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THE ROLE OF CALCITONIN IN THE PREOPERATIVE STAGE AS THE PREDICTOR OF MEDULLARY THYROID CANCER METASTASES

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Abstract: *the aim of the stydy was to analyze the detectability of medullary thyroid metastases in patients at treatment and diagnostic stages, to investigate the applicability of serum calcitonin level as predictor of possible presence of medullary thyroid metastases. The study included data from 148 patients who underwent surgical treatment for the initial diagnosis of medullary thyroid cancer. The age of patients ranged from 12 to 83 years, the mean age was 48,2±1,9 years; the distribution by gender was as follows: men – 34 (23%), women – 114 (77%). Patients were divided into two groups depending on the pathomorphological report: 1 group (100 (67,6%) – patients without metastases), 2 group (48 (32,4%) – patients with locoregional metastases). Among 148 studied patients with medullary thyroid cancer, as a result of the histopathological conclusion, in 48 (32,4%) metastases were detected in regional lymph nodes, among which 10 (6,7%) patients had metastases only in the central collector and 38 (25, 7%) –both in the central and lateral collectors. At the preoperative stage, the level of undiagnosed metastases by ultrasound was 64,58% (31 patients). Subsequently, at the intraoperative stage, during the rapid histological biopsy, the number of undiagnosed metastases decreased to 37,5% (18 patients), and in the postoperative period, according to the results of histopathological examination, the remaining patients were diagnosed with the medullary thyroid cancer metastases. Ultrasound helped to detect metastases in 17 patients, which was 35,42% of all detected metastases. At the stage of intraoperative study, the detection of metastases increased and amounted to 30 (62,5%), and in the postoperative period as a result of histopathological examination metastases were confirmed in 48 patients (100%). Quantitative indicators of both detected and undiagnosed metastases at all stages of treatment and diagnostic search are statistically significant (p<0,01). The detection of metastases in the central lymphatic collector (N1a) at the preoperative stage was 2,08%, this index has doubled (to 4,16%) after intraoperative rapid histological conclusion, and after histopathological conclusion the index has increased more than 10 times (20,84 %). This tendency to grow of metastaseses detection was followed also on lateral collectors: N1b and psilateral were observed at 15 (31,2%) patients at the preoperative stage, their number increased to 23 (47,9%) intraoperatively and to 31 (64,6%) postoperatively; N1b contralateral was observed in 1 (2,1%), 5 (10,4%) and 7 (14,6%), respectively. Such a low percentage of metastases detection at the preoperative stage by ultrasound prompted to CT level study as the predictor of possible metastases. We investigated the preoperative basal blood CT value as a marker of the medullary thyroid cancer metastases presence probability. Due to the small number of the group (n=10) with N1a, the association of CT (cut-off level 137 pg/ml) with the possible presence of metastases was not significant (AUC = 0.594), while in the group with N1b there was a more significant difference. Thus, CT cut-off levels of 358 pg/ml for N1b ipsilateral, and 498 pg/ml for N1b contralateral detection of possible metastases in collectors, with AUC: 0.877 and 0.832, respectively, which justifies the importance of the lateral neck dissection in addition to the mandatory central dissection in order to remov possible medullary thyroid cancer metastases. Thus, ultrasound is insufficiently reliable method of metastases verifying in medullary thyroid cancer (DE = 35.4% at d mts <0.6 cm). In the absence of ultrasound data (or fine needle aspiration (FNA) biopsy results) on the presence of metastases to raise awareness of the disease prevalence, to clarify the prognosis of its development it's important to use the additional criterion – the calcitonin level. Basal calcitonin level is the reliable predictor of the medullary thyroid cancer metastases. Its cut-off level of 137 pg/ml indicates the possible presence of metastases in the central group (N1a) (AUC=0,594). The CT cut-off level – 358 pg/ml (AUC=0,793) suggests the presence of the medullary thyroid cancer metastases (N1a+N1b). CT cut-off levels – 358 pg/ml for N1b ipsilateral, and 498 pg / ml for N1b contralateral (AUC: 0,877 and 0,832), respectively. The calculated values of the countersensitivity test to detect metastases for different levels of basal CT in the preoperative stage in the clinical setting will help the practitioner in deciding on treatment tactics to determine the extent of surgery in patients diagnosed (or suspected) with the medullary thyroid cancer metastases.*

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Key words: calcitonin, thyroid neoplasms, neoplasm metastasis, ROC Curve, thyroid gland.

