Efficiency of the Crile Procedure in the Removal of Thyroid Malignancies Invaded into the Internal Jugular Vein

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Abstract: Aim: This work aims to determine the effectiveness of the Crile procedure for optimizing the diagnosis and treatment of patients with locally advanced thyroid malignancies.

Objects: The objects of the study were the results of treatment of patients with thyroid cancer using two techniques: Crile procedure and vein resection with sealing and preservation of blood flow.

Materials and Methods: The research was carried out experimentally using Crile surgical intervention and vein resection with sealing and preservation of blood flow. The effectiveness of the treatment was assessed by observing the recurrence and mortality rates. The patient’s quality of life was assessed through the conversation and questionnaire survey.

Results and Findings: It was found that Doppler ultrasonography of the main vessels in the neck helps to establish the internal jugular vein invasion, as well as its tumour thrombosis at the preoperative stage in clinical cases of suspected extrathyroidal extension of thyroid tumours in addition to radiological methods. A thyroid gland with a tumour invaded into the internal jugular vein must be radically removed with simultaneous resection of the affected part of the vein. We proved that the Crile procedure — resection of a vein with sealing of stumps and interruption of blood flow on one side of the neck — is a safe technique. It reduces the trauma and duration of the operation and reduces the likelihood of recurrence as it does not require further plastic surgery or vascular shunting with the restoration of blood flow. At the same time, bilateral interruption of blood flow in cases of resection of both internal jugular veins can lead to serious complications and requires a blood flow restoration operation from the side of the smaller tumour invasion.

Keywords: Malignant tumours, thyroid gland, invasion, internal jugular vein, vein thrombosis, treatment prognosis.

1. INTRODUCTION

1.1. Relevance

Malignant thyroid tumours account for up to 3% of all human cancers [1]. The updated global analysis revealed geographic heterogeneity of incidence rates and cases of overdiagnosis of thyroid cancer. This confirms the relevance of improving diagnostic models for the development of individual prevention strategies to limit overdiagnosis with its clinical and financial consequences [2]. In most cases, highly differentiated papillary forms of thyroid cancer occur in the initial stage of the disease and have a good prognosis [3]. The incidence of neglected malignant tumours of the thyroid gland with an extrathyroidal extension of medium and low morphological differentiation, respectively, medullary, poorly differentiated, anaplastic cancer, and primary lymphomas of the thyroid gland has been increasing in recent years [4,5]. Most researchers consider the tumour extension to the organs surrounding the thyroid gland, tissues of the neck and mediastinum, and the low morphological structure of the tumour as the main factors that worsen the prognosis [6]. A well-differentiated thyroid carcinoma is defined as locally advanced when there is additional thyroid enlargement, for example, when surrounding structures such as the trachea, larynx, esophagus, and major blood vessels are affected by cancer. Diagnosing organs affected by thyroid cancer is often difficult. Patients with thyroid cancer with additional spread to adjacent organs have a poor prognosis, and resection of the entire tumour is a key factor in their survival [7]. Variations in thyroid cancer types in several genetic and/or epigenetic alterations, the number of interactions between the tumour and the surrounding microenvironment, and, for example, differences between patients contribute to the great complexity of tumour development from cancer cells [8].

In their research, Lim H et al. experimentally confirm this tendency. In particular, in the USA, the total incidence of thyroid cancer increased by 3% annually during the last 50 years. At the same time, a significant increase in morbidity and mortality was observed at the late stage of papillary thyroid cancer. These results are consistent with the actual increase in thyroid cancer in the United States [9]. The results obtained by researchers from Iran also confirmed this [10].

Horgan et al. emphasize the need for improved international and national collaboration between cancer networks and scientific societies. It is also important to
raise the patients’ awareness about this type of cancer, which should contribute to the detection of the disease at earlier stages [11]. Houten R. et al. suggest using the catalogue when conducting economic modelling of thyroid cancer. This approach expands the range of health states that can be considered in cost-effectiveness modelling by incorporating mapped values [12].

