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ABSTRACT

of the dissertation for the degree of Doctor of Philosophy

**EARLY DIAGNOSIS AND TREATMENT OF PAPILARY
THYROID MICROCARCINOMAS**

Specialty: 3224. 01 Oncology

Field of science: Medicine

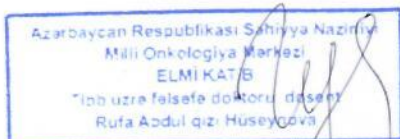
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INTRODUCTION

The relevance of the topic. Papillary thyroid microcarcinoma (PTMC) is a thyroid cancer with small tumors that are 1.0 cm and smaller. It is characterized by slow development and low metastatic potential. In some literary sources, this tumor is called as "hidden cancer of the thyroid gland", "early cancer", "small cancer", "microscopic cancer" etc. The generally accepted term "papillary microcarcinoma" is less traumatic to the patient's psyche, correctly describes the size of the tumor and refers to the presence of papillary cell carcinoma¹.

Previously, papillary thyroid microcarcinoma was discovered incidentally in autopsy or in surgery for nodular goiter. Studies show that papillary thyroid microcarcinoma is detected in 1-36% of cases in autopsy².

The disease is more common in women than in men (1: 8.9).³

The most extensive studies on thyroid microcarcinomas are conducted at the Noguchi Thyroid Clinic and Hospital Foundation in Japan. 1,500 thyroid surgeries are performed annually in the clinic. Archival data have been collected from patients with thyroid carcinoma since 1922.⁴

Latent thyroid carcinoma is most common in Japan (28.4%). Compared to Japan, it is 9.1% in Poland, 6% Canada, and 5.6% Colombia.⁵

Papillary thyroid microcarcinoma is similar to papillary carcinoma in terms of both tumor characteristics and recurrence. Recurrence occurs many years after surgery.

¹ Pacini, F. Thyroid microcarcinoma / F. Pacini// Best Practice & Research Clinical Endocrinology & Metabolism. -2012, -V. 26, p.381–389.

² Əliyev Ə.C., Qalxanabənzər vəzi /Əliyev, Ə. C.// Baş-boyun şişlərin cərrahi müalicəsi, dərslik, -2015, Fəsil 5, -səh. 121-170.

³ Noguchi, S. Papillary microcarcinoma / S.Noguchi, H.Yamashita, S.Uchino, S.Watanabe // World Journal of Surgery, -2008, -Vol.32, №5, -P 747-53.

⁴ Ezzat S. [et al.] Thyroid incidentalomas - prevalence by palpation and ultrasonography / S. Ezzat// Arch. Intern. Med, – 1994, - Vol.154, - P. 1838 - 1840.

⁵ Əliyev, Ə.C. Qalxanabənzər vəzinin papilyar karsinomaları zamanı birincili və residivli xəstələrdə diaqnostika və müalicə taktikasının seçilməsi. // Ə.C.Əliyev, İ.C.Əliyeva, A.M.Əliyeva / Azərbaycan Onkologiya Jurnalı, -2016, № 1, -s. 24-30.

Although these tumors have a long course in 99% of cases, sometimes there are aggressive cases, such as lymph node metastasis, recurrent laryngeal nerve injury, esophageal invasion. Therefore, early diagnosis of tumors is great importance.⁶

When extracapsular invasion is observed in primary tumors, the chance of recurrence is more than 60.5 % when the tumor invaded to esophagus and recurrent laryngeal nerve.⁷

Recurrence is more aggressive in patients with invasion of tumor to recurrent nerve and esophagus than other patients⁸.

Recent studies by Italian experts have shown that tumor size, lymph node condition, extrathyroidal invasion, follicular variant, multifocality are risk factors for recurrence in microcarcinomas.⁹

Lymph nodes metastasis from microcarcinomas occurs in 10-20% of cases. Sudden onset of metastasis is a negative prognostic factor. Multifocalism, invasion to surrounding tissues can lead to distant metastases¹⁰.

Distant metastases are mostly found in the lungs, bones, and mediastinum.

As the Republic of Azerbaijan is considered an endemic zone of iodine deficiency, thyroid disease is more common. Most patients have non-palpable nodules. Previously, surgery was not recommended when

⁶ Zhang, P. Risk factors and clinical indication of metastasis to lymph nodes posterior to right recurrent laryngeal nerve in papillary thyroid carcinoma: A single-center study in China./ P. Zhang, B.Zhang, J. Bu, Y.Liu // *Head Neck*, -2014 Sep 27, V.36(9), -p.1335-42

⁷ Pisan, UA. Nodal metastasis and recurrence in papillary thyroid microcarcinoma / U.A.Pisan, A. Saba, M.Podda, İReccia, A.Uccheddu // *Endocrine*, - 2014, -Vol. 399, №2, -p. 229-36.

⁸ Chow SM. Papillary microcarcinoma of the thyroid-prognostic significance of lymph node metastasis and multifocality / SM. Chow, SC. Law SC, JK.Chan et al. // *Cancer*, -2003, -v.98, p-31-40.

⁹ Park JP. Risk factors for central neck lymph node metastasis of clinically noninvasive, node-negative papillary thyroid microcarcinoma / JP.Park, JL.Roh, JH.Lee, JH.Baek, G.Gong, KJ.Cho // *American Journal of Surgery*, -2014, -vol.208, №3, -p. 412-8.

¹⁰ Ross DS. Recurrence after treatment of micropapillary thyroid cancer / DS.Ross, D.Litofsky, KB.Ain et al// *Thyroid*, -2009, -v.19, -p.1043-1048.

nodules that were 1 cm or smaller were detected by ultrasound (US) examination. Dynamic observation should be performed and surgery is recommended if the nodule is enlarged. Recent advances in clinical oncology – ultrasound-guided fine needle aspiration biopsy (FNAB), modern approaches to surgical operations, increasing radicalism of surgery (thyroidectomy, central and lateral neck dissection), application of radioactive iodine treatment after surgery led to the early detection of papillary thyroid microcarcinomas, timely treatment and improvement of the overall survival of patients.

