure.

A control group of 20 patients was observed among 145 patients with invasive tumors of T4 stage. These patients underwent palliative or symptomatic surgical interventions with incomplete removal of the primary tumor and removal of compression from the URT as part of a complex treatment plan for a number of reasons, in some patients with the application of a stable tracheostomy Taking into account various factors, the main ones being low morphological differentiation with rapid growth of the neglected tumor, older age and bad general condition of patients with untreated comorbidities, it was impossible to perform radical traumatic surgery or neoadjuvant chemotherapy.

Consequently, we have determined that despite the highly differentiated structure of papillary and follicular thyroid cancers, these cancers should be treated as potentially low-differentiated, employing all possible methods of complex treatment, including the most radical surgery. This is because radioiodine therapy is ineffective or inefficient in the majority of cases (63.6 %). Of the patients with highly differentiated cancer and subtotal tumor removal, only two survived for more than five years. They received multiple therapeutic courses of radioiodine therapy and, in one case, several courses of Sorafenib, which allowed for the avoidance of progression and, in the case of Sorafenib, the near-complete regression of the final tumor. Nine patients with medium- or low-differentiated tumors following palliative surgery, despite adjuvant chemoradiotherapy, which was ineffective and more palliative in nature, died within 2–13 months. The median survival in three cases of intermediately differentiated tumors was 10 months, and in six patients with low-grade tumors, it was five months. These findings once again indicate the need for the most radical surgical intervention as part of a comprehensive treatment in the case of any histological structure of a neglected thyroid malignancy.

Consequently, the five-year survival rate for the control group of patients who underwent palliative or symptomatic surgery as part of a complex treatment regimen was 10 %, and for those with intermediate and low-grade tumors, it was 0 %, based on the final tumor progression of the disease.

A total of 56 patients underwent various macroscopically radical resections of the trachea and, in some cases, the larynx, depending on the extent and stage of tumor invasion in the URT. In 13 patients with localized invasion of up to three rings of the second or third degree of the anterior or lateral wall of the trachea and/or cricoid cartilage of the larynx, without circular spread, a “window” resection of the URT was performed with the application of a temporary tracheostomy or microtracheostomy with its closure in one stage within 10-20 days after surgery. The window defect of the URT was replaced with a skin and fat flap.

In 18 patients with invasion of more than four rings of III–IV degree, tracheal wall and/or cricoid cartilage of the larynx, a circular spread of the tumor of 50 % or more of the circumference of the URT was observed in the majority of cases. These patients underwent anterior-lateral extended resections of the URT, with replacement of the lateral wall of the trachea, and, if necessary, the larynx, with a skin and fat flap, which was excised at the beginning of the operation through a skin incision.

In such patients, a stable tracheostomy was created by inserting a tracheostomy cannula. The tracheostomy was subsequently closed in several stages, with the formation of a breathing tube and replacement of the URT defect with skin and fat flaps, within 1–4 months after surgery. In all patients, we were able to completely close the tracheostomy and restore respiratory function through natural means. These staged operations did not prevent us from continuing the adjuvant stages of complex treatment for patients.

In 33 patients (22.8 % of the total study group), preoperative vocal function impairment, laryngeal paresis, were present. These patients underwent endoscopic laryngeal examination or indirect laryngoscopy with visualization of vocal fold mobility both before and after surgery. Four patients remained in the palliative surgery group, while 29 underwent radical surgery. In 14 patients, there was tumor compression of the recurrent nerve or initial invasion of the perineurium, and after removal of the tumor and shaving it off the nerve, vocal function improved or was completely restored. In 12 patients, there was unilateral invasion of the recurrent nerve, and in 2 cases, bilateral nerve damage with bilateral laryngeal paresis and respiratory impairment. Patients underwent radical resection of the tumor, with the recurrent nerve, if necessary, being removed on both sides. In 10 patients, unilateral laryngeal paresis persisted without respiratory impairment, which was present prior to surgery. In two cases of bilateral lesions and nerve resection, one simultaneous and one delayed thyrotomy with lateral fixation of the vocal fold on the larger side of the invasion was performed. In cases of unilateral resection of the recurrent nerve, it is crucial to exercise caution when removing the opposite lobe of the thyroid gland to prevent trauma to the recurrent nerve on the other side. Three patients who underwent unilateral nerve resection developed postoperative bilateral laryngeal paresis with laryngeal stenosis. They were placed on temporary tracheostomies, with one case being planned due to the resection of the URT. It is also noteworthy that among the 15 patients with lesions of the recurrent nerve, seven had a combination of URT invasion and resection, and in some cases, a planned tracheostomy. In these instances, laryngeal function was determined by endoscopic examination. Local recurrences were observed in 3 patients with poorly differentiated tumors and were most commonly associated with combined URT invasion.