In our opinion, the most important prognostic factors in the case of neglected malignant thyroid tumours are histological differentiation and the extent of tumour invasion. Therefore we also divided tumours into highly differentiated (papillary and follicular cancer), moderately differentiated (medullary, oncocytic and squamous cell carcinoma), and poorly differentiated tumours (low-differentiated and anaplastic cancer, B-cell lymphomas and rare types of tumours with high malignant potential), which is more than enough for the prognosis and selection of treatment tactics for patients.

The development of knowledge about the molecular aspects of thyroid cancer has improved the diagnosis of thyroid cancer and allowed to selection of individual therapeutic options for individual patients with the most aggressive forms of the disease. Guidelines from many societies around the world reflect these changes, which focus on a more individualized approach to clinical management [13]. Many advances have also been made in the genetic characterization of thyroid cancer in recent years, creating molecular markers for diagnosis, risk stratification, and treatment targets [14].

The primary tumour of the thyroid gland, which is located near the external fascia, extends first of all to the prethyroid muscles, and then to the internal jugular vein surrounding the thyroid gland, the spinal fascia, and the carotid artery, usually with massive metastasis to the regional lymph nodes of the neck [15,16]. According to the latest 8th edition AJCC, local invasion of the tumour into the wall of the internal jugular vein is classified as T4a, and such a tumour can be radically operated on at the first stage. However several authors classify extraluminal vascular invasion into the internal jugular vein with massive thrombosis as T4b, such cases are rare [7,15,17]. Intravascular extension of the tumour in the form of a thrombus in the jugular vein without invasion of its wall is also rare [18]. In any case, most authors suggest aggressive surgical tactics with reconstructive vein operations (shunting, prosthetics, or vein plastic surgery) [17-19]. No less attention is paid to drug treatment, taking into account the genotype of the tumour and maintaining the dosage of the selected drug [20-22].

Given a small number of cases of treatment and observation of patients with invasion of a malignant tumour into the internal jugular vein, the relevance of the issue is determined by the lack of a single treatment tactic, depending on the extent of invasion and histological differentiation of the tumour. The choice of the scope of surgical interventions, and the need to perform operations on the veins to restore blood flow is not determined.

So, the urgent areas of the research are the improvement of existing methods of narrow diagnosis of the type of thyroid cancer, a comparative analysis of various methods of surgical intervention in the treatment of this pathology, and the assessment of their impact on indicators of the quality of life and overall mortality of patients.

This work aims to determine the effectiveness of the Crile procedure to optimize the diagnosis and treatment of patients with locally extended malignant tumours of the thyroid gland.

The aim involved the fulfilment of the following research objectives:
- carry out initial diagnosis and develop a treatment strategy;
- assess the patient's condition after surgery;
- analyse the effectiveness of various surgical intervention methods;
- determine total mortality.

2. MATERIALS AND METHODS

2.1. Research Design

The research was conducted from 2004 to 2021. Figure 1 shows the algorithm of the research.

2.2. Sample

The patients were selected based on compliance with the declared criteria of the experiment: the pathology being studied, the need for surgical intervention, and the patient’s compliance with the chosen treatment strategy.

The data were collected after the preliminary division of patients into 3 subgroups according to the
degree of morphological differentiation of tumours (16, 14, and 9 patients in the high-, medium-, and low-differentiated subgroups, respectively). The patients were surveyed through questionnaires and conversations.

