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Lymph Node Metastases Papillary Thyroid Carcinoma and their Importance in Recurrence of Disease

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ABSTRACT

Background: The purpose of this study is to establish whether the lymph node metastases of the papillary thyroid carcinoma are a significant factor in recurrence of the disease by analyzing the time until recurrence of the disease and frequency of recurrence of the disease.

Methods: From 1 January 1995 until 30 June 2017, 102 patients were treated at the Public Health Institute Hospital "Sveti Vracevi" in Bijeljina for PTC. In all patients, surgery of the thyroid gland and/or lymph nodes of the neck was performed. Total thyroidectomy (TT) was performed in 20 patients and near-total thyroidectomy leaving <1 g thyroid tissue adjacent to the recurrent laryngeal nerve in 7 patients. TT and lymph nodes dissection were performed in 71 patients. Palliative surgery and biopsy due to locally advanced disease were performed in 3 patients. **Results:** In our study, 102 patients with PTC were analyzed. 82 patients experienced pure PTC (80.4%), the other 20 patients (19.6%) experienced other variants of PTC. 24 patients (23.5%) experienced multi centric or bilateral tumors. 71 patients (69.6%) experienced histologically verified metastases in the lymph nodes of the neck. 7 patients (6.8%) experienced distant metastases. 20 patients underwent total thyroidectomy (TT), and 7 near-total thyroidectomy. Total thyroidectomy + dissection of central and lower jugular lymph nodes with frozen section histopathology verification was performed in 71 patients (69.6%). Out of these 71 patients, in 50 patients (70.4%) metastases were verified in the lower jugular lymph nodes. A modified lymph node dissection (MRND) was also performed in these patients. **Conclusion:** Lymph node metastases of the papillary thyroid carcinoma are a plausible prognostic factor. They are important for recurrence of the disease, but not for survival.

Keywords: papillary thyroid carcinoma, recurrence, survival, Bijeljina.

1. INTRODUCTION

Thyroid carcinoma (TC) is not as common as tumors of other body parts. The most common TC is papillary thyroid cancer (PTC). It is more likely to occur in younger people and it shows a tendency towards early lymph node metastases. The tendency towards hematogenic metastasis (in lungs and bones) is lower (1).

Significant prognostic factors in PTC are: age, histological grade, distant metastases, extracapsular tumor extension, tumor size, and stage of disease. Lymph node metastases are a debatable prognostic factor, having relevance in recurrence of disease, but have no relevance in survival rate of patients (2, 3).

PTC metastasizes lymphogenously into: recurrent, jugular, spinal, supraclavicular, and upper and middle mediastinal lymph nodes. The frequency of metastasis in the lower mediastinal lymph nodes is lower (4).

Surgical options for primary tumors include near-total thyroidec-

tomy (leaving <1 g of thyroid tissue adjacent to the recurrent laryngeal nerve); and total thyroidectomy (removing all visible thyroid tissue (5). Overall, near-total or total thyroidectomy is recommended for the management of thyroid cancer in which the primary tumor measures ≥ 1.0 cm to 2.0 cm (6). Subtotal lobectomy and unilateral lobectomy used to be performed in the past, but they are now deemed inappropriate for the treatment of patients with thyroid cancer (6, 7).

Based on the knowledge of the biology of PTC and its way of metastasizing, the principle of the necessity of removal of lymph nodes together with the primary tumor, whenever possible, is to be respected and accepted (8).

2. PATIENTS AND METHODS

From 1 January 1995 to 30 June 2017, 102 patients were treated at the Public Health Institute-Hospital "Sveti Vracevi" in Bijeljina for

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PTC. In all patients, surgeries of the thyroid gland and/or lymph nodes of the neck were performed. Total thyroidectomy (TT) was performed in 20 and near-total thyroidectomy leaving <1 g of thyroid tissue adjacent to the recurrent laryngeal nerve was performed in 7 patients. TT and lymph node dissection was performed in 71 patients. Palliative surgery and biopsy due to locally advanced disease were performed in 3 patients. For all patients in this period, data related to disease and treatments were recorded in our clinical survey. The following was done in preoperative diagnosis and selection for operative treatment of patients, besides general and local status: laboratory treatment, scintigraphy of neck and possibly of chest, bio assays (Thyroid hormones T4 and T3, thyroid-stimulating hormone (TSH), thyroglobulin (Tg) and thyroglobulin anti body (TgAb); radiography of chest, trachea and possibly oesophagus with contrast, and, if necessary, radiography of skeletal system and ultrasonography of liver, neck and retroperitoneum and otorhinolaryngological examination.

