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Secondary tumours revealed during fine needle aspiration of the thyroid — analysis of prevalence and characteristics of ultrasound image

Nowotwory wtórne ujawniane podczas BAC tarczycy — analiza częstości występowania i charakterystyka obrazu ultrasonograficznego

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Abstract

Introduction: Metastases to the thyroid are revealed at autopsy with a frequency of 2–24%; however, clinically they appear less frequently, at 0.1–3%. The aim of the study was analysis of the frequency of revealing metastases to the thyroid (TM) and to the regional lymph nodes (NM) (neoplasms other than primary thyroid tumours) in preoperative diagnostics of the thyroid in patients with positive (C+) and negative (C–) history of cancer; analysis of ultrasound (US) images of metastases.

Material and Methods: Results of US/fine needle aspiration (FNA) of the thyroid in 1276 C+ patients and 18,947 C- patients.

Results: TM and NM were diagnosed/suspected in 57 patients (0.3% of all examined; 40 TM, 22 NM, 5 both), and their frequency was higher in the C+ group (2.9% *vs.* 0.1% in C–, $p < 0.0001$). In the C+ group, diagnosis of metastasis accounted for 72.3% of FNA results from the category "malignant neoplasm"; in the C– group it was 9.5% ($p < 0.0001$). The highest relative frequency of TM was found for cancers infiltrating thyroid by direct extension (> 10%), lymphomas (7.7%), and kidney (5.3%) and lung (4.9%) cancers. The mean age of patients with metastasis (63.9 ± 11.7 years) was similar to that of the C+ group and higher than the C- group (53.9 ± 14.8 years, $p < 0.0001$). The proportion of males among the patients with metastasis was three-fold higher than in the patients without metastasis ($p < 0.0001$). TM lesions presented suspicious borders in US twice as often as primary cancers .

Conclusions: Metastases to the thyroid are rare; however, for patients with a history of cancer, their presence is more likely than primary thyroid cancer. US/FNA imaging of metastases allows the selection of patients requiring further diagnostics and treatment.

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Key words: *thyroid; metastasis; fine needle aspiration biopsy; ultrasound; thyroid cancer*

Streszczenie

Wstęp: Przerzuty do tarczycy ujawnia się podczas autopsji z częstością 2–24%, jednak klinicznie stwierdza się je rzadziej: 0,1–3%. Celem pracy była analiza częstości ujawniania podczas diagnostyki tarczycy przerzutów do tarczycy (TM) i węzłów chłonnych szyi (NM) (nowotworów innych niż pierwotne tarczycy) u osób z dodatnim (C+) i ujemnym (C–) wywiadem nowotworowym; analiza obrazu ultrasonograficznego przerzutów.

Materiały i metody: Wyniki US/FNA tarczycy 1276 osób z grupy C+ oraz 18947 z grupy C-.

Wyniki: TM lub NM rozpoznano/podejrzewano u 57 osób (0,3% wszystkich badanych; 40 TM, 22 NM, 5 oba), częstość ich ujawniania była wyższa w grupie C+ niż C– (2,9% *vs.* 0,1%, $p < 0,0001$). W grupie C+ rozpoznania przerzutu stanowiły 72,3% wyników FNA należących do kategorii nowotwór złośliwy, w grupie C–: 9,5% ($p < 0,0001$). Najwyższą względną częstość ujawniania przerzutów stwierdzono dla nowotworów naciekających tarczycę przez ciągłość (> 10%), chłoniaków (7,7%), raków nerki: 5,3% i płuca 6,2% (4,9% bez NM). Średni wiek pacjentów z przerzutem: 63,9 ± 11,7 lat był podobny do wieku osób z grupy C+ i wyższy od wieku osób z grupy C– (53,9 ± 14,8, $p < 0,0001$). Odsetek mężczyzn wśród osób z przerzutem był 3-krotnie wyższy niż wśród osób bez przerzutu ($p < 0,0001$). Ogniska TM — 2-krotnie częściej niż pierwotnych raków tarczycy miały podejrzane granice w US.