The overall 5-year survival rate in the study group of patients (125 patients) who underwent radical extended surgery as part of complex treatment and staged surgical interventions was 57.6 %. The best rate was in the group of highly differentiated tumors and amounted to 70.2 %, and all deceased patients had low efficiency or refractoriness, especially with repeated courses, to adjuvant radioiodine therapy. It should also be noted that out of 33 patients who had disease recurrence due to repeated surgeries and chemoradiotherapy, a quarter of patients managed to live more than 5 years, which amounted to 24.2 %. For intermediate-differentiated tumors, the 5-year survival rate was 53. 8%, and only 1 patient lived more than 5 years with disease recurrence. Only 6 patients lived for more than 5 years with low-differentiated tumors, which were 21.4 %, of whom 5 patients were recurrence-free, 2 patients had primary lymphoma and 3 patients had low-differentiated cancer. Only one case with low-grade thyroid cancer, which lived for more than 5 years, had a single regional recurrence in the neck lymph node removed. Despite repeated surgeries and chemoradiotherapy in case of disease recurrence in all morphologic cases of advanced tumors, a very poor prognosis for the life of patients is noted because in the group of highly differentiated tumors.

It can be concluded that the use of the most radical, “aggressive” surgical interventions in complex treatment can significantly improve survival rates and reduce the number of recurrences in cases of highly differentiated tumors. In addition, the use of radical surgical methods has improved the effectiveness of treatment of intermediately differentiated thyroid tumors. Considering the use of aggressive radical surgery in the complex treatment of patients, the worst indicators remain in cases of low-differentiated forms of the disease, but the quality of life and life expectancy are significantly improved, which is also important in cases of neglected tumors of low morphological structure [1, 5].

Thus, the prognosis of complex treatment of patients with invasive LAMTT depended mainly on the extent of radical surgical interventions and the degree of morphological structure of the tumor.

We have determined that surgical treatment of LAMTT should be as radical and aggressive as possible, if necessary with sternotomy and lateralization of the vocal fold, as well as the use of all possible methods of chemoradiation treatment to prevent persistence and recurrence of the disease, in which the prognosis for recovery is unfavorable. We recommend the gentle method of "shaving" the tumor from the superficial layers of the trachea only in the case of local invasion of highly differentiated tumors, in other cases, more extensive resections of the respiratory tract are necessary, observing the principle of removal within healthy tissues.

The choice of resection method should be individualized. We recommend performing a primary anastomosis without protection of the upper airway during wedge or circular resection if the tumor invades less than 3 tracheal rings and there is no tension in the anastomotic area. In general, it is more expedient to leave at least a small protective tracheostomy to prevent the development of serious complications (mediastinitis), which was discussed in the following papers [1, 5, 10].

Conclusions

1. In cases of invasive T4 stage LAMTT, the treatment of patients should be comprehensive and include all possible antitumor methods of chemotherapy, surgery, hormonal and radiotherapy, which can be useful and prevent prolongation and recurrence of the disease.

2. Considering the great severity and number of lethal complications in cases of tumour stenosis of the URT during emergency tracheostomy, if possible, we recommend quickly setting up the patient for radical or palliative surgery in a prepared operating room in a planned manner with intubation.

3. In cases of T4b stage LAMTT with a radically inoperable primary tumor, a neoadjuvant course of antitumor chemotherapy is indicated for tumor regression and its transfer to the operable stage and subsequent surgical treatment. On the other hand, it is necessary to take into account the general condition, age and concomitant diseases of the patient, with a possible delay in the main stage of treatment due to the development of specific complications, especially in cases of highly differentiated tumors.

4. In the primary plastic surgery of defects, especially in cases of large circular or wedge-shaped resections of the URT with tension of the anastomosis zone, given the significant percentage of serious complications associated with suture failure, we recommend the placement of a protective temporary tracheostomy below the anastomosis zone.

5. In the case of tumorous lesions of the internal jugular vein, there is no need for plastic surgery with preservation of blood flow, given the absence of complications, it is advisable to perform a Crile procedure with suturing of the vein stumps. However, in the case of bilateral lesions of jugular veins, in order to prevent serious complications, including those of cerebral circulation, we recommend vein plastic surgery with preservation of blood flow on the less affected side.

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