Introduction. Medullary thyroid cancer (MTC) is a rare type of the thyroid gland malignant tumor that originates from parafollicular cells (Master & Burns, 2021), or C-cells derived from the neural crest, which produce calcitonin – a thyroid hormone that can be used as a specific marker of thyroid cancer (Park, et al., 2021). Despite the relatively infrequent occurrence of medullary thyroid cancer, which accounts for up to 5% of all cases of thyroid cancer (Miller, et al., 2018), it is the cause of a disproportionately large number of deaths (according to various sources13.4% -38.0%) (Kuo, et al., 2017) of patients with this pathology; the disease tends to metastasize rapidly, and it is refractory to modern methods of non-surgical treatment (Kebebew, et al., 2000). To date, surgery remains the main method of thyroid cancer treatment, and when planning the surgical scope (lymph dissection) at the preoperative stage, there is always the problem of probable metastases detection; however, existing methods of visualization (ultrasound, MSCT, PET-CT) do not have a sufficiently high diagnostic efficiency to verify metastases (Kouvaraki, et al., 2003; Kiesewetter, et al., 2021). The imperfection of the preoperative neck ultrasonography is possible to be one of the main reasons for the detection in the postoperative period of elevated calcitonin levels in more than half of patients with metastatic MTC (Van Heerden, et al., 1990). It is known that the recurrence and survival rate depend on the initial volume of the operation, and a better level of biochemical remission is the result of adequate neck dissection (Fleming, et al., 1999). Thyroidectomy with central neck dissection is recommended for almost all patients with MDR; however, indications for lateral dissection remain controversial (Roman, et al., 2006; Pelizzo, et al., 2007; Bartz-Kurycki, et al., 2021).

The possibility of the medullary thyroid cancer metastases predicting at the diagnostic and treatment stage, we present in our own work.

The aim of the stydy was to analyze the detectability of medullary thyroid cancer metastases in patients at treatment and diagnostic stages. To investigate the possibility of serum calcitonin using to predict the possible presence of medullary thyroid metastases and to determine the extent of surgery.

Materials and methods. The study included data from 148 patients who underwent surgical treatment at the Center for the initial diagnosis of medullary thyroid cancer. The age of patients ranged from 12 to 83 years, the mean age was 48.2±1.9 years; the distribution by gender was as follows: men – 34 (23%), women – 114 (77%). Patients were divided into two groups depending on the presence of metastases according to the pathomorphological study: 1 group (100 (67.6%) – patients without metastases), 2 group (48 (32.4%) – patients with existing locoregional metastases.

All patients in the preoperative and postoperative stages were measured for basal serum calcitonin levels, its values were considered normal at ≤18 pg/mL. The study was performed on the automatic immunochemiluminescent analyzer «MAGLUMI» (manufacturer «Snibe Diagnostic», China). Reagents from the same manufacturer were used. Ultrasound was also performed to establish the spread of the process.

Accumulation and primary data processing were performed in MS Excel 2013, statistical processing was performed using StatPlus (license #21735752) and MedCalc (trial. ver.) Using descriptive statistics, parametric and nonparametric methods for testing statistical hypotheses (Student's criteria, Mann-Whitney, angular Fisher transform), conjugation tables analysis, ROC analysis. Depending on the type of distribution of the variation series, the results of the calculations are presented as the mean value and the standard error or median and the 25th and 75th percentiles (Me (Q25; Q75)). The results at $p < 0.05$ were considered statistically significant.

Results and discussion.

1. The effectiveness of MTC locoregional metastases detection at the treatment and diagnostic stages.

Among 148 studied patients with thyroid cancer, 48 (32,4%) as a result of pathohistological findings revealed metastases to regional lymph nodes, of which 10 (6,7%) patients had metastases only in the central collector and in 38 (25,7%) – both in the central in lateral collectors.

Table 1. Detectability of thyroid cancer metastases by ultrasound at different treatment and diagnostic stages

Presence of metastases / Stage	Preoperative	Intraoperative	Postoperative
Nx	31 (64,58%)**	18 (37,5%)	0
N1a	1 (2,08%) **	2 (4,16%) **	10 (20,84%)
N1b ipsilateral	15 (31,26%) **	23 (47,92%) *	31 (64,58%)
N1b contralateral	1 (2,08%) **	5 (10,42%)	7 (14,58%)
∑N1a,b	17 (35,42%) **	30 (62,5%) **	48 (100%)

1. * - the difference compared to the postoperative stage is significant (p<0,05);
2. ** - the difference compared to the postoperative stage is significant (p<0,01)..

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Table 2. The level of basal preoperative calcitonin as a predictor of metastases

Observation parameters / Observation groups		Primary MTC (%)
∑		148 (76,3%)
N stage	N 0	100 (67,6%)
	N1a	10 (6,8%)
	N1в	38 (25,7%)
Number of metastatic lymph nodes	Average value M ± SE	2,5 ± 0,4
	Number of cases Na,b/%	49/33,3 %
	Median Me (Q_{25}; Q_{75})	6,0 (3,0; 10,0)
	Range (minimum - maximum)	0 – 24
Preoperative calcitonin	Median Me (Q_{25}; Q_{75})	456,4 (136,4; 1267,50)
	Range (minimum - maximum)	4,92 - 6000,0

The presence of metastases at the preoperative stage by ultrasound was 11,5% (17 patients), and their subsequent detection at the treatment and diagnostic stages is shown in table 1.

