The fine-needle aspiration biopsy efficacy of small thyroid nodules in the area of recently normalized iodine supply

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Abstract

Objective: To evaluate the incidence of focal lesions in the thyroid in the area of recently normalized iodine supply as well as to compare the efficacy of fine-needle aspiration biopsy (FNAB) of small (infracentimetric) and large thyroid lesions in this area.

Methods: The outcomes of 13,646 ultrasound (US) examinations, 13,437 US-guided FNABs of the thyroid and 1694 results of post-operative histopathological examinations were analysed.

Results: Infracentimetric nodules (INs ≤ 10 mm) were revealed by US examinations in 43.5% of patients; in the majority of the cases (82.2%) INs were multiple. The percentage of revealed carcinomas by aspiration of INs is similar to that observed when large nodules (LNs > 10 mm) are examined cytologically. However, the efficiency of preoperative diagnosis of INs is lower than LNs with respect to both US selection of lesions for FNAB and the percentage of false negative results of FNAB (29.8 vs 5.4%, P < 0.001). In post-operative histopathological examination, extrathyroidal extension of thyroid cancers was observed in nearly 30% of microcarcinomas.

Conclusions: In endemic or post-endemic areas, the efficiency of FNAB is lower in the case of small lesions than larger ones. In spite of this, the percentage of cytologically revealed carcinomas among small lesions is not lower than larger ones. Thus, it is particularly indicated to follow up small thyroid lesions with repeated US examinations in such areas.

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Introduction

Thyroid nodules can be revealed by palpation in 4–7% of adult patients in the areas of sufficient iodine supply, and in 10–15% in the areas of mild to moderate iodine deficiency (1–3). The use of ultrasound (US) imaging raises ten times the rate of discovering thyroid lesions in comparison with palpatory examination (4–6). Many of these lesions do not exceed 10 mm in diameter. The increasing number of revealed thyroid nodules in many medical centres leads to the growing number of lesions examined cytologically, in spite of the current recommendations of the American Association of Clinical Endocrinologists (AACE), American Thyroid Association (ATA) and European Thyroid Association (ETA) (7–9). These recommendations do not indicate US as a screening for thyroid nodules and advise in patients without increased risk of cancer to perform US-guided fine-needle aspiration biopsy (FNAB) of only selected non-palpable lesions smaller than 10 mm. However, some recent papers have brought convincing data on the high percentage of carcinomas (some of them with extrathyroidal invasion) in small lesions subjected to FNAB (10–14). The majority of these reports come from the countries with natural high iodine supply (Japan, Korea) or those with long-established iodine prophylaxis. The data on the effectiveness of FNAB of small lesions in iodine-deficient areas or areas with newly corrected iodine supply are rather scarce. In such areas, the thyroid lesions are non-neoplastic in the vast majority and are usually multiple (15, 16). In Poland, iodine prophylaxis had been started in the 1930s and continued (with an interruption during World War II) until 1980, when it was dropped for economical reasons. In the years 1992–1993, a nationwide study, performed in about 20,000 schoolchildren, showed that Poland was an area of mild or moderate iodine deficiency (17). Thus, obligatory iodine prophylaxis using household salt iodized with 30 ± 10 mg KI/kg was established in 1997. Until now, a bulk of data has been accumulated confirming the effectiveness of iodine supplementation in Poland (18).

The aim of this paper is to evaluate the incidence of focal lesions in the thyroid with respect to their size, echogenicity and single versus multiple occurrences in the area of recently normalized iodine supply in the patients of an endocrinological outpatient clinic. The other goal is to compare the efficacy of FNAB of small and large thyroid lesions in diagnosing thyroid cancers in this area.
Materials and methods