The purpose of the study

Early diagnosis of papillary thyroid microcarcinomas and evaluation of improvement of treatment results.

Research objectives:

1. Comparative analysis of various diagnostic methods in the early detection of papillary thyroid microcarcinomas and assessment of the diagnostic role of ultrasound-guided fine-needle aspiration biopsy.

2. The effect of extent of surgery and other prognostic factors (age, hormonal status, tumor size, extracapsular extension, regional and distant metastases) on treatment outcomes.

3. The study of the role of concomitant diseases in papillary thyroid microcarcinomas.

4. Development of clinical recommendations for early diagnosis and treatment of papillary thyroid microcarcinomas.

Research methods: The study was conducted on patients diagnosed with papillary thyroid microcarcinoma who underwent surgery at the National Center of Oncology applying comprehensive medical examinations (US examination, FNB, CT). The patients' complaints, anamnesis, US examination, ultrasound-guided fine needle aspiration biopsy, comorbidities, hormonal status, surgical plan, and preoperative preparations of the patients were reviewed. Depending on the presence of central or lateral metastases, surgical tactics, extent of surgery, postoperative complications and outcomes were studied. The impact of aggression factors on prognosis, relapses, factors affecting the quality of life and survival of patients were investigated.

Main provisions of the dissertation

- As a result of organizing screening programs, prophylactic ul-

trasonography, ultrasound-guided aspiration biopsy from suspicious nodules of the thyroid gland, the early detection of thyroid microcarcinomas has increased significantly.

- Determining regional and distant metastases before surgery, selecting the most appropriate treatment strategy, performing lateral or central neck dissection and, if necessary, postoperative radioactive iodine treatment directly affected the long-term prognosis and patient survival.

- Tumor aggression was confirmed in patients with multifocal, extracapsular, follicular variant. These patients should be informed in detail about postoperative radioactive iodine treatment and be under more careful and dynamic monitoring. The conclusion is that timely detection of the disease allows to reduce the incidence of relapses and metastases, improve the effectiveness of treatment.

Scientific novelty of the results

For the first time in the Republic of Azerbaijan, at the National Center of Oncology, early detection of microcarcinomas by ultrasound (US) - guided fine needle aspiration biopsy (FNAB) from smaller thyroid nodules before surgery, connection with other thyroid diseases, age characteristics, frequency of regional spread, regional and distant metastatic features, features of extracapsular invasion, the choice of treatment tactics (thyroidectomy, sometimes performing thyroidectomy with central or lateral neck dissection) and 5-year survival rates were studied. The importance of thyroidectomy with prophylactic central neck dissection in all patients with a malignant biopsy of thyroid gland, as well as the importance of thyroidectomy with lateral neck dissection in all patients with malignant biopsy if the thyroid gland and lateral cervical lymph node were studied.

Practical significance of the study

Results of the study will provide science-based recommendations for early diagnosis and treatment of thyroid microcarcinomas in practical oncology. These recommendations will allow to reduce the incidence of relapses and metastases in patients with thyroid microcarcinoma, improve overall survival and treatment effectiveness.

Approbation of the dissertation:

The main materials of the dissertation are presented at the scientific-practical conference dedicated to the birthday of national leader

Heydar Aliyev (Baku, 2015, 2016, 2022), "Congress of oncologists and radiologists of Eurasia and CIS" (Minsk, 2016, Sochi 2018), Annual Congress of European Association of Nuclear Medicine (EANM'17-Vienna, Austria), meeting of the Azerbaijan Society of Oncologists (Baku, May 2022), conference dedicated to the 70th anniversary of the Scientific-Surgical Center (Baku, 2022), interdepartmental conference of the National Center of Oncology (NCO) (Baku, 10 June 2022, protocol №3), at the meeting of the scientific seminar of the Dissertation Council FD 1.02 under the National Oncology Center 3224.01 – “Oncology” on September 15, 2022 (Protocol № 4).

Published research articles.

The main theoretical and practical provisions of the dissertation were presented in 17 published scientific works. The scientific works were published both in Azerbaijan (6 articles, 4 theses) and in foreign journals. (4 articles, 3 theses).

Application of the study

The results of the study are applied in the clinical practice in the National Center of Oncology of the Ministry of Health of the Republic of Azerbaijan, and are used in the educational process and lectures in the Azerbaijan State Advanced Training Institute for the Doctors named after A. Aliyev.

The organization in which the dissertation is carried out

The dissertation was carried out at the National Center of Oncology of the Ministry of Health of the Republic of Azerbaijan.

The volume and structure of the dissertation

The dissertation is presented on 146 (228.175) pages of typewritten text and consists of an introduction, literature review, research materials and methods, Unit 3 individual research, results, conclusion, practical recommendations and list of references. The dissertation was illustrated with 14 tables, 21 diagram and 14 figures. The literature consists of 179 sources, 173 of which are in foreign languages.

Research materials and methods

The study was based on the analysis of 203 patients who underwent comprehensive medical examinations and surgery for papillary thyroid microcarcinoma in the Department of Head and Neck

Tumors of the National Center of Oncology of the Republic of Azerbaijan in 2014-2018.

Diagnosis of papillary thyroid microcarcinoma (PTMC) was carried out on the basis of modern recommendations for examination of patients, and includes the determination of the most important parameters of the disease. These parameters were determined using the necessary clinical, laboratory-instrumental examinations. The diagnosis of all patients was confirmed histologically after surgery. Postoperative prevalence of PTMC, regional and distant metastases were evaluated according to the TNM classification.