The above data show that at the preoperative stage the level of undiagnosed metastases by ultrasound was 64,58% (31 patients). Subsequently, at the intraoperative stage, during rapid histological biopsy, the number of patients with undiagnosed metastases decreased to 37,5% (18 patients), and in the postoperative period, according to the results of histopathological findings, the remaining patients were diagnosed with MTC metastases. The use of ultrasound helped to detect metastases in 17 patients, which accounted for 35,42% of all detected metastases. At the stage of intraoperative examination, the metastases detection increased and amounted to 30 (62,5%), and in the postoperative period, as a result of pathohistological findings, metastases were confirmed in 48 patients (100%). Quantitative indicators of both detected and undiagnosed metastases at all stages of medical and diagnostic search are statistically significant ($p<0.01$). The detection of metastases in the central lymphatic collector (N1a) at the preoperative stage was 2,08%, this number doubled (to 4,16%) after receiving the intraoperative rapid conclusion, and when obtaining the histopathological conclusion it increased more than 10 times (20,84%). This tendency of metastaseses detection growth followed also on lateral collectors (N1b): N1b ipsilateral were observed at 15 (31,2%) patients at the preoperative stage, their number increased to 23 (47,9%) intraoperatively and to 31 (64,6%)) postoperatively; N1b contralateral was observed in 1 (2,1%), 5 (10,4%) and 7 (14,6%), respectively.

Thus, ultrasound, as the method that is most widely used for topical diagnosis of the MTC prevalence does not have the necessary diagnostic efficiency. False-negative ultrasound findings on the metastases presence are found more often in the central than in the lateral collector and when the size of metastases is <0.6 cm, their detection does not exceed 36%, both due to the limited capabilities of the equipment and expressed author-dependence (Товкай та ін., 2020).

2. The level of basal preoperative calcitonin as a predictor of metastases.

Given the unsatisfactory result in the detection of thyroid metastases at the preoperative stage by ultrasound (35,42%), we considered calcitonin as another predictor of metastases (Opsahl, et al., 2019).

For the group without metastases (N0) the level of calcitonin was in the range (minimum - maximum) 4,92 – 4234,0 pg/mL, for the group with metastases only to the central collector (N1a): 63,3-5595, for the group with metastases in the central and lateral collectors (N1b) the range was 219-6000,0. Thus, the range of preoperative calcitonin levels for both non-metastatic and metastatic tumors has large cross-sectional areas. To determine the possibility of using the level of calcitonin to determine it as a predictor of metastases, ROC analysis was performed (Fugazzola, et al., 2021; Giovanella, et al., 2021) and good quality models for all levels of metastases were identified (Fig. 1 a, b, c, d).

Therefore, we have the opportunity to determine the cut-off thresholds of cSealcitonin depending on the level of metastases and the main operational characteristics of this test (Table 3).

As can be seen from the above data, at a blood calcitonin level of 136,9 pg/mL, the possibility of detecting metastases to the central lymphatic collector (N1a) is not have a highly significant: the area under the curve (AUC) is 0,594. This may be due to the small sample size (n=10). The cut-off level of calcitonin was 137 pg/mL for the presence of possible MTC metastases in N1a. The relationship between calcitonin levels and the detection of MTC metastases in lateral collectors (N1b) was more significant. Thus, the cut-off level of calcitonin for possible ipsilateral (N1b) metastases was 358 pg/mL,