The outcomes of 13,646 US examinations and 13,437 FNABs of the thyroid were analysed, which had been performed in our department in the years 2000–2005 in patients referred by endocrinologists from outpatient clinics. US examinations were performed in nearly all patients with the suspicion of any thyroid disturbance (palpable nodule, goitre, functional disturbances, previous laboratory or US findings). FNAB was performed in patients with palpable nodules or focal thyroid lesions revealed in US examination (with diameter of at least 5 mm). In multinodular goitre one to four lesions were biopsied, usually dominant or malignancy suspected nodules – hypoechoic or containing small calcifications or presenting with irregular blurred margins or with increased blood flow. In the cases with multiple lesions of a similar picture, one or two of the largest lesions were biopsied. All the US examinations were performed with the same equipment, namely Elegra Advanced (Siemens) with a 7.5 MHz linear transducer and power Doppler capability. Its state-of-the-art technology allows visualization of tiny lesions within the thyroid (their diameter ≥ 1 mm) and aids aspirating very small lesions (more specifically, the lesions thinner than 5 mm were not examined). All the biopsies were US guided. In order to obtain a sufficient amount of diagnostic material, usually two or three aspirations of each examined lesion were performed. Ten millilitre syringes, mounted in the aspirating syringe holders with 25 gauge (0.5 or 0.42 mm) needles were used in the process. In the case of cystic lesions the cytocentrifugation technique was employed for aspirate preparation, enabling the cell condensation from any residual material which was left in the syringe. All smears were fixed in 95% ethanol and stained with haematoxylin and eosin.

At the first stage of our study, the frequency of lesions revealed in US examination was assessed with respect to their size and single versus multiple occurrences in goitre. The lesions were divided into infracentimetric nodules (INs) – the lesions with the maximal diameter not exceeding 10 mm, and large nodules (LNs) – the lesions with the maximal diameter exceeding 10 mm. The assessment included the outcomes of 2742 US examinations performed in 2004 (the year with the highest number of US thyroid examinations at our department), in each case by a physician with several years of experience. The echogenicity and echostructure of the lesions was also evaluated.

Then the analysis of 1000 lesions, successively examined by FNAB in 2004, was performed to find the rates of INs and LNs between biopsied lesions as well as to establish the frequency of obtaining non-diagnostic specimens in both groups of lesions.

Next, the contribution of IN and LN lesions into the FNAB outcome categories was assessed. The evaluation included all malignant and suspected lesions diagnosed cytologically in the years 2000–2005, as well as 500 successively examined benign lesions and 200 successive lesions with non-diagnostic cytological outcome. Only the lesions with ascertained length, width and thickness were analysed. The guidelines of the Papanicolaou Society of Cytopathology were accepted as the criteria for non-diagnostic smears (19). The category ‘benign lesions’ included the outcomes with ‘benign lesions’ in conclusion or with ‘nodular goitre’, ‘thyroiditis’ or ‘thyroid cyst’ diagnosed – apart from haemorrhagic cysts. The category ‘suspected lesions’ included the outcomes with ‘follicular neoplasm/tumour’, ‘oxyphilic neoplasm/tumour’ and with disturbing, hardly diagnosable cytological picture – ‘unclassified suspected lesions’. The category ‘malignant lesions’ included the outcomes with malignant tumour diagnosed. The precise methods of classifying FNAB outcomes into categories were fully described previously (16, 20).

Finally, the cytological outcomes were compared with the results of post-operative histopathological examination of the thyroid. The thyroid surgeries were performed at several clinics in our city and, in general, the patients were referred to surgical treatment by endocrinologists from outpatient clinics. Histopathological outcomes were analysed only for the patients treated surgically within 12 months of FNAB. The incidence of non-neoplastic lesions, benign neoplasms and malignant tumours (including TNM classification) was assessed in the operated patients. The number of false negative (FN) FNABs in relation to the size of malignant lesion was examined with special emphasis placed on the diagnosis of thyroid microcarcinoma. The diagnostic value of FNAB (with the exclusion of non-diagnostic outcomes) was assessed in terms of sensitivity, specificity, positive and negative predictive values. In the specific epidemiological situation in Poland, with relatively recent iodine prophylaxis, the risk of cancer – if follicular neoplasm has been discovered with FNAB – is lower than in the case of other suspected lesions (16). Thus, three different definitions of false positive (FP) diagnosis were applied: i) the case of either suspected or definite malignancy in cytology, which was benign in histopathology; ii) from the set defined as above, all lesions of ‘follicular neoplasm/tumour’ cytological subcategory were excluded and treated as negative results (with respect to malignancy diagnosis); iii) ‘follicular neoplasm/tumour’ were excluded from analysis.

Continuous variables (like the age of patients) were analysed with ANOVA and Newman–Keuls test. The comparison of frequency distributions was performed with χ² test. The value of 0.05 was assumed as the level of significance.