Wnioski: Przerzuty do tarczycy są rzadkie, jednak u pacjentów z dodatnim wywiadem nowotworowym ich obecność jest bardziej prawdopodobna niż pierwotnych raków tarczycy. Obraz US/FNA przerzutów umożliwia wyodrębnienie pacjentów wymagających dalszej diagnostyki i leczenia. **(Endokrynol Pol 2015; 66 (6): 495–503)**

Słowa kluczowe: *tarczyca; przerzut; biopsja aspiracyjna cienkoigłowa; ultrasonografia; nowotwory złośliwe tarczycy*

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Introduction

Secondary tumours of the thyroid may be a consequence of metastasis from distant organs as well as infiltration of the gland by tumours from adjacent structures. The frequency of revealing such tumours is much higher in autopsy studies than in clinical studies [1]. This is mainly due to the detection of many clinically silent lesions. However, also in the autopsy the frequency of metastases varies from 5% in the general populations to 10% in patients with recognised primary cancer, and even to 24% in patients with widespread malignancy (including patients with lymphomas and tumours infiltrating the thyroid by direct extension from the neighbouring organs) [2–6]. Some authors, following Willis, suggest that the thyroid is protected from the settlement of cancer cells through rapid blood flow within the gland, high partial pressure of oxygen, and high iodine concentration [3]. These factors may cause the gland to become a place of metastasis only at later stages of generalised neoplastic disease.

Metastases to the thyroid are revealed clinically with a frequency of 0.1–3% in patients diagnosed or operated for thyroid nodules/cancer [1, 7–16]. Hegerova et al. found metastases in 97 out of 10,798 (0.9%) patients identified from a database of cytological material archived over 30 years at the Mayo Clinic [17]. Wood et al. revealed them in 15 out of 1016 (1.5%) patients undergoing surgery for malignant disease of the thyroid gland in the period of 17 years [18]. Research carried out in Poland by Cichoń et al. brought similar observations — they revealed 17 cases of secondary tumours in 10,057 patients operated during 20 years due to thyroid disease (0.2%), which accounted for 2.1% of all malignant thyroid neoplasms [19].

It is obvious that the frequency of detection of metastasis to the thyroid depends on the characteristics of the examined population, especially in respect to the incidence of neoplastic diseases and their clinical stage, the age of patients, and the applied diagnostic procedures. Therefore, the aim of our study was to assess the frequency of revealing metastases during the ultrasound (US) and fine needle aspiration biopsy (FNA) of the thyroid in patients with thyroid nodules (TNs) treated at the endocrine outpatient clinic. In addition, a comparison was made of the incidence of metastases in patients with positive (C+) and negative (C–) history of cancer, and ultrasound images of metastases were characterised. Because US and FNA of the thyroid include evaluation of the regional lymph nodes, the frequency of revealing metastases to the lymph nodes (NM) of other-than-primary thyroid carcinomas was also analysed.

Material and methods

The study consisted of a retrospective analysis of the results of US and FNA of the thyroid performed at a single centre in patients referred by physicians of the Endocrinology Outpatient Clinic in the years 2000–2013. In that period examinations were performed in 20,223 patients, including 1276 C+ patients, and 18,947 C– patients. The prevalence of FNA results with the diagnosis or suspected presence of TM or NM (tumours other than primary thyroid cancer — nTC) was determined in both groups. In addition, the frequency of obtaining results considered as an indication for surgical treatment (i.e. malignant neoplasm — MN, suspicious for malignancy — SM, and suspicious for follicular neoplasm — SFN) was compared between the C+ and C– groups. Then, in patients of the C+ group the relative frequency of revealing metastases was determined depending on the type of malignancy they suffered from. Table I presents data on types of malignancy diagnosed in patients of the C+ group. Results of histopathological examination were also analysed in 4032 patients after surgical treatment of the thyroid, who had been diagnosed at our centre. On this basis, part of the cytological diagnoses of TM/NM was verified. Tumours infiltrating the thyroid by direct extension from neighbouring organs and lymphomas were included in the analysis. The details on FNA protocol and cytological outcome classification at our department were reported previously [20]. Surgical thyroidectomy specimens were processed by standard procedures. If necessary, immunohistochemical procedures were applied.

Ultrasonographic images of TM and NM were characterised. In the case of TM the presence of the ultrasonographic malignancy risk features (MRFs) in metastatic lesion was analysed: solid hypoechoic structure, taller-than-wide shape, irregular, blurred margin, intranodular vascularisation, and microcalcifications. The incidence of these MRFs was compared between TM and 250 consecutive benign lesions (BL) of the thyroid as well as 105 primary thyroid cancers (TC) that were diagnosed at our centre in the same period and confirmed histopathologically. In the case of NM the presence of ultrasonographic risk features for metastasis in the lymph node (NRFs) was analysed, such as hypoechogenicity without visible hilum, cystic degeneration, presence of calcifications, suspected shape (thickness > 0.5 length), enlargement (any diameter > 10 mm), and clustering of nodes. Ultrasound examinations were performed with two high-resolution sonographs (Siemens Elegra Advanced, Siemens Medical Systems, Inc., Issaquah, WA, USA, before September 2011, and then Aloka Prosound Alpha 7, ALOKA Co. Ltd., Tokyo, Japan).