Since 2004, 2,190 patients with malignant tumours of the thyroid gland have been treated at the Endocrine Surgery Centre of the Mechnikov Hospital. According to the TNM classification provided in the 8th edition of the AJCC, 160 patients with locally disseminated malignant tumours with various invasions of the organs and tissues surrounding the thyroid gland were included in category T4, which was 7.3%. Of these, 31 patients had internal jugular vein invasion, or veins from two sides, who were included in the studied group. In all patients we observed direct invasion into the vein wall, in 7 patients — with local thrombosis. There was no individual thrombosis without damage to the wall in the group. However, we observed several patients with extremely neglected tumours and thrombosis up to the superior vena cava with the development of the syndrome of the same name, in whom it was impossible to perform radical surgical interventions and to determine direct vein wall invasion. A total of 24 patients had the vein invasion of the primary tumour, and in 8 cases — the vein invasion of the metastatic lymph nodes of the neck. It should also be noted that only 4 patients did not have metastases in the regional lymph nodes of the neck. The frequency of patients with N1 regional metastasis in the group was 87.1%. There were also 2 patients with distant metastases, in one case — in the lung, in the other — in the lower jaw.

In 24 patients, only the internal jugular vein was invaded, while there were two simultaneous invasions in 5 patients: in three cases, the vein and trachea, and the vein and esophagus in one case, and the vein and prevertebral fascia in another one case. In 2 patients, three invasions were observed at the same time — in the trachea, the recurrent nerve, and the internal jugular vein. 4 patients had simultaneous invasions of the internal jugular veins on both sides, in 3 cases the invasions were a primary bilateral tumour and had a low morphological structure (2 lymphomas and poorly differentiated cancer), and in the case of follicular cancer on one side — a primary tumour invasion on the other side by a metastatic lymphatic node. In general, it should be noted that the degree or number of invasions was proportional to the degree of morphological differentiation of the tumour. The lower the differentiation, the more massive invasion into the vein wall and several organs and tissues surrounding the tumour.

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**Figure 1: Research design.**
We also divided patients into 3 subgroups according to the degree of morphological differentiation of tumours for further analysis of the long-term results of treatment. 16 patients had highly differentiated (14 papillary and 2 follicular cancers), 6 patients were moderately differentiated (5 medullary and 1 squamous cell carcinoma), and 9 were poorly differentiated (4 lymphomas, 4 poorly differentiated and 1 anaplastic cancer) tumours.

2.3. Data Collection

Standard general clinical, X-ray, instrumental, and hormonal tests with detection of thyroglobulin and calcitonin were performed on all patients. Ultrasound examination of the thyroid gland and lymph nodes of the neck was made, in recent years — with the definition of criteria according to the TI-RADS system. Fine needle aspiration biopsy with determination of stratification according to the Bethesda System was made. A trephine or incisional biopsy with the determination of the histological type of the tumour at the preoperative stage was also conducted was conducted if necessary. In case of signs of invasion or widespread tumours, additional spiral computer or magnetic resonance imaging of the neck and chest cavity, and endoscopy of the trachea and esophagus were performed. Doppler ultrasonography or contrast angiography with the study of the arterial and venous phase was performed in case of signs of invasion or compression of the main vessels of the neck.

At the initial stage of treatment, all patients underwent radical operations, an extension of thyroidectomies in healthy tissues with resections of tumor-affected organs and tissues of the neck, and modified or radical neck dissection. Out of 27 cases of unilateral invasion into the internal jugular vein, radical resection of the vein was performed in 17 cases — Crile procedure with blocking of blood flow and sealing of the vein stumps. In 10 cases of small vein wall invasion, its resection was performed in healthy tissues and linear plastic surgery of the vein with preserved blood flow in it. Out of 4 cases of bilateral damage to both internal jugular veins, bilateral Crile procedures were performed in 2 cases. In two other cases, the Crile procedure was performed on one side, while vein resection and plastic surgery with preserved blood flow — on the other side. In cases of tumour thrombus of the vein, the latter was also radically removed.