Results

Focal lesions in the thyroid gland were found in 77.0% of the patients (2112/2742) subjected to US
examination during the analysed year 2004 (Table 1). INs were revealed in 43.5% of all patients (1194/2742). In the majority of these patients (82.2%), INs were accompanied by other lesions: in 48.9% of the cases (583/1194) by other INs and in 33.3% of the cases (398/1194) by LNs. LNs were found in 37.7% of the examined patients (1035/2742) and were solitary in 25.1% of the cases (260/1035).

INs in comparison with LNs were significantly more frequently normoechoic and hypoechoic (19.2 vs 5.4%, \(P<0.0001\) and 51.6 vs 41.9%, \(P<0.05\) respectively) and less frequently in homogeneous or mixed echostucture (16.9 vs 49.6%, \(P<0.0001\)).

There were no significant differences in the average age between the patients with INs and the patients with LNs. The average age of all patients was 54.3 ± 14.6 years (\(\bar{x}\pm S.D\)). Among the examined persons, females predominated over males (89.4 vs 10.6%).

The analysis of 1000 subsequently biopsied lesions showed that LNs constituted 65.3% and INs 34.7%. The non-diagnostic specimens were obtained from 12% of all lesions, and the percentage of the non-diagnostic outcomes did not differ significantly between LN and IN (Table 2).

Analysis of all FNABs performed in the years 2000–2005 showed that diagnostic material from at least one of the examined lesions was obtained in 93.6% (12 579) of examinations (Table 3). Among diagnostic outcomes, as many as 94.5% (11 894) were categorized as benign lesions. Such a high percentage of these outcomes was the result of frequent, one or two control FNABs in patients with benign lesions (usually every 12–18 months). Suspected lesions were diagnosed in 611 of the analysed FNAB outcomes (4.5%). Among those outcomes, 287 (47.0%) diagnoses were of "follicular neoplasm/tumour", 107 (17.5%) "oxyphilic neoplasm/tumours" and 217 (35.5%) "unclassified suspected lesions". The suspected lesions were diagnosed in 605 patients, where in six of them FNAB was performed twice, and both cytological outcomes revealed unclassified suspected lesions in each case. The malignant lesions were diagnosed in 74 patients. There were 48 papillary cancers, 2 follicular cancers of oxyphilic cell type, 9 medullary cancers, 7 undifferentiated cancers, 2 metastases to the thyroid gland (of oat cell cancer and prostatic cancer) and 6 cancers of unknown origin. The percentage of males in the group of patients with thyroid cancer was higher than in the groups with other thyroid lesions (24.3 vs 10.1%, benign lesions; 10.0%, suspected lesions of follicular neoplasm/tumour type; 10.3%, suspected lesions of oxyphilic neoplasm/tumour type, 9.8%, unclassified suspected lesions; 13.6%, non-diagnostic FNABs; \(P<0.0001\) in all cases). The average age of all patients subjected to FNAB was 56.4 ± 13.8 years (\(\bar{x}\pm S.D\).), the youngest patient was 10 and the oldest being 85. The average age of patients with malignancy in FNAB was significantly lower than that of patients with benign lesions (54.2 vs 57.7, \(P<0.05\)) and that of patients with non-diagnostic biopsies (59.1, \(P<0.005\)).

The comparison of the FNAB outcomes and the categories of lesions’ sizes showed that the occurrence of LNs and INs between outcomes categorized as the malignant lesion or the benign lesion was similar and proportional to the numbers of biopsied nodules of each size class (Table 4). More than 30% of the cancers diagnosed using FNAB were found in infracentimetric lesions; it corresponded to the frequency of biopsying those lesions which constituted above 30% of all cytologically examined nodules. In contrast, within the outcomes categorized as ‘follicular neoplasm/tumour’, ‘oxyphilic neoplasm/tumour’, ‘unclassified suspected lesion’ or ‘non-diagnostic’ LN were found more frequently than in the total examined groups, and particularly more frequently than in the ‘benign lesion’ group (84.9%, 77.2%, 73.8%, 72.0% vs 63.6%, \(P<0.0001\), \(P<0.01\), \(P<0.01\), \(P<0.05\) respectively). Among diagnosed thyroid malignant tumours, smaller than 10 mm, papillary cancers predominated (19 cases), followed by four medullary cancers and one cancer of unknown origin.