The criteria for radical surgical procedure were based on histologically proven thyroid gland cancer in preoperative diagnosis, on a positive finding of frozen section histopathological verification of the thyroid gland tumors and/or lymph nodes of neck, as well as on the basis of the general condition of the patients.

The degree of local extension of TC was determined intraoperatively, as well as the presence or absence of lymph node metastases - it being confirmed by frozen section histopathological verification.

Three weeks after surgery postoperative scintigraphy of the neck and chest was performed, of skeletal system as well where necessary, and the level of thyroid hormones and the serum marker were measured. Since total thyroidectomy was performed in all patients, substitution or substitution-suppressive therapy was applied using L-Thyroxine at a dose of 2.2 ug/kg/day.

3. RESULTS

In our study, 102 patients with PTC were analyzed. The majority of patients were of female sex and were less than 45 years of age. At the time of diagnosing PTC with bilateral metastases in the lymph nodes of the neck and lungs the youngest patient was an 8 year old girl.

Papillary thyroid gland carcinoma was present in 102 patients or 78.12% of all patients who were treated for well-differentiated thyroid carcinoma (DTC).

* 82 patients experienced pure PTC (80.4%), and the other 20 patients (19.6%) experienced other variants of PTC. 24 patients (23.5%) experienced multi center or bilateral tumors.

* 16 patients (15.7%) had histological tumor size from 0 to 10 mm. 23 patients (22.5%) had from 11 to 20 mm and 37 patients (36.2%) had from 21 to 40 mm. 21 patients (20.5%) had tumor size greater than 40 mm. Extracapsular tumor extension was observed in 12 patients (11.7%) (Table 1).

* 71 patients (69.6%) experienced histologically verified metastases in the lymph nodes of the neck.

Histological size of the tumor	Number (N)	Percentage (%)
0 to 10 mm	16	15,7%
11 to 20 mm	23	22,5%
21 to 40 mm	37	36,2 %
Over than 41 mm	19	18,6 %
Extracapsular tumor extension	7	6,8 %
Total	102	100%

Table 1. Histological size of the tumor

Type of operation	Number (N)	Percentage (%)
Biopsy	1	0,9
Tumor reduction	3	2,9
Total thyroidectomy	27	26,5
Total thyroidectomy + dissection central lnn* + lower jugular lnn*	21	20,6
Total thyroidectomy + dissection central lnn + MRND	50	49
Total	102	100

Table 2. Scope of operations due to PTC. Legend: lnn- lymph node

Localization of the recurrence	Numer (N)	Percentage (%)
Local recurrence in the thyroid lobe	2	14,3
Recurrence in undissected lnn*-unilateral	4	28,5
Recurrence in undissected lnn*-bilateral	5	35,7
Recurrence in already dissected lnn	2	14,3
Recurrence + distant metastases	1	7,1
Total	14	100

Table 3. Localization of the recurrence. Legend: lnn- lymph node

* 7 patients (7.8%) experienced distant metastases; 1 patient (a child) in the lungs and 6 patients, over 45 years of age, experienced metastases localized in the lungs and bones.

In total, 102 patients with PTC were operated on. Total thyroidectomy (TT) was performed in 20 patients, and near-total thyroidectomy leaving <1 g thyroid tissue adjacent to the recurrent laryngeal nerve in 7 patients. Total thyroidectomy + dissection of the central and lower jugular lymph nodes was performed in 71 patients (69.6%), with ex tempora hp verification.