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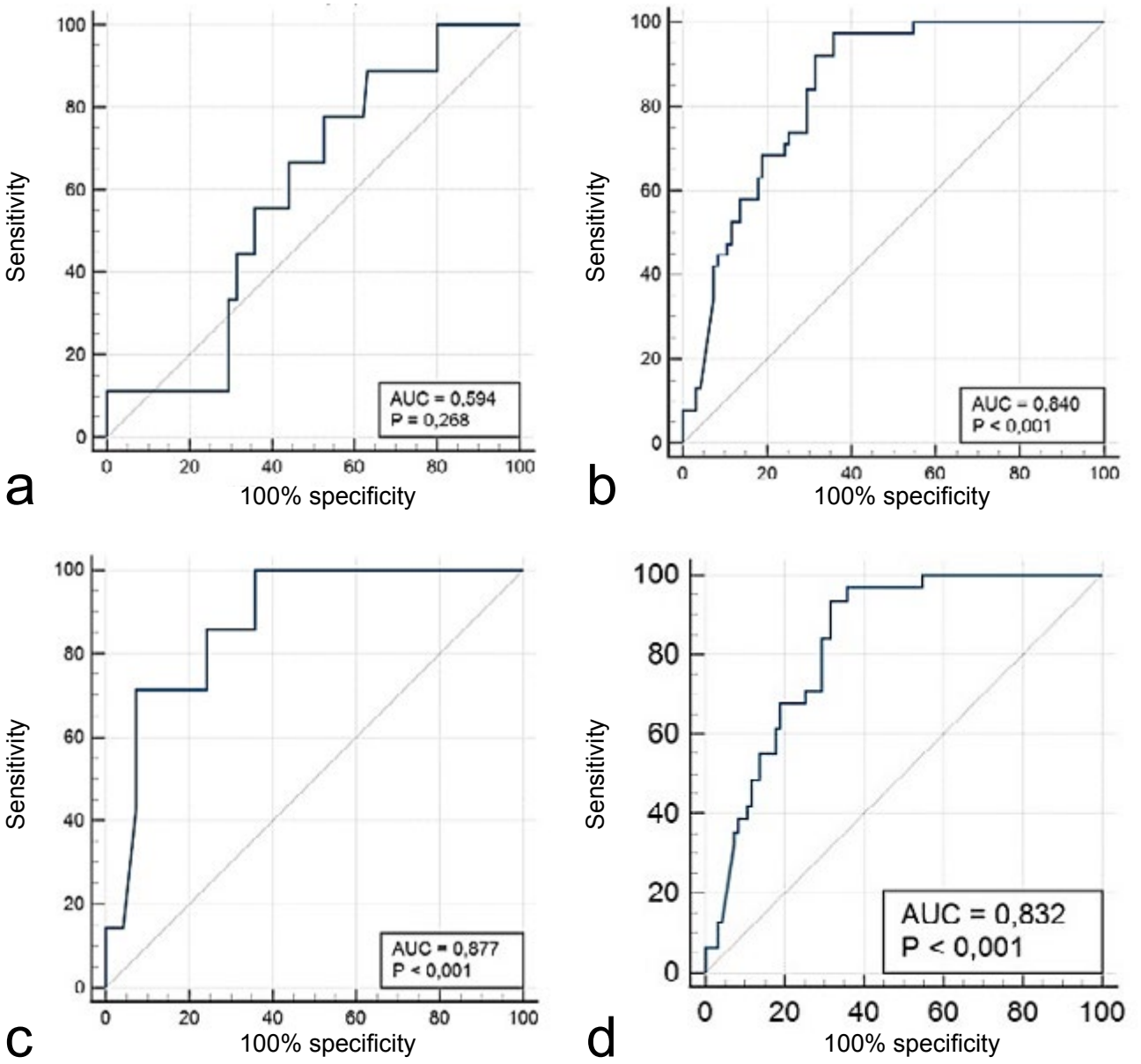

Fig. 1. ROC curve, the relation of preoperative calcitonin levels with the metastases presence: a) in the central collector (n= 0); b) in the lateral lymphatic collectors (n=38); c) in the ipsilateral collector (n=31); d) in the contralateral lymphatic collector (n=7).

The level of metastases	Cut-off, pg/mL	AUC	Youden's Index J	Sensitivity	Specificity
N1a, n=10	136,9	0,594	0,257	0,889	0,368
N1b , n=38	358	0,840	0,616	0,974	0,642
N1b, ipsilateral, n=31	358	0,877	0,642	1,000	0,642
N1b contralateral, n=7	498	0,832	0,620	0,936	0,684
∑ (N1a, N1b), n=48	358	0,793	0,535	0,894	0,642

Table 3. Thresholds of cut-off values of preoperative blood calcitonin depending on the extention of metastases. The main operational characteristics of the test

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Preoperational calcitonin, pg/mL	False negative sensitivity, *CoSe*	Preoperational calcitonin, pg/mL	False negative sensitivity, *CoSe*
60,7	0,000	980,8	0,426
63,5	0,021	1054,0	0,447
147,5	0,043	1059,0	0,468
220,0	0,064	1076,5	0,489
228,1	0,085	1086,0	0,511
314,5	0,106	1267,5	0,532
365,6	0,106	1293,5	0,553
377,7	0,128	1447,5	0,574
385,4	0,149	1478,0	0,596
410,2	0,170	1716,0	0,638
506,7	0,191	1854,2	0,660
511,7	0,213	1965,5	0,681
516,3	0,255	1990,0	0,702
546,1	0,277	2182,5	0,872
557,5	0,298	2576,2	0,894
573,4	0,319	3082,7	0,915
582,1	0,340	5297,5	0,936
619,5	0,362	5614,0	0,957
674,0	0,383	5816,5	0,979
870,5	0,404	6001,0	1,000

Table 4. Correspondence of preoperative blood calcitonin level and false negative sensitivity in patients with medularly thyroid cancer

and for contralateral metastases (N1b) – 498 pg/mL, with a sufficiently high AUC: 0,87 and 0,82, respectively. In general, for lateral metastases, the AUC was 0,783 with the cut-off calcitonin level of 358 pg/mL.