Table I. *Characteristics of malignant tumours occurring in patients with a history of cancer (C +) — localisation of tumours, the incidence of metastases to the thyroid or lymph nodes, and sex distribution*

Tabela I. *Charakterystyka nowotworów złośliwych występujących u pacjentów z dodatnim wywiadem nowotworowym (C+) — lokalizacja guzów, częstość ujawniania przerzutów do tarczycy lub okolicznych węzłów chłonnych, dystrybucja płci*

Type/Location of the primary lesion malignancy	Number/% of all cancers	Number/% of men	Number/% of patients with metastasis*	Number/% of men among patients with metastasis
Breast	**408/30.8**	**2/0.5**	**2/0.5** a**	**0/0.0**
Genitourinary system	**383/28.9**	**78/20.4**	**11/2.9 b**	**4/36.4**
Reproductive organ	241	–	6/2.5 b	–
Prostate	39	39/100.0	1/2.6	1/100.0
Bladder	22	7/31.8	–	–
Kidney	76	27/35.5	4/5.3	3/75.0
Others	**5**	**5/100.0**	**–**	**–**
Digestive system	136/10.3	33/24.3	**1/0.8** b	1/100.0
Colorectal	124	31/25.0	1/0.8 b	1/100.0
Liver	9	1/11.1	–	–
Pancreas	3	1/33.3	–	–
Skin	**123/9.3**	**17/13.8**	**–**	**–**
Melanoma	50	4/8.0	–	–
Others	73	13/17.8	–	–
Head and neck	**90/6.8**	**24/26.7**	**9/8.9**	**5/55.6**
Salivary gland	19	4/21.1	2/10.5	0/0.0
Larynx	18	10/55.5	2/11.1	2/100.0
Others — Head	16	0/0	1/6.3	0/0.0
Others — Neck	37	10/27.0	4/10.8	3/75.0
Respiratory system (lung)	**81/6.1**	**24/29.6**	**5/6.2**	**3/60.0**
Blood diseases	**60/4.5**	**14/23.3**	**4/6.7–**	**2/50.0**
Lymphoid tissue	52	11/21.2	4/7.7	2/50.0
Others	8	3/37.5	–	–
Other tumours of the chest and abdomen (including tumours of unknown origin)	**42/3.2**	**1/11.9**	**2/4.8**	**1/50.0**
TOTAL	**1323/100.0**			
Number of patients	1276	185/14.5	34/2.7	18/52.9

*three patients were excluded in whom post-operative histological examination revealed papillary carcinoma (2) and non-neoplastic changes following radioiodine therapy (1); **in one patient with breast cancer the FNA result revealed metastasis of laryngeal cancer; a — $p < 0.0001$ *vs*. those with head and neck cancer; b — $p < 0.005$ *vs*. those with head and neck cancer

In 45 patients (12 males) two neoplasms occurred at the same time. The most frequent coexistences were the occurrence of breast cancer with cancer of the gastrointestinal tract (7), cancer of the reproductive organ (6), lung cancer (4), melanoma (3), and meningioma (2); also occurrence of lung cancer with skin cancer (4), bladder cancer with skin cancer (3), kidney cancer with prostate cancer (3) and meningioma (2), and cancer of the reproductive organ with cancer of the gastrointestinal tract (2) and skin cancer (2). In one person three tumours coexisted (lung cancer, breast cancer, and melanoma). In other cases a single combination of two malignant tumours were observed

Continuous variables (like the age of patients) were analysed with ANOVA and Newman-Keuls tests. The comparison of frequency distributions was performed with chi-square test (or with Yates corrected chi-square test). A value of 0.05 was assumed as the level of significance. The study design was approved by the Local Bioethics Committee.