Outpatients or patients detected by a screening program are examined with modern examination methods. When a thyroid nodule is suspicious, the next step is usually ultrasound-guided fine needle aspiration biopsy. Patients with a cytologically confirmed diagnosis of carcinoma undergo CT scan of neck, if necessary. Based on the examination methods, the surgical planning is developed and surgical tactics are selected. Depending on the extent of the surgery, possible postoperative complications in patients were determined. Depending on the results of histological examination, radioactive iodine treatment was prescribed in some patients. The study also assessed patients' quality of life, relapse-free survival, 5-year survival rates, recurrence and mortality rates.

The traditional principles of clinical oncology are the basis for all PTMC patients receiving treatment.

The results of the research were processed by variational statistical methods. To characterize a group of homogeneous units, their mean value (M), its standard error (m) and the variation interval (min-max) were determined. According to the occurrence of signs, their absolute value and percentage and its standard error are determined. Non-parametric methods were used to evaluate the statistical integrity of the difference between indicators. The statistical significance of the difference between indicators was determined using the χ^2 test or Fisher's exact test. The use of the last mention method is more preferable in 2x2 tables, especially when the index is less than 5. The difference between the indicators was considered statistically honest when $p < 0.05$.

Statistical processing of the data was carried out on a personal

computer using MS Excel table processor and on-line statistical calculator (Social Science Statistics -www.socscistatistics.com).

THE RESEARCH RESULTS AND THEIR DISCUSSION

Of the 203 patients included in the study, 19 were male and 184 were female (1:9). In the study, 1 patient (0.49%) in the 0-17 age group, 20 patients in the 18-29 age group (9.85%), 58 patients in the 30-39 age group (28.57%), 41 patients in the 40-49 age group (20.19%), 53 patients in the 50-59 age group (26.10%), 24 patients in the 60-69 age group (11.82%) and 6 patients (2.95%) in the age group of 70 and older were diagnosed with thyroid microcarcinoma.

Most of papillary thyroid microcarcinomas were found in 152 patients aged 30-59 years, accounting for 74.87%. (Average statistical age is 44.5 ± 0.92 .) (Diagram 1).

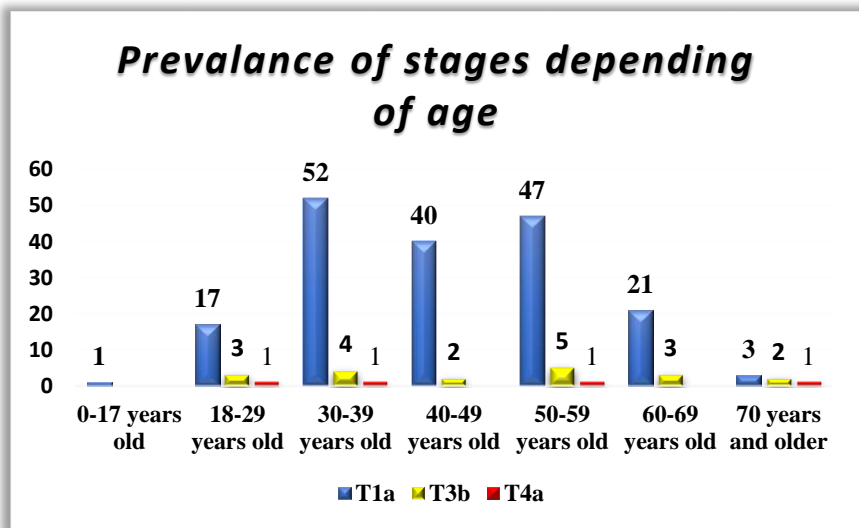


Diagram 1. Prevalance of stages depending on age

Among the most common patient groups, lymph node metastases were $p = 0.0886$ ($p > 0.05$) for the 30-39 age group and 40-49 age group, $p = 0.2180$ ($p > 0.05$) for the 40-59 age group and 50-59 age group, and $p = 0.6367$ ($p > 0.05$) for the 30-39 age group and the

50-59 age group. It was found that although thyroid microcarcinomas are very common between the ages of 30-59 in the study, the age is not statistically significant.

In the study, patients were divided into stages according to their age groups. In the 0-17 age group, 1 (0.49%) patient with stage T1a, in the age group of 18-29 years 17 (8.37%) patients with stage T1a, 3 (1.47%) patients with stage T3b, 1 patient (0.49%) with stage T4a were registered. In the 30-39 age group, 51(25.12%) patients with T1a, 4 patients (1.97%) with T3b and 1 (0.49%) patients with T4a were recorded. In the age group of 40-49years, 40 (19.70%) patients with stage T1a and 2 (0.98%) patients with T3b were identified. In the 50-59 age group, 47 patients with T1a (23.15%), 5 patients with T3b (2.46%), and 1 patient with T4a (0.49%) were identified. In the 60-69 age group, 21 (10.34%) patients with T1a and 3 (1.47%) patients with T3b were found. In the age group of 70 years and older, 3 (1.47%) patients with stage T1a, 2 (0.98%) patients with T3b, and 1 (0.49%) patients with T4a were recorded (table 1).