Therefore, the possibility of using ROC analysis to predict the presence of MTC metastases depending on the level of preoperative calcitonin has been proven; numerical values of false negative sensitivity calculated, i.e. the probability of obtaining a negative test result in patients with metastases, for different cut-off thresholds (Table 4).

There is a possibility to get a negative test result in the patient (in our case – to miss metastases). When the test threshold (calcitonin value) is low, we can potentially detect all cases of metastases, i.e. the sensitivity of the test is 100% (there will be a pre-diagnosis) (Palamarchuk,2020). At the same time false negative sensitivity is zero (as shown by the graph in Fig. 2).

The calculated values of countersensitivity show a change in the probability of the negative test result obtaining in patients with metastases. Thus, when the basal calcitonin level is obtained in the patient with MTC, or if this type of tumor is suspected, the practitioner has the opportunity to determine and assess the expected probability of metastases and decide on further treatment tactics to determine the extent of surgery.

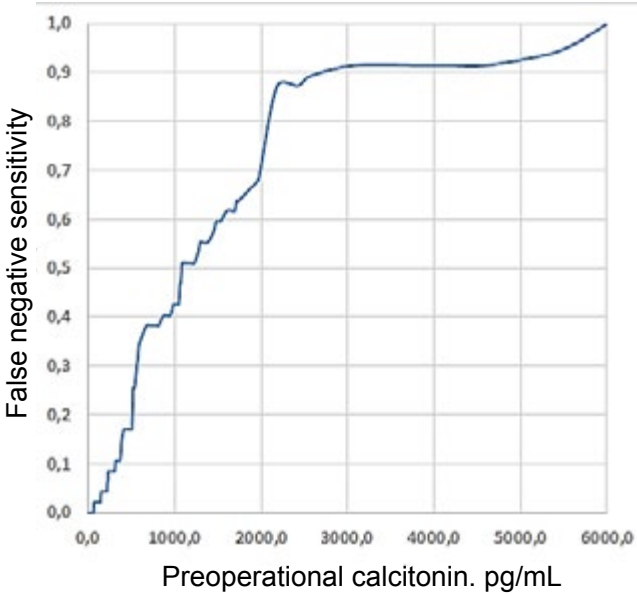

Fig. 2. The probability of metastases missing in a patient depending on the preoperative calcitonin level.

To date, surgery remains the only treatment for MTC (Ceolin, et al. 2019). Approximately 35% of patients with MTC, whose palpation reveals thyroid nodules, already have metastases to the lymph nodes of the neck. About 10% (7-23%) have distant metastases at the onset of the disease (Filetti, et al., 2019).

According to Dal Maso, distant metastases occur during their detection in approximately 20-40% of patients with MTC and they are the leading cause of death associated with the disease (Dal Maso, et al., 2017). Another study confirmed that metastases were the leading cause of death in> 90% of cancer patients (Fares, et al., 2020).

Due to the high risk of early metastases in this type of cancer in the preoperative stage, the problem of the metastases presence always arises. Existing diagnostic methods (ultrasound is most widely used in hospitals, MSCT, PET-CT) are not high enough diagnostic efficiency due to limited technical capabilities of the equipment, and it largely depends on the experience of the doctor who performs the diagnosis. Thus, false-negative ultrasound findings on the metastases presence are observed in approximately one third of the examined patients (Machens, et al., 2010; Rukanskienė, et al., 2020). According to published data, false-negative ultrasound findings on the metastases presence are more common in the central than in the lateral collector and with the size of metastases <0.6 cm. Their detection does not exceed 47% (Huang, et al., 2020). In our study, the number of undiagnosed metastases at the prehospital stage by ultrasound was 64,58%, which illustrates the data on the effectiveness lack of this method (Cheng, et al., 2020). A reliable fact ($p<0.01$) is the increase in the number of diagnosed metastases to N1a in the preoperative, intraop-

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erative and postoperative stages, from 2,08% to 4,16% and 20,84%, respectively. With N1b ipsilateral metastatic lesions, the number of diagnosed metastases at the diagnostic and treatment stages increases – 31,26%, 47,92% and 64,58%, for N1b contralaterally – 2,08%, 10,42% and 14,58%, respectively.

Thus, the ultrasound method allowed to detect metastases in the preoperative stage in almost a third (35,4%) of patients with metastatic neck lesions, which were determined in the postoperative period as a result of histopathological findings. Such a low detection rate of MTC metastases allows us to speak about the low efficiency of the ultrasound method and its imperfection. The same opinion is shared by other authors, whose works prove the imperfection of this method, which is one of the reasons for the detection in the postoperative period of elevated calcitonin levels and it reduces the chances of cure (Gimm, et al., 1997; Chen, et al., 2020).