Results

The results of FNA, in which the presence of TM or NM was diagnosed or suspected, were formulated in 57 patients (25 males, 32 females), who represented 0.3% of all the patients subjected to FNA (Fig. 1). In 40 cases the results concerned TM, and in 22 — NM; in five patients

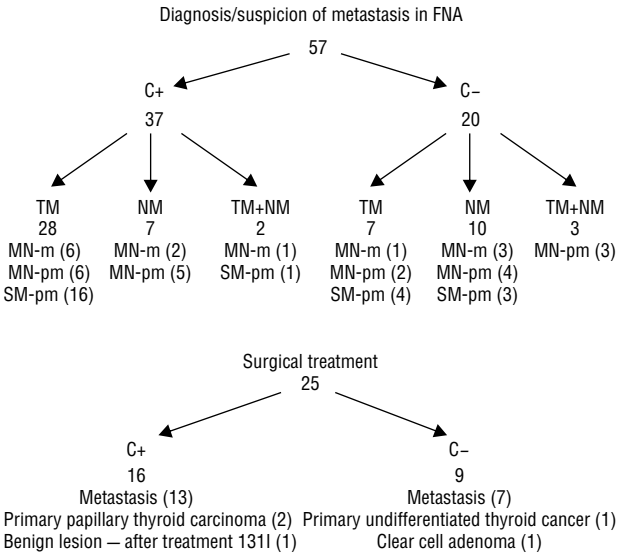

Figure 1. *Characteristics of metastases identified/suspected in FNA in patients with a positive (C+) and negative (C–) history of cancer*

Rycina 1. *Charakterystyka przerzutów rozpoznanych/ /podejrzewanych w FNA u pacjentów z dodatnim (C+) i ujemnym (C–) wywiadem nowotworowym*

Table II. *Characteristics of patients with positive (C +) and negative (C–) history of malignancy, who underwent FNA — comparison of all examined patients and patients with TM or NM diagnosed/suspected*

Tabela II. *Charakterystyka pacjentów z dodatnim (C+) i ujemnym (C–) wywiadem nowotworowym poddanych FNA — porównanie z osobami z rozpoznaniem/podejrzeniem przerzutu*

All examined patients	**Study groups**		**p**
	C+ (n = 1276)	**C– (n = 18 947)**	
Mean age ± SD	63.8 ± 11.1	53.9 ± 14.8	p < 0.0001
No/% of males	185/14.5%	2235/11.8%	p < 0.005
No/% of patients treated with ^{131}I	108/8.5%	1023/5.4	p < 0.0001
No/% of patients after thyroid surgery	216/16.9%	2842/15.0	NS
No/% of patients with FNA result constitutes an indication for surgery	91/7.1%	864/4.6%	p < 0.0001
No/% of patients with cytological diagnosis MN	47/3.7%	211/1.1%	p < 0.0001
No/% of patients diagnosed/suspected of metastasis (TM, NM, TM + NM)	37/2.9%	20/0.1%	p < 0.0001
Patients with TM or NM			
No of metastases	39	23	
No/% of TM	30/76.9%	10/43.4%	p < 0.01
No/% of NM	9/23.1%	13/56.6%	p < 0.01
Mean age ± SD	64.7 ± 11.2	62.1 ± 12.6	NS
No/% of males	18/48.6%	7/36.8%	NS
No/% of patients treated with ^{131}I	3/8.1%	1/5.0%	NS
No/% of patients after thyroid surgery	5/15.6%	4/20.0%	NS

TM — metastasis to the thyroid gland, NM — lymph node metastasis (of cancer other than primary thyroid cancer)

the presence of metastasis was diagnosed/suspected in both localisations (TM + NM). In 13 patients cytological examination accurately identified the presence of metastasis (malignant neoplasm —metastasis: MN-m); in 20 patients the result of FNA included diagnosis of MN without specifying its histogenesis, but with the consideration for metastasis (malignant neoplasm — possible metastasis: MN-pM); and in 24 other patients it corresponded to SM, also with a suggestion of taking into account a secondary tumour (suspicious for malignancy — possible metastasis: SM-pM) (Fig. 1). In 37 (64.9%) cases the diagnosis of metastasis related to C+ patients, and in the remaining 20 (35.1%) cases — to the patients of the C– group. In the C– group the FNA result specified the probable source of metastasis in one case only (of TM), indicating breast cancer.

Surgical treatment was performed, according to medical records, in 25 of 57 patients with metastases. Histopathological examination confirmed the presence of thyroid malignancy in 23 (92.0%) operated patients, and metastasis in 20 of them (13 in the C+ group and 7 in the C– group) — see Figure 1. In the group of 20 patients with surgically confirmed metastasis six patients (30.0%) had metastasis of renal cell carcinoma (3 C+, 3 C–), two had lung cancer (both C+), two had salivary gland cancer (1 C+ 1 C–), two had larynx carcinoma (2 C+), one had ovarian cancer (C+), and one had secondary lymphoma (C+). Six patients (3 C+, 3 C–) had infiltration of the thyroid by direct extension of a tumour from the neighbourhood, including one patient with synchronous tracheal cancer and primary papillary carcinoma.