Out of these 71 patients, metastases in the lower jugular lymph nodes were verified in 50 patients (70.42%). In these patients, a modified lymph node dissection (MRND) was also performed. A reduction in tumor mass and biopsy was made in 4 patients (3.9%), due to the enormous tumor size and disease progression. Scope of operations due to PTC is shown in Table 2.

Recurrence in patients with PTC

Recurrence of the disease was observed in 14 patients (13.7%) who were treated for PTC. The localization of the recurrence is shown in Table 3. The highest number of patients were with recurrence in undissected lymph nodes of the neck. A low number of patient had recurrence in the already dissected lymph nodes of the neck (Table 3).

The time until recurrence was statistically analyzed in relation to the following risk factors: sex, age, presence of metastases in the lymph nodes of the neck, presence of

Gender	Number (N)	Recurrence		With Inn* metastases		Without Inn* metastases	
		Yes	No	Number	Recurrence	Number	Recurrence
Female	55	6	49	36	5	19	1
Male	47	8	39	40	6	7	2
X				X = 3,91, p=0,048			

Table 4. Frequency of recurrence of the disease in relation to the presence of metastases in the lymph node of the neck and gender of the patients. Legend: Inn- lymph node

distant metastases, histological variant of PTC, histological tumor size and extracapsular tumor extension.

Male patients experienced, statistically significance, much earlier recurrence of disease compared to female patients (Test: Log rank $X^2 = 4.28$, $P = 0.0039$).

Patients who had metastases in the central lymph nodes of the neck and who did not have a dissection of the lateral group of lymph nodes of the neck experienced, statistically significance, much earlier recurrence of the disease compared to patients with a lateral group of lymph node neck dissection. (Test: Log rank $X^2 = 5.80$, $p = 0.016$).

Patients in whom only TT was performed experienced, statistically significance, much earlier recurrence of disease compared to patients with TT + MRND (Test: Log rank $X^2 = 5.42$ $p = 0.02$).

Recurrence frequency

A group of patients diagnosed with recurrence of the disease was analyzed in relation to the absence and presence of metastases in the lymph nodes of the neck. The presence or absence of metastases in the lymph node of the neck is set as a constant, and the frequency of recurrence of the disease is analyzed through other risk factors: sex, age, presence of initial distant metastases, extracapsular tumor extension and tumor size.

Men with metastases in the lymph nodes of the neck more often experience recurrence compared to women with metastases in the lymph nodes of the neck (Test: Log rank $X^2 = 3.91$, $p = 0.048$ (Table 4). Patients older than 45 years of age are more likely to experience recurrence of the disease compared to patients under the age of 45 years, regardless of the presence or absence of metastases in the lymph nodes of the neck. But that has no statistical significance. Patients with distant metastases and metastases in the lymph node of the neck were statistically more likely to experience recurrence of the disease compared to patients who did not have metastases and metastases in the lymph node of the neck (Test: Fisher, $p = 4 \times 10E-6$). Patients with a tumor size > 40 mm and metastases present in lymph nodes of the neck significantly more often experience recurrence of the disease compared to patients with a tumor size < 40 mm (Test: Log rank $X^2 = 9.92$, $p = 0.002$).

Therapy of recurrence

Out of 14 patients who experienced recurrence of the disease: 2 patients (11.1%) were operated on due to recurrence in the loge of thyroid gland, MRND was performed in 7 patients (38%) and radical neck dissection (RND) was performed in 5 patients (29.7%). 131 J and external radiotherapy were applied in 4 patients.

4. DISCUSSION

The aim of this paper is to demonstrate whether lymphogenic metastases of papillary carcinoma are significant for recurrence of the disease. The literature says that the lymphogenic metastases of the thyroid gland papillary carcinoma are significant for recurrence but not for survival (5, 6, 7).

In our clinical study in the group of 102 patients operated on, people aged 40-60 years dominate, and women, who are more likely to suffer from PTC, represent 73.22% of the analyzed group. The ratio M:F = 1:2.73 (10).