Table 1
The incidence of metastases depending on age

Age groups	0-17 (n=2)	18-29 (n=12)	30-39 (n=27)	40-49 (n=11)	50-59 (n=8)	60-69 (n=5)	70 and over (n=3)
Central LNM		3 25% ±12.5	14 51.85% ±9.6	8 72.72% ±13.4	5 62.5% ±17.1	2 40% ±21.9	1 33.3% ±27.2
Lateral LND	1 50% ±35.4	7 58.33% ±14.2	11 40.74% ±9.5	2 18.18% ±11.6	3 37.5% ±17.1	1 20% ±17.9	1 33.3% ±27.2
Distant metastases	1 50% ±35.4					2 40% ±21.9	1 33.3% ±27.2
Recurrence		2 16.66% ±10.8	2 7.40% ±5.0	1 9.09% ±8.7			

As shown in Table 1, the incidence of lateral and central lymph node metastases does not depend on age ($p = 0.318$, χ^2 -6.66). However, for different age groups: lateral metastases predominated ($p = 0.0391$, $p < 0.05$) in the age group of 18-29, and central metastases ($p = 0.0861$, $p < 0.05$) in the 40-49 age group. In the 30-39 age group, central and lateral metastases are distributed approximately equally which means

that the prevalence of metastases in patients aged 30-59 years was generally $p = 0.0392$, $p < 0.05$.

Depending on age groups of patients, regional and distant metastases and recurrences were studied (Table 1). In the 0-17 age group, 1 patient with stage T1a (50%), 1 patient with lateral lymph node metastasis (LLNM) (50%), 1 patient with distant metastases (lungs) were found. In the 18-29 age group, 17 patients with stage T1a, 3 patients with stage T3b, 3 patients with central lymph node metastases (CLNM) (25%), 7 patients with lateral lymph node metastases (58.33%), and recurrence in 2 patients (16.66%) were found. In the 30-39 age group, 51 patients with stage T1a, 4 patients with T3b, 1 patient with T4a, 14 patients with central lymph node metastasis (51.85%), 11 patients with lateral lymph node metastasis (40.74%), recurrence in 2 (7.40%) patients were found. In the 40-49 age group, 40 patients with stage T1a, 2 patients with T3b, central lymph node metastasis in 8 (72.72%) patients, lateral lymph node metastasis in 2 (18.18%) patients, and recurrence in 1 (9.09%) patients were observed. In the 50-59 age group, 47 patients with stage T1a, 5 patients with stage T3b, 1 patient with stage T4a, 5 patients with (62.5%) central lymph node metastasis, and 3 patients with (37.5%) lateral lymph node metastasis were found. In the 60-69 age group, 21 patients with T1a, 3 patients with T3b, central lymph node metastasis in 2 (40%) patients, lateral lymph node metastasis in 1 (20%) patients, 2 (40%) patients with distant metastases (lung, bone) were identified. In the age group of 70 years and older, 3 patients with T1a, 2 patients with T3b, 1 patient with T4a, 1 (33.3%) patient with central lymph node metastasis, 1 (33.3%) patient lateral lymph node metastasis, 1 patient (33.3%) with distant metastasis (lung) were detected.

General clinical examination was performed for all patients. General examination, palpation, assessment of the patient's general condition, development of an examination plan were carried out. Complex medical examinations include chest X-ray, ECG, EchoCG, ultrasound examination of the neck, ultrasound-guided fine-needle aspiration biopsy. After the diagnosis was cytologically confirmed, CT was performed to determine the invasion of metastases in the neck to neurovascular bundle and surrounding tissues.

The patients' complaints, anamnesis, US examination, ultrasound-guided fine needle aspiration biopsy, comorbidities, hormonal status, surgical plan, and preoperative preparations of the patients were reviewed. Based on histological results, tumor size, multifocality, presence of follicular variant, extracapsular invasion, central and lateral metastases were investigated. Depending on the presence of central or lateral metastases, surgical tactics, extent of surgery, post-operative complications and outcomes were studied. During surgery operation, the localization of the tumor, its size, invasion of the surrounding tissues, trachea or the returning nerve, the state of the regional lymph nodes, the surgical boundaries, and capsule invasion were studied.

Random ultrasound examination revealed thyroid microcarcinoma in 106 patients (52.21%) with nodes of 0-10 mm, 53 patients (27.08%) with nodes of 11-15 mm, 44 patients (33.67%) with nodes larger than 16 mm ($p>0.05$)

106 of the patients diagnosed with papillary microcarcinoma (52.21%) had nodules smaller than 1.0 cm detected by ultrasound examination before surgery. In 97 (47.78%) patients, the size of the nodules was 1.1-1.6 cm detected by US, and then followed by histological determination of papillary thyroid microcarcinoma.

The diagnosis of microcarcinoma was confirmed after surgery in 104 patients with calcification (51.23%). It indicates that the presence of calcification in the node is one of the risk factors. Ultrasound examination revealed that 104 patients (51.23%) had calcification, 123 (60.59%) had nodules with well-defined margin, 81 (39.90%) had ill-defined nodules, 69 (33.99%) had solid nodules, 74 (36.45%) had hypochoic nodules, 55 (27.09%) had central hemorrhagic nodule.

In 104 patients with calcination detected by US, the biopsy revealed malignancy in 66 patients (63.46%), malignant suspicion in 32 patients (30.76%), and follicular neoplasia in 5 patients (4.80%). In 99 patients without calcination, malignant was found in 7 patients (7.07%), suspicious for malignancy in 12 patients (12.12%), follicular neoplasm in 30 patients (30.30%), atypia of undetermined significance in 13 patients (13.13%), benign in 12 patients (12.12%).

In our study, 178 of 203 patients underwent ultrasound-guided

aspiration biopsy of suspicious nodes. Cytological results were classified according to the Bethesda System. The cytological response was benign in 12 patients (6.74%), atypia of undetermined significance in 13 patients (7.30%), follicular neoplasm in 35 patients (19.66%), suspicious for malignancy in 44 patients (24.71%), malignant in 7 patients (41.01%), non-diagnostic result 1 patient (0.56%). (Diagram 2).

As shown on the Diagram 2, 117 (65.73%) ($p < 0.001$) patients had already been diagnosed with carcinoma before surgery. It demonstrates the importance of US-guided aspiration biopsy in the timely detection of papillary microcarcinomas in small nodules. Although only 12 patients (6.12%) had cytologically benign response, papillary microcarcinoma was detected after surgery.