The frequency of revealing metastasis was significantly higher in the C+ group than in the C– group: 2.9% *vs.* 0.1%, respectively, p < 0.0001 (Table II). TM was revealed more frequently in the C+ group, while NM was observed more frequently in the C– group (p < 0.01). In addition, the C+ group was characterised by higher incidence of FNA results with an indication for surgery (MN, SM, SFN) (p < 0.0001) and the results corresponding to the MN category (p < 0.0001). In the C+ group, both among results indicating surgery and MN diagnoses, the percentage of diagnosed/

/suspected metastases was higher than in the C– group (respectively, 40.7% *vs.* 2.3% and 72.3% *vs.* 9.5%, $p < 0.0001$ in both cases).

The mean age of patients in the C+ group was significantly higher than in the C– group ($p < 0.0001$). The mean age of patients with diagnosed/suspected metastasis was 63.9 ± 11.7 years (mean ± SD, min. 25, max. 83) and was similar in both groups and higher than the average age of the patients of the C– group without metastases ($p < 0.001$). Among the patients with diagnosed/suspected metastasis the percentage of males was more than three times higher than in the patients without such a diagnosis ($p < 0.0001$ in both the C+ and C– groups). In both the C+ and C– groups, the frequency of previous treatment with radioiodine or surgery was similar in patients with TM and other patients (Table II).

Table I provides data on the relative incidence of metastases in patients in the C+ group depending on primary tumour origin. The highest relative frequency of revealed metastases was observed in patients with neck and head cancers (8.9%), and in the case of tumours of the salivary glands, the larynx, and other tumours of the neck (mainly tracheal and oesophageal) the relative incidence of metastasis exceeded 10%. In 7 of 9 (77.8%) cases these tumours infiltrated the thyroid by direct extension from the neighbouring organs: one salivary gland cancer and two cancers of the larynx, the trachea, and the oesophagus each. Furthermore, metastases were most frequent in patients with lymphomas (7.7 % — only TM), kidney cancer (5.3 % — only TM), and lung cancer (6.2 %; after exclusion NM type lesions — 4.9%). Metastases to the lymph nodes — without involvement of the thyroid — were found in seven patients, including six women: four with reproductive system cancers (two — ovarian cancer, two — cervical cancer), one lung cancer, one breast cancer (but the metastasis to the lymph node concerned the cancer of the larynx, of which it was the first sign), and in one male with unidentified primary origin.

The mean interval between the diagnosis of cancer and revealing TM/NM metastasis was 56.3 ± 65.7 months (min: 2, max: 240 months). Six patients out of 57 (10.5%; 4 TM and 2 NM) had symptoms indicating the presence of a malignant tumour in the region of the neck — hoarseness, swelling, rapid nodule enlargement. In 27 patients (67.5%) TM was located in the enlarged thyroid, and in 31 patients (77.5%) TM was one of many lesions/nodules in the gland. Table III shows a comparison of the frequency of MRFs in TM and lesions corresponding to BL and TC. It was found that both primary and secondary malignant tumours of the thyroid showed the presence of more than one MRF more often than BL. In particular, the TM and TC had pathological vascularisation several times more frequently than BL; they were two and three times more likely to contain microcalcifications, respectively, and were more often hypoechoic. TM differed from the primary tumours of the thyroid gland, both benign and malignant, with more than two-times higher incidence of blurred, irregular borders. The smallest lesion of TM was 0.17 cm^3 in volume, the largest one was 175 cm^3; due to the blurred borders of the lesions we often could not accurately determine the size of the TM. The lymph nodes with metastasis in 20 of 22 (90.9%) patients were enlarged and hypoechoic. In seven (31.8%) patients they formed packets, in six patients (27.2%) they were characterised by an irregular shape, in three (13.6%) patients they contained calcifications, and in one patient (4.5%) they showed features of cystic degeneration and had suspected shape.

Table III. ***Comparison of the incidence of ultrasonographic malignancy risk features (MRFs) in lesions corresponding to metastasis to the thyroid gland (TM), benign lesion (BL), and primary thyroid cancer (TC)***

Tabela III. ***Porównanie częstości występowania ultrasonograficznych cech ryzyka złośliwości (MRF) w ogniskach odpowiadających przerzutom do tarczycy (TM), zmianach łagodnych (BL) i ogniskach pierwotnych raków tarczycy (TC)***