The analysis of the post-operative histopathological outcomes comprised 1694 operated patients (the average age ± s.d.: 51.5 ± 12.8 years). Only 294

| Table 1 | The frequency of revealing thyroid focal lesions with respect to their size and single versus multiple occurrence (based on the analysis of all ultrasound (US) examinations performed in year 2004). |
|---|---|---|---|
| Size category of lesions found in the thyroid | Number of patients | % of examined patients (2742) | % of patients with focal lesions (2112) | % of patients with IN (1194) |
| Single LN | 213 | 7.8 | 10.1 | 17.8 |
| Multiple LN | 583 | 21.2 | 27.6 | 48.8 |
| Both LN and larger | 398 | 14.5 | 18.8 | 33.4 |
| All patients with IN | 1194 | 43.5 | 56.5 | 0.0 |
| Single LN | 260 | 9.5 | 12.3 | 0.0 |
| Multiple LN | 377 | 13.7 | 17.8 | 0.0 |
| Any nodule | 2112 | 77.0 | 0.0 | 0.0 |

| Table 2 | Number and percentage of non-diagnostic aspirates in relation to the size of lesion – evaluation of 1000 subsequently biopsied lesions. |
|---|---|---|
| Cytological material | LN | IN |
| Diagnostic | 568–64.5% | 312–35.5% | 880–100% |
| Non-diagnostic | 87.0% | 89.9% | 88.0% |
| Total | 653–65.3% | 347–34.7% | 1000–100% |
| Size of lesion | 100% | 100% | 100% |

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(17.4%) patients were subjected to surgery for findings suggestive of malignancy in thyroid FNAB. Others were referred to surgeons mainly because of large goitres or nodular goitres with numerous palpable nodules. In 79.6% of the surgically treated patients (1349/1694) non-neoplastic lesions in the thyroid were found, in 13.3% of the patients (225/1694) benign neoplasms were diagnosed and in 7.1% (120/1694) malignant neoplasms. Among malignant neoplasms, papillary carcinomas prevailed in 93 (77.5%) patients. The comparison of the histopathological results and the corresponding cytological outcomes is shown in Table 5.

The percentage of malignant tumours in the group of the lesions diagnosed cytologically as ‘benign lesion’ was 2.4%, ‘suspected lesions of follicular neoplasm/tumour type’ was 4.3%, ‘suspected lesions of oxyphilic neoplasm/tumour type’ was 15.6% and ‘malignant lesions’ was 95.5%. In two out of three FP with FNAB outcomes classified as ‘malignant lesion’, papillary carcinoma was diagnosed in patients with trabecular hyalinising adenoma.

In Table 6 the data are presented on sensitivity, specificity and predictive value of FNAB outcomes for all versions of categorization of the outcomes as positive or negative with respect to thyroid cancer diagnosis. The exclusion of ‘follicular neoplasm/tumour’ results from the group of outcomes positive for cancer diagnosis (second and third version of the analysis) caused negligible decrease in sensitivity and almost double increase in positive predictive value. However, it caused a twofold increase in the number of undiagnosed cancers of >10 mm (from three to six cases) and a 15% increase in the case of infracentimetric cancers (from 14 to 16 cases). The negative predictive value remained high – above 97% – irrespective of the version of the analysis.

Among the malignant tumours were 58 (48.3%) cancers corresponding to LN and 62 cancers diagnosed in IN (51.7% of all malignant neoplasms). Those infracentimetric cancers included 58 papillary cancers, 1 follicular cancer of oxyphilic cell type and 3 medullary cancers. Out of 47 (75.8% of the infracentimetric cancers) examined by FNAB, 33 cases (70.2%) were cytologically diagnosed as malignant neoplasms or suspected lesions (Table 7). In 15 patients with infracentimetric cancers, not examined cytologically, larger coexisting lesions were biopsied during FNAB. In the group of cancers with diameters over 10 mm (including 35 papillary cancers, 5 follicular cancers of oxyphilic cell type, 2 follicular cancers, 9 medullary cancers, 5 anaplastic cancers and 2 metastases), 56 out of 58 tumours (96.6%) were biopsied, and in 53 cases the outcome was categorized as malignant or suspicious (94.6%). In two non-biopsied cases, some other lesions in multinodular goitre were aspirated as the lesions with cancers did not present any suspicious features in US images. Among the cancers subjected to FNAB, the
percentage of misdiagnosed cancers was significantly higher in the group of carcinomas not exceeding 10 mm than in the group of larger carcinomas, independently on the classification of 'follicular neoplasm/tumour' outcomes as positive or negative for malignancy – first version: 29.8 (14 cases) vs 5.4% (3 cases), \( P!0.001 \); second version: 34.0 (16 cases) vs 10.7% (6 cases), \( P!0.001 \). In one case, misdiagnosis of a cancer larger than 10 mm, despite the correct selection of the lesion for biopsy, resulted from non-diagnostic specimens (the patient was not referred to the second FNAB). In another case, the explanation for the FN result may be the 11 months that elapsed between FNAB and the surgery in the patient with metastasis of kidney cancer to the thyroid. In the third case, the repeated evaluation of cytological specimens revealed some features that might be suggestive of papillary cancer, but within a dominating picture of chronic thyroiditis. A similar cause of FN cytological outcome was found in two cases of papillary microcarcinoma, but in the other cases of misdiagnosed cancers \( \leq 10 \) mm no errors in the evaluation of cytological specimens were found.