Serum calcitonin in patients with MTC is the important diagnostic, prognostic and predictive biomarker due to its direct relationship with C-cells (Giraudet, et al., 2008; Gambardella, et al., 2019).

We considered the possibility of using preoperative calcitonin levels as a marker of possible metastases. Current recommendations of the American Thyroid Association (ATA) advise to measure the calcitonin level in the blood serum in cases where the cytological conclusion in patients diagnosed (or suspected) of thyroid cancer and the calcitonin level may be a predictor of the disease (Wells, et al., 2015; Silvestre, et al., 2019).

The recommendations of the European Medical Oncology Association (ESMO) generally recommend total thyroidectomy with central and bilateral neck dissection at least at levels IIA, III and IV, even if serum calcitonin levels are between 50 and 200 pg/mL in patients with negative ultrasound of the neck (Kim & Kim, 2021). There is no need for prophylactic central neck dissection in small intrathyroid MTC with preoperative calcitonin levels <20 pg/mL due to the absence of lymph node metastases risk.

We investigated the significance of preoperative basal blood calcitonin levels as the marker of thyroid metastases presence. Thus, according to our data at the level of calcitonin <60,7 no metastases were detected. At the calcitonin level of 60,7 - 358 pg/mL (cut-off level 137 pg/mL) it is possible to detect metastases in the central collector, but it does not exclude the detection of metastases in the ipsilateral collector. It was proved that the calcitonin level >58 pg/mL suggests the presence of MTC metastases in the ipsilateral collector (AUC=0,877), and at the of calcitonin level >498 pg/mL it suggests possible metastases in the contralateral collector (AUC = 0,832). The practical significance of this of calcitonin indicator is to justify the required volume of neck dissection in addition to the mandatory central dissection in order to remove possible expected metastases of thyroid cancer.

Conclusions. Ultrasound is the insufficiently reliable method of metastases verifying in medullary thyroid cancer (DE=35,4% at d mts<0,6 sm). In the absence of ultrasound data (or TAPB results) on the presence of metastases to raise awareness of the disease prevalence, to clarify the prognosis of its development it should be used the additional criterion – the calcitonin level.

The basal calcitonin level is the reliable predictor of MTC metastases. Its cut-off level of 137 pg mL indicates the possible presence of metastases in the central group (N1a) (AUC=0.594). The cut-off calcitonin level – 358 pg/mL (AUC=0.793) suggests the presence of MTC metastases (N1a+N1b). Calcitonin cut-off levels are 358 pg/mL for N1b ipsilateral, and 498 pg/mL – for N1b contralateral (AUC: 0.,877 and 0,832, respectively).

The calculated false negative sensitivity values of the metastases test for different basal calcitonin levels in the preoperative stage in the clinical setting will help the practitioner in deciding on treatment tactics to determine the extent of surgery in patients diagnosed (or suspected) of MTC.

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Authors contribution: concept, methodology, formal analysis - P.V., S.V., S.R., M.O.; research, resources, data curation, written - T.O., N.O., K.V., M.O.; original project preparation, review and editing, visualization, supervision, project administration, acquisition of financing - S.V., T.O, K.V., , M.O.

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РОЛЬ КАЛЬЦИТОНІНУ НА ДООПЕРАЦІЙНОМУ ЕТАПІ ЯК ПРЕДИКТОРА МЕТАСТАЗУВАННЯ МЕДУЛЯРНОГО РАКУ ЩИТОПОДІБНОЇ ЗАЛОЗИ

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Анотація*:* метою роботи було проаналізувати виявляємість метастазів МРЩЗ у хворих на лікувально-діагностичних етапах. Дослідити можливість використання показника кальцитоніну сироватки крові для прогнозування можливої наявності метастазів МРЩЗ та визначення об'єму хірургічного втручання. В дослідження включені дані 148 хворих, які проходили хірургічне лікування в Центрі з приводу первинно встановленого діагнозу МРЩЗ. Вік хворих варіював від 12 до 83 років, середній вік становив 48,2±1,9 років; розподіл за гендерним типом виглядав наступним чином: чоловіків – 34 (23 %), жінок– 114 (77%). Пацієнти були розподілені на дві групи в залежності від наявністі метастазів за даними патоморфологічного дослідження: 1 група (100 (67,6%) – хворі без метастазів), 2 група (48 (32,4%) – хворі з наявними локорегіонарними метастазами). Серед 148 досліджуваних хворих на МРЩЗ, у 48 (32,4%) за результатом патогістологічного висновку були виявлені метастази в регіонарні лімфатичні вузли, з яких у 10 (6,7%) пацієнтів метастази були локалізовані тільки в центральному колекторі та у 38 (25,7%) – в центральному та в латеральних колекторах. На дооперацийному етапі рівень недіагностованих метастазів за результатами УЗД становив 64,58% (31 хворих). В подальшому на інтраопераційному етапі, при проведенні експрес-гістологічної біопсії кількість недіагностованих метастазів скоротилась до 37,5% (18 хворих), а в післяопераційному періоді, за результатами патогістологічного висновку, у решти хворих були підтверджені метастази МРЩЗ. Застосування УЗД допомогло виявити метастази у 17 хворих, що становило 35,42% серед усіх виявлених метастазів. На етапі інтраопераційного дослідження виявляємість метастазів збільшилась і становила 30 (62,5%), а в післяопераційному періоді за результатом патогістологічного висновку метастази були підтверджені у 48 хворих (100%). Кількісні показники як виявлених, так і недіагностованих метастазів на всіх етапах лікувально-діагностичного пошуку є ста-