MRFs	No/%			p
	TM* (n = 26)	BL (n = 250)	TC (n = 105)	
Hypoechogenicity	26/100.0	177/70.8	95/90.5	$p < 0.005$ TM *vs.* BL $p < 0.0001$ TC *vs.* BL
Pathological vascularisation	13/50.0	23/9.2	55/52.4	$p < 0.0001$ TM *vs.* BL $p < 0.0001$ TC *vs.* BL
Blurred, irregular borders	10/38.5	36/14.4	15/14.3	$p < 0.005$ TM *vs.* BL $p < 0.005$ TM *vs.* TC
Micro-calcifications	8/30.8	36/14.4	48/45.7	$p < 0.05$ TM *vs.* BL $p < 0.0001$ TC *vs.* BL
Thickness ≥ width	4/15.4	24/9.6	18/17.1	$p < 0.05$ TC *vs.* BL
> 1 MRF	21/80.8	79/31.6	73/69.5	$p < 0.0001$ TM *vs.* BL $p < 0.0001$ TC *vs.* BL

*included only cases with complete data from ultrasound

Discussion

The first description of metastasis to the thyroid gland was published in the nineteenth century [1]. Currently, the total number of clinically revealed and described metastases stands at 1500, but data from individual centres typically involve only a few to tens of patients

Table IV. *Metastases to the thyroid gland in the clinical trials of various centres — publications over the last 20 years dedicated to the evaluation of the most frequent location of the primary tumour with at least 10 cases of metastases*

Tabela IV. *Przerzuty do tarczycy w badaniach klinicznych różnych ośrodków – publikacje z ostatnich 20 lat poświęcone ocenie najczęstszej lokalizacji ogniska pierwotnego z minimum 10 przypadkami przerzutów*

Authors	Country	Years	Method: FNA/CNB/HE	No of cases	Age (mean, min, max) (years)	% of men	The most common primary focus	Time to reveal metastasis (min., max.) (months)
Nakhajavani et al. [11]	US	1985–1994	FNA/HE	43	66 47–86	46.5	Kidney	1–312
Lam et al. [3]	China	1971–1996	FNA	79	62 12–94	48.1	Lung	0–84
Chen et al. [9]	US	1986–1994	HE	10	58 48–70	70.0	Kidney	0–234
Wood1 et al. [8]	United Kingdom	1985–2002	HE	15	63 26–76	33.3	Kidney	0–180
Kim et al. [12]	Korea	1997–2003	HE	22	55 34–74	27.3	Breast	8–180
Mirallié et al. [27]	France	1982–2002	FNA/HE	29	62 41–78	48.3	Kidney	0–192
Aron et al. [15]	India	1982–2002	FNA	24	nd 28—72	70.8	Continuity/Lung*	nd
Cichoń et al. [19]	Poland	1984–2003	HE	17	62 46–76	23.5	Kidney	2–204
Papi et al. [8]	Italy	1993–2003	FNA/HE	46	64 48–89	47.2	Lung	nd
Calzolari et al. [13]	Italy	1995–2005	HE	25	61 42–77	56.0	Kidney	0–215
Nixon et al. [44]	US	1986–2005	HE	21	68 39–83	57.1	Kidney	0–195
Hegerova et al. [17]	US	1980–2010	FNA/HE	97	60 22–86	45.4	Kidney, Lung	2–240
Moghaddam et al. [6]	US	1993–2013	FNA/HE	10	59 43–75	30.0	Lung	0–72
Pusztaszeri et al. [14]	US/ Switzerland	1992–2014	FNA	62	59 34–84	45.2	Continuity/ Kidney*	0–156
Romero-Arenas et al. [28]	US	2000–2011	FNA/HE	90	61 28–79	48.9	Kidney	0–210
Yoon et al. [30]	Korea	2003–2009	FNA/CNB/HE	23	66.7 46–85	56.5	Lung	0–192
Our results, this study	Poland	1994–2013	FNA/HE	57	64 25–83	43.9	Continuity/ Kidney*	0–240

HE — histopathological examination, FNA — fine needle aspiration biopsy, CNB — core needle biopsy; nd — no data; *after exclusion of cases with direct extension of tumour from primary lesions in the head and neck and/or lymphomas

(Table 4). It is usually indicated that the primary tumour for metastases is located in the kidney, breast, lung, or large intestine [1, 7–10, 12–14, 21–23]. However, it is difficult to reliably determine which of these tumours dominates, due to differences between studied populations in the incidence of these cancers and the variety of diagnostic methods applied to reveal metastases. If analysis is based on the results of postoperative histopathological examination, it should be taken into consideration that not all patients with clinically revealed metastasis receive surgical treatment. Early diagnosis including a thyroid FNA result allows the avoidance of unnecessary thyroid surgery in some cases. On the other hand, when analysis is mainly based on biopsy results, the limitation is a frequent impossibility to distinguish primary, especially non-differentiated, thyroid cancers from secondary tumours [11, 14, 23–25]. In such cases the FNA result indicates only the need to take into account

metastasis in differential diagnosis. However, the current indications for biopsy, based on the results of US [26], lead to more frequent exposure of metastases in a phase when they are clinically asymptomatic.