Table 5 Comparison of cytological outcomes with results of post-operative histopathological examinations (analysed only for patients treated surgically within 12 months of fine-needle aspiration biopsy, FNAB).

<table>
<thead>
<tr>
<th>Categories of cytological outcomes</th>
<th>Benign non-inflammatory lesions</th>
<th>Inflammatory lesions</th>
<th>Benign neoplasms</th>
<th>Malignant neoplasms</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign lesion</td>
<td>1145</td>
<td>45</td>
<td>139</td>
<td>33</td>
<td>1362</td>
</tr>
<tr>
<td>Suspected lesion of follicular neoplasm/tumour type</td>
<td>62</td>
<td>2</td>
<td>47</td>
<td>5</td>
<td>116</td>
</tr>
<tr>
<td>Suspected lesion of oxyphilic neoplasm/tumour type</td>
<td>23</td>
<td>5</td>
<td>12</td>
<td>8</td>
<td>48</td>
</tr>
<tr>
<td>Unclassified suspected lesion</td>
<td>39</td>
<td>2</td>
<td>13</td>
<td>10</td>
<td>64</td>
</tr>
<tr>
<td>Malignant lesion</td>
<td>–</td>
<td>–</td>
<td>3</td>
<td>63</td>
<td>66</td>
</tr>
<tr>
<td>Non-diagnostic aspirates</td>
<td>25</td>
<td>1</td>
<td>11</td>
<td>1</td>
<td>38</td>
</tr>
<tr>
<td>Total</td>
<td>1294</td>
<td>55</td>
<td>225</td>
<td>120</td>
<td>1694</td>
</tr>
<tr>
<td>Females/males</td>
<td>1178/116</td>
<td>55/–</td>
<td>186/39</td>
<td>106/14</td>
<td>1525/169</td>
</tr>
</tbody>
</table>

The features of invasiveness, such as extracapsular growth or spread to the lymph nodes, were present in 34.4% of the cancers (31 out of 90 cancers – excluding the cases without histopathological evaluation of lymph nodes), and they were more frequent in the case of larger tumours – LN versus IN – 38.1 (25/59) vs 28.6% (10/31); \( P!0.05 \). Two cases of invasive cancers \( \leq 10 \) mm and one case of larger invasive cancer were not subjected to FNAB. The invasive cancers related to hypoechoic lesions more frequently than other malignant nodules – 75.8 vs 47.6%; \( P!0.05 \). These differences were even more noticeable in the IN group – all small invasive cancers were hypoechoic in the US examination. The other US features (presence of microcalcification, irregular, blurred margins or increased blood flow) did not differ significantly between invasive cancers and those limited to the thyroid gland.

The average age of the operated patients with thyroid neoplasms (both malignant and benign) was significantly lower than that of the patients with non-neoplastic lesions (49.8 vs 52.0; \( P!0.01 \)), and the percentage of males was higher in the group with neoplasms (15.4 vs 8.6%, \( P!0.0005 \)). No significant differences were found in the average age or gender of the patients between groups with thyroid cancer and benign lesion or between groups with invasive and non-invasive cancers.

Table 6 Indices of diagnostic effectiveness of fine-needle aspiration biopsy (FNAB) of the thyroid gland verified against histopathological examinations (follicular neoplasm/tumours were regarded as results positive for diagnosing cancer in first version, as negative in second version and were excluded from analysis in third version).