РОЛЬ КАЛЬЦИТОНИНА НА ДООПЕРАЦИОННОМ ЭТАПЕ КАК ПРЕДИКТОРА МЕТАСТАЗИРОВАНИЯ МЕДУЛЯРНОГО РАКА ЩИТОВИДНОЙ ЖЕЛЕЗЫ

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Аннотация: целью работы было проанализировать выявляемость метастазов МРЩЖ у больных на лечебно-диагностических этапах. Исследовать возможность использования показателя кальцитонина сыворотки крови для прогнозирования возможного наличия метастазов МРЩЖ и определения объема хирургического вмешательства. В исследование включены данные 148 больных, проходивших хирургическое лечение в Центре по поводу изначально установленного диагноза МРЩЖ. Возраст больных варьировал от 12 до 83 лет, средний возраст составлял 48,2±1,9 лет; распределение по гендерному типу выглядело следующим образом: мужчин – 34 (23%), женщин – 114 (77%). Пациенты были распределены на две группы в зависимости от наличия метастазов по данным патоморфологического исследования: 1 группа (100 (67,6%) – больные без метастазов), 2 группа (48 (32,4%) – больные с имеющимися локорегионарными метастазами). Среди 148 исследуемых больных МРЩЖ у 48 (32,4%) по результату патогистологического заключения были обнаружены метастазы в регионарные лимфатические узлы, из которых у 10 (6,7%) пациентов метастазы были локализованы только в центральном коллекторе и у 38 (25, 7%) – в центральном и в латеральных коллекторах. На дооперационном этапе уровень недиагностированных метастазов по результатам УЗИ составил 64,58% (31 больных). В дальнейшем на интраоперационном этапе, при проведении экспресс-гистологической биопсии, количество недиагностированных метастазов сократилось до 37,5% (18 больных), а в послеоперационном периоде по результатам патогистологического заключения у остальных больных были подтверждены метастазы МРЩЗ. Применение УЗИ помогло выявить метастазы у 17 больных, что составило 35,42% среди всех выявленных метастазов. На этапе интраоперационного исследования выявление метастазов увеличилось и составило 30 (62,5%), а в послеоперационном периоде по результату патогистологического заключения метастазы были подтверждены у 48 больных (100%). Количественные показатели как выявленных, так и недиагностированных метастазов на всех этапах