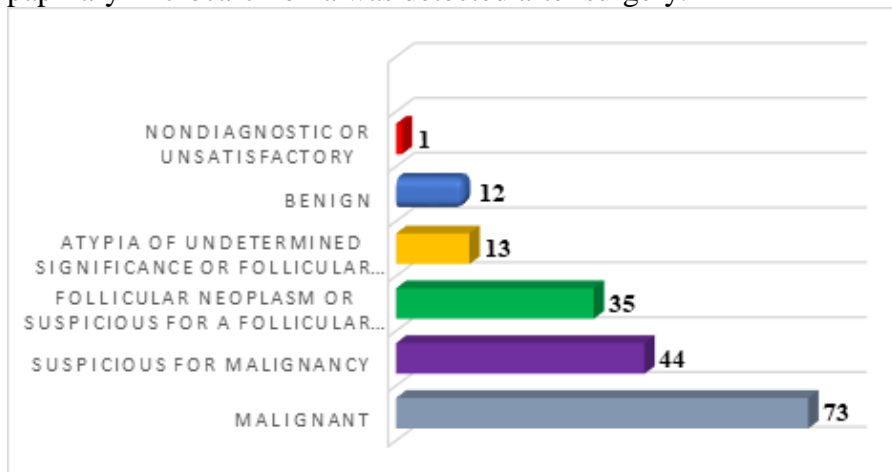


Diagram 2. A comparative description of results of ultrasound-guided aspiration biopsy.

Although preoperative ultrasound-guided FNAB biopsy was benign in three patients, 1 mm papillary microcarcinoma was found after surgery. Numerous and large nodules were observed in both parts of the thyroid gland in all three patients. These patients also reported having a long-term medical history.

Regional lymph nodes metastases were observed in 65 of 203 patients. Only 79 (38.91%) of these patients underwent CT scan. Of these, 74 patients underwent contrast computed tomography, and 5 patients

underwent non-contrast CT (native). Lateral cervical lymph nodes metastasis was observed in 27 (13.30%) of these patients. In 22 of those 27 patients (10.83%) was found unilateral lateral cervical lymph nodes metastasis and bilateral lateral cervical lymph nodes in 5 (2.46%) patients. Central lymph nodes metastasis was found in 38 patients (18.71%). Pathological lymph nodes in the regional lymph nodes in 56 of these 79 patients were found by ultrasound examination before CT scan.

Tumor cells (malignant and suspected malignancy) were detected in the US-guided fine needle aspiration biopsy of the lymph nodes in 49 of 65 patients with regional lymph nodes metastasis. FNA biopsy results were incorrect in 2 patients.

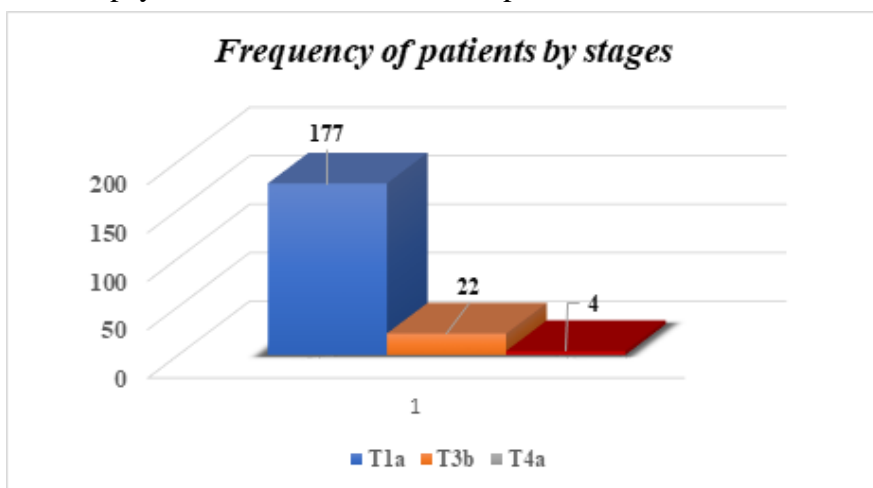


Diagram 3. Frequency of patients by stages

Radicality of surgery in PTMC is one of the most important factors affecting prognosis in thyroid carcinomas. Taking all this into account, it is very important to decide on the scope of the operation before the surgery.

177 patients were diagnosed in stage T1 (87.19%), 22 patients in stage T3b (10.83%), and 4 patients in stage T4a (1.97%). (Diagram 3).

129 (63.54%) of the 203 patients in the study underwent total thyroidectomy (TT), 43 (21.18%) total thyroidectomy with central lymph dissection (TT+CLD), 29 (14.28%) total thyroidectomy with

lateral lymph dissection (TT+LLD) and 2 (0.98%) patients hemi-roidectomy (HT).¹¹

In the postoperative pathohistological examination, thyroid microcarcinoma was detected in 79 patients with a size of 0-4 mm (38.91%), in 96 patients with a size of 5-8 mm (47.29%), in 28 patients with a size of 9-10 mm (13.79%).

As a result of postoperative histological analysis of the patients, the central lymph nodes metastases were detected in 38 patients (18.71%). The lateral cervical lymph nodes metastasis was detected in 27 (13.30%) of these patients. 22 (10.83%) of the patients with to the lateral cervical lymph nodes metastases had unilateral lateral cervical lymph nodes metastases, and 5 (2.46%) - bilateral lateral cervical lymph nodes metastases. Lung metastases were observed in 3 patients (1.47%) and bone metastases in 1 (0.49%) patients.¹²

Before the surgery, blood tests were done to check thyroid hormones (free T3, free T4, hTSH, anti-TPO, calcitonin, thyroglobulin) and calcium (Ca) in all patients in accordance with the protocol. Hashimoto's thyroiditis was detected in 45 patients (22.16%) with a confirmed diagnosis of papillary thyroid microcarcinoma ($p < 0.001$). This suggests that patients with Hashimoto's thyroiditis should be carefully examined and treated in a timely manner. As a result of laboratory tests, hypothyroidism was detected in 25 patients (12.31%) and hyperthyroidism in 14 patients (6.89%). Papillary thyroid microcarcinoma was diagnosed histologically after thyroidectomy for Graves' disease in 2 patients (0.98%)¹³.