Our study relates to patients diagnosed for a thyroid disease in an endocrine outpatient clinic, in whom a routine ultrasound examination was performed, with subsequent biopsy of revealed lesions. Oncological patients represented only 6.3% of that population, in contrast to centres specialising in the diagnosis and treatment of cancers that present many reports on metastases to the thyroid gland [13, 27–28]. Probably for this reason, in our study the percentage of patients with secondary cancer (0.3%) was lower than in typical oncological centres, and similar to that found in centres involved in the diagnosis of thyroid disorders [15, 25] and in general centres (non-specialised) [8] (Table IV). Regardless of that fact, our data showed regularity in higher risk of metastasis in patients with malignant disease than in those with negative history of cancer. Moreover, according to our observations, in patients with cancer the probability of metastasis in the thyroid is more than three-times higher than the probability of primary cancer. Similar results were reported by Shimaoka et al. [7]. Therefore, in our opinion, the appearance of a new nodule in the thyroid in patients with (non-thyroid) cancer should be regarded as a potential metastasis and considered as an indication for FNA.

Another feature that distinguishes our population is a high proportion of women, resulting from the epidemiology of thyroid diseases. This affected the type of cancer found in our patients — half of them had breast cancer or reproductive organ cancer. However, these tumours were responsible for only 10% of metastases to the thyroid gland and/or lymph nodes. In a group of over 400 patients with breast cancer metastasis to the thyroid gland was found in only two patients (< 1%). Similarly, Mirallié et al. (2005) in a group of 29 patients with metastasis to the thyroid gland did not find any case of breast cancer metastasis [27]. After taking into account the relative frequency of metastases (in relation to the number of patients subjected to FNA with a specific cancer) we observed that the dominant type of metastases was a tumour infiltrating the thyroid by direct extension from the neighbouring primary lesion. Also other authors showed that tumours of the head and the neck were the most common [14–15] or frequent [8] source of metastasis. However, most of the authors limited their analyses to metastases from distant organs only. They also excluded lymphomas, for which it is difficult to judge whether the process is primary or secondary. After applying such a model to our data, the dominating sources of metastases were kidney and lung cancers — as seen in many other reports (Table IV). It should be noted that in many published studies the influence of the relative frequency of particular cancers in an examined population was not analysed. Thus, in such studies frequent sources of metastases to the thyroid gland also included breast cancer and gastrointestinal tract cancers [10, 12, 16]. In our study metastasis of malignant tumours of the gastrointestinal tract were rare and concerned (like metastasis of breast cancer) < 1% of patients with those tumours.

Among patients with metastases the percentage of males was much higher (more than 40%) than in the group of all patients with cancer (about 15%). It probably shows a higher predisposition for cancers that more readily spread to the thyroid gland among males. Actually, cancers of the larynx, lungs, and kidneys are significantly more common in males (in Poland: 86%, 68%, and 58% of cases in 2011, respectively) [29]. But this explanation is not complete as the percentage of males among patients with metastases of those tumours was two-times higher than that among all the patients with these tumours subjected to FNA (Table I). Similarly, in other studies [14, 17, 28, 30] males constituted 40%–50% and even more than 70% [15] of patients with metastasis to the thyroid gland. It should also be stressed that the percentage of males among patients with secondary thyroid tumours was much higher than the percentage of males among patients with primary thyroid cancers, which in our data was 11% [31].

The mean age of patients with metastases to the thyroid gland in our study was 64 years and was higher than the average age of all patients referring for FNA at our centre, and close to the average age of those with a cancer-positive history. Similarly, other authors indicate that metastases to the thyroid gland usually involve people in the 6th–7th decade of life [8, 11, 14, 32]. On the other hand, the youngest patient with metastasis in our study was 25 years old (infiltration of the thyroid was the first sign of cancer), and Pusztaszeri et al. showed clear cell sarcoma metastasis in a seven-year-old child [14].