At the second stage of treatment, all patients underwent adjuvant radiation or chemoradiation treatment. For highly differentiated cancers, a course or several courses of high-dose radioiodine therapy (4.5-6.0 GBq) and suppressive therapy with Levothyroxine, for medium and low-differentiated tumours — radiotherapy of 50-70 Gy, and antitumour chemotherapy. A long-term screening of patients was also carried out for at least 5 years, 8 patients treated less than 5 years ago are under observation. Tumour markers (thyroglobulin, calcitonin) were tested, ultrasound examination of the neck, and computed tomography scan were performed if necessary. Repeated surgical interventions, courses of radioiodine therapy, palliative antitumour chemotherapy, and symptomatic therapy were performed in cases of relapse of the disease.

2.4. Ethical Criteria

The work was carried out in compliance with the provisions of the Convention for the Protection of Human Rights and Dignity of the Human Being concerning the Application of Biology and Medicine (1997), Ethical Principles for Medical Research Involving Human Subjects adopted by the 18th WMA General Assembly (2000), Universal Declaration on Bioethics and Human Rights adopted by the Resolution of the General Conference of UNESCO (2005), the Declaration of Helsinki (1964), as well as the current regulations of Ukraine.

At the beginning of the study, the participants of the experiment gave informed written consent to the examination and application of the selected treatment strategy, as well as further statistical processing and use of the data obtained in the study.

3. RESULTS AND DISCUSSION

3.1. Primary Diagnostics and Planning Treatment Strategy

At the preoperative stage of primary diagnostics, spiral computer or magnetic resonance imaging was used to determine the size, localization, and spread of the tumour in the surrounding organs and tissues of the neck and mediastinum, as well as metastases in the regional lymph nodes. In the case of tomographic signs of the internal jugular vein invasion, doppler ultrasonography of the main vessels of the neck was performed to determine the localization and extent of invasion, and the presence of thrombosis, for planning further surgery. However, the internal jugular vein invasion was found during the operation in 9 cases. These patients had no tomographic signs of vein
invasion. Doppler ultrasonography of the vessels of the neck with undetermined invasion was performed only in one case, where there was a local invasion of less than 1.0 cm. vein wall without thrombosis. In general, the invasions were local up to 1.0 cm into the vein wall without thrombosis in all cases of accidental findings. Therefore, the objective effectiveness of determining the internal jugular vein invasion using tomographic methods is 24.8% less than detecting internal jugular vein invasion using Doppler ultrasonography (Figure 2).

3.2. Assessment of Patients’ Postoperative Condition

We determined early postoperative complications. There were 2 cases of postoperative bleeding from the area of vein sealing requiring repeated operations to stop the bleeding in cases of unilateral resections with vein plastic. No complications were observed in cases of unilateral Crile procedures with unilateral blood flow blockage. There were also no complications in two patients with unilateral Crile procedure and resection with plastic surgery and blood flow preservation of the opposite internal jugular vein. However, we observed a large swelling of the soft tissues of the face, severe headache in two cases of bilateral Crile procedure and blockage of the blood flow of the internal jugular veins on both sides and in one case — neurological symptoms in the form of temporary hemiparesis of the upper limb and facial nerves. These symptoms disappear within 4-5 days, but it indicates a temporary increase in intracranial pressure, which can lead to the development of a haemorrhagic stroke.

3.3. Analysis of the Effectiveness of Surgical Intervention Methods

The crile procedure involves the excision of the invaded part of the vein compatible with the tumour block and sealing the stump of the vein with ligatures and requires a short time. For vein plastic surgery, it is necessary to single out it, take it with clamps, and make an excision of the affected part of the vein with sequential sealing of the defect, which requires much more time. It is necessary to take into account the oncological principles of vein resection within healthy tissues, which are easier to perform during the Crile procedure, and also take into account the extension of invasion and the morphological structure of the tumour. The greater the extension of invasion of the vein and the lower the differentiation of the tumour, the more extensive resection of the vein is needed.