In 50 patients (24.63%) ($p < 0.001$) of 203 patients, thyroglo-

¹¹ Алиев, А.Д. Роль интраоперационной морфологической диагностики в выборе объема хирургического вмешательства у больных папиллярным раком щитовидной железы / Н.А.Гулиев, Э.Р.Искендеров, А.М.Алиева, Г.С.Асадли // *Azərbaycan Onkologiya Jurnalı*, -2014, №2,-s.84-86

¹² Aliyev, A.J. Ectopic thyroid gland microcarcinoma with metastasis to the cervical lymph nodes and lungs. Case report /A.J.Aliyev, I.J.Aliyeva, A.M.Aliyeva // *LikiUkraina* 2017 , №4, s.9-14.

¹³ Алиев, А.Д. Первичная лимфома щитовидной железы / А.Д.Алиев, А.М.Алиева, Б.Э.Аббасов, А.Т.Казымов // *Евразийский онкологический журнал* / -2017, том 5, №1,- с. 160-167.

bulin was higher than normal. The lateral lymph node metastases were observed in 8 (16%) out of 50 patients with high thyroglobulin. 16 patients (32%) ($p < 0.001$) had the central lymph nodes metastases. 26 (52%) patients had only a thyroid tumor without metastasis.

Histological analysis of the patients showed that aggression factor ($p < 0.001$) was found in 141 patients (69.45%). Multifocal variant was detected in 77 patients (37.93%), an extracapsular variant in 35 (17.24%) patients. Follicular variant of papillary microcarcinoma was found in 29 (14.28%) patients (Table 2).

Table 2
Aggressive papillary thyroid microcarcinomas in tumor aggressiveness factors

Histological variant	Multifocal (n=77)		Follicular (n=29)		Extracapsular (n=35)	
Central metastasis	30	38.96%	10	34.48%	14	40%
Ipsilateral metastasis	16	20.77%	7	24.13%	6	17.14%
Bilateral metastasis	3	3.89%	2	6.89%	2	5.71%
Total thyroidectomy (without metastasis)	25	32.46%	10	34.48%	13	37.14%
Recurrence	1	1.29%	2	6.89%	1	2.85%
Distant metastasis	2	2.59%	1	3.44%		
N.recurrence invasion					3	8.57%
Tracheal invasion			1	3.44%	3	8.57%
Mortality	1	1.29%				

As shown in the table (Table 2), in a group of 77 patients with a multifocal variant on postoperative histological examination, central metastasis occurred in 30 patients (38.96%), ipsilateral metastasis in 16 patients (20.77%), bilateral metastasis in 3 patients (3.89%), and total thyroidectomy (TT) in 25 patients (32.46%), relapse in 1 patient (1.29%), distant metastasis in 2 patients (2.59%), death in 1 patient (1.29%). For the multifocal variant, the aggressiveness rate of the lymph node metastases was $p < 0.001$.

In a group of 27 patients with follicular variant, central metastasis occurred in 10 patients (34.48%), ipsilateral metastasis in 7 patients

(24.13%), bilateral metastasis in 2 patients (6.89%), and TT in 10 patients (34.48%), relapse in 2 patients (6.89%), distant metastasis in 1 patient (3.44%), tracheal invasion in 1 patient (3.44%) ($p = 0.0347$, $p < 0.05$).

In total, the extracapsular variant was detected in 33 patients. In these group of patients, central metastasis occurred in 14 patients (40%), ipsilateral metastasis in 6 patients (17.14%), bilateral metastasis in 2 patients (5.71%), 13 patients with total thyroidectomy (37.14%), recurrence in 1 patient (2.85%), recurrent laryngeal nerve invasion in 3 patients (8.57%) and tracheal invasion in 3 patients (8.57%). The aggressiveness rate of the lymph nodes metastases for extracapsular variant was $p = 0.0551$, $p > 0.05$. A 20-year-old patient had cervical lymph node metastases 1 year after the first surgery (in a patient with an extrathyroid invasion) and neck dissection was performed again.

Complications were observed in the early postoperative period (0-14 days) : hypocalcemia in 74 patients (36.45%), vocal cord paresis in 16 patients (7.88%), bleeding in 2 patients (0.98%), chylous in 1 patient (0.49%), pain symptoms in 35 patients (17.24%), lymphostasis in 28 patients (13.79%), seroma was noted in 17 patients (8.37%).

In the late period, hypocalcemia was observed in 16 patients (7.88%), vocal cord paresis in 3 patients (1.53%), pain symptoms in 5 patients (2.46%), and keloid scar in 5 patients (2.46%).

Hypocalcemia is the most common complication after surgery. Hypocalcemia was observed in 34 patients (26.35%) after total thyroidectomy, in 29 patients (67.44%) underwent total thyroidectomy with central neck dissection (TT + CND), and in 11 patients (37.93%) underwent total thyroidectomy with lateral neck dissection (TT+LND).¹⁴

Hypocalcemia was detected in 29 patients (67.44%) who underwent total thyroidectomy (TT + CND) with central lymphodissection. Clinical symptoms were seen in only 26 (12.80%) patients on the postoperative days. Transient hypocalcemia was observed in 19 patients (44.18%) and permanent hypocalcemia in 10 patients (23.25%) ($p < 0.001$).