Our observations and data from other centres indicate that the time lapse from diagnosis of malignant disease to revealing metastasis to the thyroid gland can be very diverse and can range from a few weeks to more than 40 years [9, 11, 13, 18, 33–36]. On the other hand, in 35% of our cases metastasis was the first sign of cancer. As already mentioned, this was due to the routine use of US in all patients with thyroid disease, including patients without palpable thyroid nodules. Similar data were also presented by other authors (Table IV). However, the diagnosis of metastasis to the thyroid gland is usually delayed due to the lack of specific symptoms. Symptoms such as hoarseness, dyspnoea, dysphagia, and rapid enlargement of nodules are rare

and uncharacteristic [18]. In our study, only six patients presented features of malignant thyroid nodule. In the material of the Mayo Clinic only three out of 97 patients with metastases to the thyroid complained of hoarseness, dyspnoea, or rapid growth of the lesion [17]. According to the review published by Chung et al., 253 out of 338 patients presented symptoms such as: new or enlarged thyroid nodule, increasing size of the thyroid, swelling of the neck, dysphagia, dysphonia, and cough [10] — but not all of these symptoms are typical of thyroid cancer. Nakhajavani et al. reported that the longest period between the diagnosis of the primary tumour and metastasis detection was 26 years [11] and in a study by Kim et al. it was 15 years. [12]. In both of those cases the origin of the metastasis was kidney cancer. Other authors also indicate that in the case of renal cell carcinoma spreading to the thyroid gland may take a long time [14]. In our analysis, similarly, renal cell carcinoma was a source of metastasis to the thyroid 20 years after the initial diagnosis.

It should be noted that, despite the outlined above limits of cytology, FNA allowed the accurate diagnosis of metastatic disease in 80.0% of patients in the group undergoing surgical treatment, and to formulate the suspicion or diagnosis of a malignant neoplasm in as many as 92% of those patients. Similarly, other authors indicate that FNA did not always accurately diagnose metastatic disease, but it identified a thyroid malignancy in approximately 90% of cases [8, 14–15, 37–39]. Clinical data about the occurrence of cancer in a patient can help in precise cytological diagnosis [14, 25]. In the absence of such data the result usually suggests suspicion or diagnosis of malignant tumour - as in our material in the C– group.

In some publications attention is drawn to the presence of metastases particularly in patients with morphological changes within the gland [10, 16, 34]. In our material approximately 80% of the metastases were one of many nodules in the gland, accompanied by other focal lesions. In one case postoperative histopathological examination revealed the concurrent occurrence of papillary thyroid carcinoma and secondary squamous cell carcinoma. Similarly, Young et al. published a case of a patient diagnosed with both papillary thyroid cancer and metastasis of prostate cancer [40]. Interestingly, Hashimoto et al. revealed metastasis of lung adenocarcinoma to the follicular variant of papillary carcinoma [41], and Kameyama et al. and Pusztaszeri et al. described metastases to follicular adenoma [14, 42]. It is possible that the presence of thyroid pathology facilitates tumour cells settlement in the thyroid gland. Moreover, it is suggested that even disruption of the thyroid tissues, changes in blood flow in the gland, or changes in the intrathyroid iodine concentration may promote the formation of secondary tumours [12]. Our data showed no significant relationship between previous thyroid surgery or radioiodine treatment and the incidence of metastasis in the thyroid.

We found that metastases more often than primary thyroid tumours had irregular and blurred margins. In addition, similarly to primary thyroid cancers and more often than benign lesions, metastases had more than one ultrasonographic risk feature of malignancy. In the literature the typical ultrasound image of secondary tumours is not specified. The most commonly reported are heterogeneous, hypoechoic lesions with blurred margins, often with calcifications [23] or without them [30]. In our material metastatic tumours presented calcifications twice as often as benign lesions, while primary tumours showed calcifications three times more often than benign lesions. It should be noted that initially metastatic lesions have no characteristic clinical manifestation and ultrasonographically may be similar to frequent benign thyroid nodules. The lymph nodes with metastases were characterised by enlargement, hypoechogenicity, heterogeneity of the structure, the presence of calcification, and a tendency to create packages. These are features similar to those described in lymph nodes with primary thyroid cancer metastases [43].

In conclusion, metastases to the thyroid gland are rare. However, for patients with a history of cancer, their presence is more likely than primary thyroid cancers. The probability of revealing metastases during diagnostics of the thyroid is highest in patients with neighbouring cancers that may invade the thyroid by direct extension, as well as in patients with lymphoma and cancers of the lung or kidney. Less frequently metastases to the thyroid are found in patients with breast or colorectal cancer. It should be emphasised that the ultrasound and cytological image of metastases is not specific, but it usually allows the identification of patients requiring further diagnostics and treatment.

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