The results of this study have shown that PTC is the most common of all DTC. Histological analysis found that 80 patients (78.4%) experienced pure PTC and 22 patients (21.6%) experienced other histological variants of PTC. A concurent multi centric or bilateral localization of PTC being 25.18% indicates the justification of TT. Other authors also find a concurent occurrence of intrathyroid metastases in the examined preparations (11).

Residual minimal carcinoma focuses can be clinically demonstrated in 5-10% cases in less extensive surgeries (14).

In total, 102 patients were treated. TT was performed in 90 patients. In 71 patients, TT + dissection of central and lower jugular lymph nodes were performed with an ex tempore histopathological check. Of these 91 patients metastases in the lower jugular lymph nodes were verified histopathologically in 50 patients. TT + MRND were performed in these patients. Tumor mass reduction and biopsy due to enormous tumor size and disease progression were performed in 4 patients (Table 2).

Recurrence of the disease was more frequent after TT than after TT + MRND. The frequency of local recurrence was 10.9% of patients after TT and 19.2% after subtotal thyroidectomy. Metastases of PTC are present in the lymph nodes of the neck in 20-85% of patients. Therefore, the dissection of the central lymph nodes of the neck and TT are recommended for this type of cancer. The dissection of lateral lymph nodes of the neck is recommended if the lower jugular lymph nodes are affected by metastases. The lower jugular lymph nodes are always checked ex-tempore. If metastases in the lower jugular lymph nodes are microscopically proved, the dissection of the lateral region of the neck was performed during the same operation (13, 14, 15).

In our clinical material, lymph node metastasis were detected in 71 patients (69.6%). 31 patients (28.34%) had no metastases in the lymph nodes of the neck. Our results are in correlation to results of other authors, which indicate the frequency of lymphogenous metastasis in 20% to 85% of patients (15).

Analyzing the time until recurrence in relation to localization of the metastasis of affected lymph nodes in patients with PTC, we have established that patients who had metastases in the central lymph nodes of the neck and who had no dissection of the lateral group of the lymph node, experienced the recurrence of the disease much earlier, statistically speaking, than patients with dissection of the lateral group of lymph nodes of the neck (16). Comparing the results with respect to the time until recurrence in relation to the type of surgical operation and the type of dissection of the lymph nodes of the neck, we found that the patients who were treated with only TT experienced recurrence of the disease much earlier, statistically speaking, compared to patients with TT + MRND.

The frequency of recurrence of the disease was analyzed in relation to the presence or absence of metastases in the lymph nodes of the neck. The presence or absence of metastasis in the lymph nodes of the neck is presented as a constant and the frequency of recurrence of the disease is analyzed through other risk factors. In our analysis, we found that men with metastases in the lymph nodes of the neck experienced recurrence of the disease much earlier statistically speaking, compared to women with lymph node metastases. Patients over 45 years of age with metastases present in lymph nodes of the neck experienced recurrence of the disease more often than patients who were under 45. It is statistically of no significance.

In patients experiencing recurrence of the disease, surgical reoperations were performed; MRND was performed in 7 patients (50%) and Radical Neck Dissection (RND) was performed in 5 patients (35.7%). External radiotherapy and 131 I were applied in 2 patients (14.2%).

5. CONCLUSIONS

The frequency of metastases in the lymph nodes of the neck (pretracheal and paratracheal) is at the most 71.65%. Recurrence of the disease was observed most often in undissected lymph nodes of the neck and unilaterally and bilaterally. Recurrence of the disease is most often detected on the basis of high values of Tg in serum and by palpation of enlarged lymph nodes of the neck. Metastases in the lymph node of the neck are important in the recurrence of the disease, and not for a survival. The risk of recurrence of the disease is the greatest in the first 5 years after the initial treatment. Dissection of the lymph node of the neck contributes to a more accurate determination of the stage of the disease and increases the curability due to the operation. Introduction of perioperative diagnostics of the presence of metastases in the lymph nodes significantly reduces the risk of recurrence of the disease.

• Conflict of interest: none declared.

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