¹⁴ Əliyeva A.M. Qalxanabənzər vəzin cərrahi əməliyyatlarından sonra hipokalsemiya riski // A.M.Əliyeva / Azərbaycan Onkologiya Jurnalı, -2022, №1, -s.50-53

Hypocalcemia was seen in 11 patients (37.93%) underwent total thyroidectomy and lateral neck dissection surgery (TT + LND). All of these patients had clinical symptoms. 7 (24.13%) of these patients had transient hypocalcemia and 4 patients (13.79%) had permanent hypocalcemia ($p=0.0169$, $p<0.001$). Compared to TT, the risk of hypocalcemia was $p = 0.0008$ ($p <0.001$) for CND, and $p = 0.0247$ ($p > 0.05$) for LND. This indicates that the risk of hypocalcemia is higher in lymph dissection, especially in central lymph dissection than in total thyroidectomy (Diagram 4).

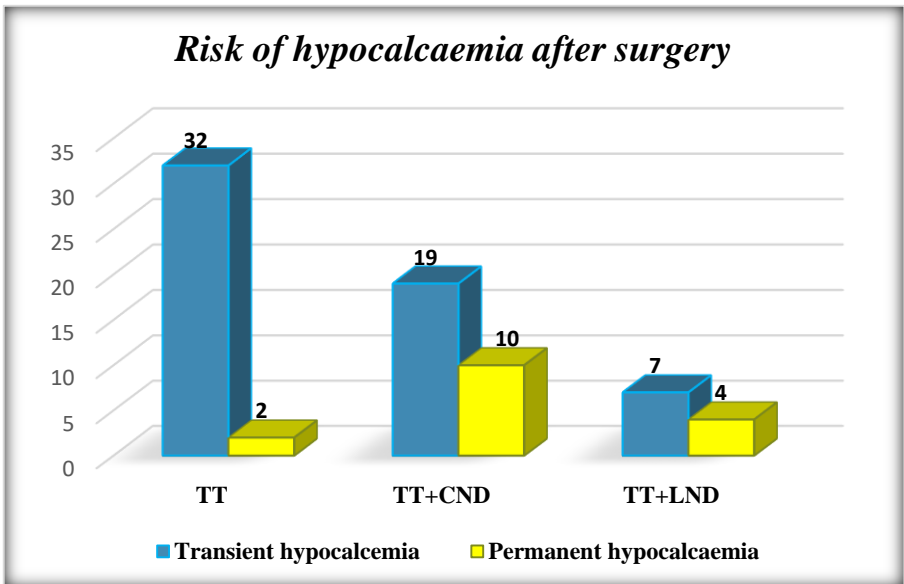


Diagram 4. Risk of hypocalcemia during surgery

However, complications such as hypocalcemia are more common in central and lateral neck dissection than in total thyroidectomy. This is due to the fact that central and lateral neck dissections are considered more traumatic and aggressive surgery. For this reason, it can result from technical trauma to the parathyroid glands, being close to metastases, as well as disorder of the blood supply.

A total of 16 patients (7.88%) were detected vocal cord paralysis. Of these, 13 patients (6.40%) had temporary paralysis. The voice

was completely recovered in 11 patients (5.41%) with temporary loss of voice after one month, and in 2 patients (1.02%) within six months. In 3 (1.47%) patients, tumor was removed because recurrent laryngeal nerve (RLN) was invaded by the tumor. Permanent loss of voice was detected in these patients. In 1 of 3 patients with permanent vocal paralysis (0.49%), nerve was resected in TT because RLN was invaded by the tumor. In 1 patient (0.49%) during TT + LND the nerve was resected because the tumor invaded the trachea and the recurrent laryngeal nerve. Permanent paralysis was observed in 1 patient (0.49%) after TT + CND. Of the patients with temporary vocal cord paralysis, 4 patients (1.97%) underwent TT, 6 patients (2.95%) underwent TT + CND, and 3 patients (1.47%) underwent TT + LND. (Table 3)

Table 3

Incidence rate of vocal cord paralysis after papillary thyroid microcarcinoma surgery

Vocal cord paralysis	Temporary paralysis		Permanent paralysis	
TT	4	2.04%	1	0.51%
TT+CND	6	3.06%	1	0.51%
TT+LND	3	1.53%	1	0.51%
Recovery within 1 month	11	5.61%		
	2	1.02%		
Life-long paralysis			3	1.47%

Among patients diagnosed with papillary thyroid microcarcinoma, 22 patients (10.83%) had type II diabetes, 9 patients (4.43%) had breast cancer, 1 patient (0.49%) had liver cancer, 1 patient (0.49%) had laryngeal cancer, and 1 patient had (0.49%) parotid gland cancer, 2 patients (0.98%) Hockin's lymphoma, 2 patients (0.98%) parathyroid adenoma, 37 patients (18.22%) ischemic heart disease, 17 patients (8.37%) hepatitis, 1 patient (0.49%) had vocal cord polyp.

The following comorbidities were the most common among patients with papillary thyroid microcarcinomas: ischemic heart disease (18.22%), diabetes (10.83%), hepatitis (8.37%), and breast cancer (4.43%).

122 (60.09%) patients received radioactive iodine (RAI) treat-

ment after surgery. 65 patients (53.27%) with metastases received iodine therapy. Thyroidectomy was performed in another 57 patients (46.72%) treated with iodine. Among patients who underwent thyroidectomy, multifocal variant was detected in 25 patients (19.37%), extracapsular variant in 13 (10.07%) patients, and follicular variant in 10 (7.75%) patients. These patients received radioactive iodine therapy.

3 patients with tracheal invasion and 3 patients with recurrent nerve invasion also received radioactive iodine treatment.