In general, relapses of the disease were observed in 12 patients in the group, in most cases, relapses were in regional nodes of the neck. The overall recurrence rate was 38.7%, only 3 patients had highly differentiated tumours, 3 patients had medullary cancer, 2 patients had poorly differentiated cancer, 2 patients had lymphoma, 1 patient had squamous cell cancer, and 1 patient had anaplastic cancer. The recurrence rate in the subgroup of highly differentiated tumours was 18.7%, while the recurrence rate was significantly worse — 66.7% and 55.6% (p<0.01) in the subgroups of moderately differentiated and poorly differentiated tumours, respectively.

Local recurrences of the disease directly in the area of the operated veins were also studied to analyse the effectiveness of different methods of internal jugular vein resection. Local recurrences were observed in 3 patients out of 12 cases of blood flow restoration operations on the internal jugular veins, which amounted to 25.0% (2 poorly differentiated and medullary cancers). At the same time, only 1 case of medullary cancer with local recurrence in the distal stump of the sutured vein was observed out of 23 Crile
procedures, which was 4.3%. A representative case of a patient with poorly differentiated thyroid cancer with bilateral internal jugular vein invasion, who underwent a Crile procedure on the side of the larger invasion, as well as resection and vein plastic surgery on the side of the smaller invasion up to 1.0 cm and the development of local recurrence on this side. It is not possible to conduct a reliable statistical analysis because of the small number of patients and the great variety of morphological differentiation of tumours. However, the greater effectiveness of Crile procedure compared to the internal jugular vein resection with its plastic surgery is determined due to the reduced time and complexity of the operation, no specific complications, and no radical intervention. However, performing the Crile procedure on both sides is extremely dangerous in cases of bilateral affection of the vein. Such cases require resection and blood flow restoration surgery from the less invaded side.

3.4. Mortality Rate Assessment

The overall mortality rate in the group (Figure 3) was 32.3% (10 patients died). The rate was the best in the subgroup of highly differentiated tumours — 6.3%. The rates were significantly worse in the subgroups of medium and low-differentiated tumours — 66.7% and 55.6%, respectively (p<0.01).

Analysis of other studies over the past 5 years showed that this direction is relevant and understudied. Kamizono K. et al., and Song J.L. et al. demonstrated that reconstruction of at least one internal jugular vein is strongly recommended in patients who need bilateral internal jugular veins. Reiter M., and Baumeister P. concluded that it is advisable to plan surgery with an anastomosis on the contralateral side in cases of internal jugular vein resection. The obtained results of our research correlate with the data of other researchers in this area.

4. CONCLUSIONS

We recommend performing Doppler ultrasonography of the main vessels of the neck in case of sonographic and tomographic signs of an extended tumour. This will help to determine the invasion of the internal jugular vein or both veins. We recommend the Crile procedure in cases of unilateral jugular vein invasion, especially with medium and poorly differentiated morphological types of tumours, which is a safe and more radical method of resection with better long-term results than plastic surgery on the internal jugular vein. In our opinion, in cases of bilateral invasion of the internal jugular veins, it is necessary to perform resection with plastic surgery and restoration of blood flow from the side of the smaller invasion to prevent severe complications associated with increased intracranial pressure and swelling of the soft tissues of the face.

The obtained results can be used in the development of the choice of diagnostic methods and treatment strategies for patients with a similar pathology.

ETHICAL CONSIDERATION

The institutional ethical committee approval was obtained before starting the study. The confidentiality of the information obtained was maintained.
RESEARCH ETHICS AND CONSENT

Informed consent was explained and obtained from every participant. The research was carried out according to the rules and ethical codes specified for research in humans.

LIMITATIONS

Limitations of the objectivity of the study are associated with a small number of respondents, which does not allow extrapolation the results of the study to a wide population.

PROSPECTS OF THE RESEARCH

An additional study is planned in this area with a wider range of respondents to confirm the obtained results.

AUTHORS’ CONTRIBUTIONS

All authors contributed equally to data analysis, drafting, and revising of the paper and approved this work.

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CONFLICT OF INTEREST

The author declared that they have no conflict of interest.

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