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тистично значимими (p<0,01). Виявляємість метастазів в центральному лімфатичному колекторі (N1a) на доопераційному етапі становила 2,08%, цей показник збільшився вдвічі (до 4,16%) після отримання інтраопераційного експрес-гістологічнгого заключення, а при отриманні патогістологічного висновку зріс більше ніж у 10 разів (20,84%). Ця тенденція зростання виявлення метастазів прослідковувалась і по латеральних колекторах: N1b іпсілатеральні спостерігали у 15 (31,2%) хворих на доопераційному етапі, їх кількість збільшилась до 23 (47,9%) інтраопераційно і до 31 (64,6%) післяопераційно; N1b контрлатеральні спостерігали у 1 (2,1%), 5 (10,4%) та 7 (14,6%) відповідно. Такий низький процент виявлення метастазів на доопераційному етапі методом УЗД спонукав до вивчення рівня кальцитоніну як предиктора можливого метастазування. Нами досліджено значення рівнів доопераційного базального кальцитоніну крові в якості маркеру вірогідності наявності метастазів МРЩЗ. Внаслідок малої чисельності групи (n=10) з N1a зв'язок кальцитоніну (рівень відсічення 137 пг/мл) з можливою наявністю метастазування був недостатньо вагомий (AUC=0,594), тоді як у групі з N1b відмічалась більш суттєва різниця. Так, рівні відсічення кальцитоніну 358 пг/мл для N1b іпсілатерального та 498 пг/мл для N1b контрлатерального виявлення можливих метастазів в колекторах з показниками AUC: 0,877 та 0,832 відповідно, що обґрунтовує необхідність проведення латеральної дисекції шиї крім обов'язкової центральної з метою видалення можливих очікуваних метастазів МРЩЗ. Таким чином, УЗД є недостатньо надійним методом верифікації метастазування при медулярному раку щитоподібної залози (ДЕ = 35,4% при d mts<0,6см). При відсутності УЗ даних (або результатів ТАПБ) про наявність метастазів для підвищення інформованості про поширеність захворювання, уточнення прогнозу його розвитку слід використовувати додатковий критерій – рівень кальцитоніну. Рівень базального кальцитоніну є достовірним предиктором метастазування МРЩЗ. Його рівень відсічення 137 пг/мл вказує на можливу наявність метастазів у центральній групі (N1a) (AUC=0,594). Рівень відсічення кальцитоніну – 358 пг/мл (AUC = 0,793) передбачає наявність метастазування МРЩЗ (N1a+N1b). Рівні відсічення кальцитоніну – 358 пг/мл для N1b іпсілатерального, та 498 пг/мл для N1b контрлатерального (AUC: 0,877 та 0,832) відповідно. Розраховані значення контрчутливості тесту на виявлення метастазів для різних рівнів базального кальцитоніну на доопераційному етапі в клінічних умовах допоможуть практикуючому лікарю у прийнятті рішення щодо лікувальної тактики з визначенням обсягу оперативного втручання у хворих з встановленим діагнозом (або підозрою) МРЩЗ.

Ключові слова: кальцитонін, медулярний рак, метастаз, щитоподібна залоза, ROC-аналіз.

лечебно-диагностического поиска являются статистически значимыми (p<0,01). Выявляемость метастазов в центральном лимфатическом коллекторе (N1a) на дооперационном этапе составила 2,08%, этот показатель увеличился вдвое (до 4,16%) после получения интраоперационного экспресс-гистологического заключения, а при получении патогистологического заключения вырос более чем в 10 раз (20,84%). Эта тенденция роста выявления метастазов прослеживалась и по латеральным коллекторам: N1b ипсилатерально наблюдали у 15 (31,2%) больных на дооперационном этапе, их количество увеличилось до 23 (47,9%) интраоперационно и до 31 (64,6%) послеоперационно; N1b контрлатеральные наблюдали у 1 (2,1%), 5 (10,4%) и 7 (14,6%) соответственно. Такой низкий процент обнаружения метастазов на дооперационном этапе методом УЗИ побуждал изучение уровня кальцитонина как предиктора возможного метастазирования. Нами исследовано значение уровней дооперационного базального кальцитонина крови в качестве маркера вероятности наличия метастазов МРЩЖ. Вследствие малой численности группы (n=10) с N1a связь кальцитонина (уровень отсечки 137 пг/мл) с возможным наличием метастазирования была недостаточно весомой (AUC=0,594), тогда как в группе с N1b отмечалась более существенная разница. Так, уровни отсечки кальцитонина 358 пг/мл для N1b ипсилатерального, и 498 пг/мл для N1b контрлатерального обнаружения возможных метастазов в коллекторах, с показателями AUC: 0,877 и 0,832 соответственно, что обосновывает необходимость проведения латеральной диссекции шеи, помимо обязательной центральной, с целью удаления возможных ожидаемых метастазов МРЩЖ. Таким образом, УЗИ является недостаточно надежным методом верификации метастазирования при медуллярном раке щитовидной железы (ДЭ = 35,4% при d mts<0,6 см). При отсутствии УЗ данных (или результатов ТАПБ) о наличии метастазов для повышения информированности о распространенности заболевания, уточнении прогноза его развития следует использовать дополнительный критерий – уровень кальцитонина. Уровень базального кальцитонина является достоверным предиктором метастазирования МРЩЖ. Его уровень отсечки 137 пг/мл указывает на наличие метастазов в центральной группе (N1a) (AUC=0,594). Уровень отсечки кальцитонина – 358 пг/мл (AUC=0,793) предполагает наличие метастазирования МРЩЖ (N1a+N1b). Уровни отсечки кальцитонина – 358 пг/мл для N1b ипсилатерального и 498 пг/мл для N1b контрлатерального (AUC: 0,877 и 0,832) соответственно. Рассчитанные значения контрчувствительности теста для выявления метастазов для разных уровней базального кальцитонина на дооперационном этапе в клинических условиях помогут практикующему врачу в принятии решения по лечебной тактике с определением объема оперативного вмешательства у больных с установленным диагнозом (или подозрением) МРЩЖ.

Ключевые слова: кальцитонин, медуллярный рак, метастаз, щитовидная железа, ROC-анализ.