Distant metastases - lung metastases were detected in 3 patients (1.47%) and in bone metastases 1 (0.49%) patient.

After total thyroidectomy or hemithyroidectomy, suppression therapy is considered important during dynamic control of patients, thyroid hormone is replaced in the form of levothyroxine tablets. In patients who need radioactive iodine, drug treatment is not carried out after total thyroidectomy, radioactive iodine treatment is started after TSH level increased, and then suppression hormone treatment is started. In dynamic monitoring, Tg and TSH level in blood should be constantly checked along with US examination. After hemithyroidectomy, levothyroxine is used. It is possible that hormone treatment should be discontinued in these patients after a period of 3-6 months. Hormonal balance can be restored due to the saved portion. In dynamic control, US examination and TSH level test are sufficient.

Of the 203 patients included in the study, 201 (99.01%) had a 5-year survival rate. Mortality was recorded in 2 patients (0.98%). One (0.49%) of these died patients had lung metastases, the other one (0.49%) had bone metastases. A patient with a lung metastasis refused radioactive iodine treatment. A patient with bone metastasis (in the spine) died despite receiving radioactive iodine treatment and radiation therapy.

Out of 201 patients living for 5 years, 196 patients (97.51%) lived without relapse and 5 (2.48%) patients had relapse. A 20-year-old patient had a relapse within one year after surgery. In the first operation of this patient, the tumor invaded the return laryngeal nerve, so along with total thyroidectomy, the recurrence laryngeal nerve was also cut. A year later, lateral neck dissection was performed. Relapses within 5 year occurred in 4 patients.

Relapse was noted in the lateral cervical lymph nodes in all patients with relapse. In 1 patient, the tumor invaded the trachea on the first surgery and the lateral lymph nodes metastases were found. 1 patient had the lateral cervical lymph nodes metastases on the first surgery. In 2 patients, central lymph nodes metastases were found on the first surgery, and relapse occurred in the lateral cervical lymph nodes.

It can be concluded that timely detection of the disease will reduce the frequency of relapses and metastases in patients with thyroid microcarcinoma, increase overall survival and effectiveness of treatment. Thus, all of these will improve the quality of life.

CONCLUSIONS

1. The diagnosis of carcinoma in 65.73% of patients by preoperative ultrasound-guided fine needle aspiration biopsy confirmed the importance of this complex examination method in the timely detection of papillary thyroid microcarcinomas in small nodules ($p < 0.001$). At this time, the detection of regional (central or lateral lymph nodes) and distant metastases in 82.3% of patients as a result of pre-operative CT examination made it possible to choose the correct surgical tactics, which had a direct effect on increasing the survival rate of patients ($p < 0.001$) [2, 5].
2. In multifocal ($54.6\% \pm 4.19$), extracapsular ($24.8\% \pm 3.64$) and follicular ($20.6\% \pm 3.4$) variants of the tumor, the incidence of metastases to lymph nodes was respectively 63.62%, ($p < 0.001$), 65.5%, ($p = 0.0347$, $p < 0.05$), 62.85% ($p = 0.0551$, $p > 0.05$), for distant metastases from 2.59% to 3.44%, as well as, recurrent laryngeal nerve invasion and tracheal invasion (3%) confirmed the aggressiveness of the tumor. All this highlights the importance of radioactive iodine treatment and more careful dynamic control after surgery [4, 8, 9, 10, 11].
3. Although the temporary quality of life decreased by $10.0 \pm 1.2\%$ and the permanent quality of life by $5.0 \pm 2.1\%$ depending on the surgical tactics in the early and late periods, the 5-year survival rate of 99.01% confirmed that aggressive surgery had a direct positive effect on the patient's survival rate [15, 17].

4. Background diseases such as hyperthyroidism, hypothyroidism, and Hashimoto's thyroiditis in 6.9%, 12.3%, and 22.16% of patients with papillary microcarcinoma of the thyroid gland require timely careful examination and treatment [6, 14].
5. In patients with papillary microcarcinoma of the thyroid gland after surgery, the overall 5-year survival rate is 99.01%, the 5-year recurrence-free survival rate is 97.51%, and the 5-year recurrence-free survival rate is 2.47%. All these, as well as, the decrease in the incidence of relapses and metastases, improvement of the overall survival rate and the quality of life indicate the necessity of early diagnosis [7, 16]

PRACTICAL RECOMMENDATIONS

1. In patients with papillary thyroid microcarcinoma, central neck lymphodissection is recommended as a preventive measure, taking into account the multifocality of the tumor and capsular invasion.
2. In order to prevent postoperative complications, it is recommended to improve the knowledge and experience of the team of doctors and medical personnel involved in each stage of treatment (pre-operative, intra-operative and post-operative periods), as well as the ability to use modern medical equipment.
3. As the risk of hypocalcemia is higher during lymphodissection than total thyroidectomy, especially during central lymphodissection, it is recommended to prevent hypocalcemia prophylactically by correcting Vit D balance before surgery.
4. It is recommended to educate the population, especially the population in endemic areas, about the benefits of using iodized salt.
5. It is recommended to organize screening programs (thyroid palpation, patient history, family cancer status, radiation history), US examination of the thyroid gland during screening, and to prepare a detailed examination plan for the patient later in case of detection of suspicious nodules smaller than 1 cm during US examination.

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LIST OF ABBREVIATION

- FNAB – fine needle aspiration biopsy
- US – ultrasound examination
- CT – computed tomography
- PTMC – papillary thyroid microcarcinoma
- ATA – American Thyroid Association
- TT – total thyroidectomy
- Tg – thyroglobulin
- TSH – thyroid stimulating hormone
- CND – central neck dissection
- LND – lateral neck dissection
- HC – hypocalcemia
- NCO – National Center of Oncology

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