<table>
<thead>
<tr>
<th></th>
<th>First version (%)</th>
<th>Second version (%)</th>
<th>Third version (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP results</td>
<td>86–5.2</td>
<td>81–4.9</td>
<td>81–5.3</td>
</tr>
<tr>
<td>TN results</td>
<td>1329–80.3</td>
<td>1440–87.0</td>
<td>1329–86.3</td>
</tr>
<tr>
<td>FP results</td>
<td>208–12.5</td>
<td>97–5.8</td>
<td>97–6.3</td>
</tr>
<tr>
<td>FN results</td>
<td>33–2.0</td>
<td>38–2.3</td>
<td>33–2.1</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>72.3</td>
<td>68.1</td>
<td>71.1</td>
</tr>
<tr>
<td>Specificity</td>
<td>86.5</td>
<td>93.7</td>
<td>93.2</td>
</tr>
<tr>
<td>Accuracy</td>
<td>85.4</td>
<td>91.8</td>
<td>91.5</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>29.3</td>
<td>45.5</td>
<td>45.5</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>97.6</td>
<td>97.4</td>
<td>97.6</td>
</tr>
</tbody>
</table>

Discussion

Our study presents the retrospective results analysis of US examination and FNAB on a large series of thyroid glands, performed in a single diagnostic centre in an area of recently corrected iodine deficiency. We showed that, in such an area, focal lesions were found in the thyroid glands of nearly 80% of the examined patients, and the frequency of multinodular goitre, irrespective of the size of lesions, was considerably high – above 77%. This constitutes a major difference in comparison with countries with high iodine supply, where the thyroid...
lesions more frequently occur as single nodules (11, 21, 22). Between INs, found in more than 40% of all examined persons, the percentage of multiple lesions was even higher – above 80%. This setting poses significant diagnostic difficulty, especially as according to many observations – mainly from iodine-reach areas – the percentage of revealed carcinomas by aspiration of small lesions is similar to that observed when larger nodules are examined cytologically (10, 11, 13, 14, 23, 24). Our data from the post-endemic region confirm these observations. The frequency of revealed small and large cancers was proportional to the frequency of the biopsied nodules of each size class.

The histopathological verification of the cytological outcomes showed that in our material, in 75.8% of cases of cancers not larger than 10 mm, the selection of lesions for FNAB was successful. In the group of larger cancers, the malignant lesions were properly selected for FNAB in 96% of cases. Undoubtedly, in the areas similar to Polish epidemiological situation, the probability of wrong selection of small lesions for FNAB is higher than in the areas of a long-term normal iodine supply. As it was mentioned above, INs were usually accompanied by other, often larger lesions, which were more frequently chosen for biopsy. As a result, the efficacy of preoperative diagnoses of small carcinomas was significantly lower than in the case of larger malignant tumours. An additional cause of that difference was a higher percentage of FNAB outcomes in the group of small lesions subjected to FNAB. In the majority of cases it was probably a consequence of missing a lesion during aspiration. On the other hand, it should be kept in mind that in the areas of iodine sufficiency the reported percentages of FN results are usually less reliable. FNAB outcomes are frequently verified not against histopathological examination but clinical follow-ups. Patients with cytologically diagnosed benign lesions are not usually surgically treated, and as a result there may be some misdiagnosed cases of thyroid microcarcinomas in that group of patients.

The finding that extrathyroidal extension of malignancy or regional lymph node metastases were present in nearly one-third of the thyroid microcarcinomas is of particular importance. Similar data on the high rate of extrathyroidal extension of thyroid small carcinomas have been reported from other regions suffering from iodine deficiency, as well as from iodine-rich areas (13, 14, 25–27). In our material, preoperative diagnoses failed to discover two cases of small invasive cancers. It could be explained by the progression of microcarcinoma in the period between FNAB and the surgery. It may also be argued that the applied criteria for selection of lesions for FNAB were inefficient. The number of performed FNABs is very high in relation to the number of revealed cancers, but in spite of this, some invasive cancers were missed. On the other hand, some indolent cancers, which probably never become aggressive, were revealed (28, 29). In the regions of a high number of patients with multinodular goitre, it seems reasonable to use more powerful and rigorous criteria for selecting lesions for FNAB. We found that all small invasive cancers were hypoechoic, but this feature is very non-specific especially in the group of small lesions. It could be helpful to use the more specific set of features for diagnosing invasive thyroid microcarcinoma but an optimal definition of such a set is still being sought. In order to increase the chances of early detection of small invasive cancers, it seems reasonable to follow up small lesions revealed in the thyroid with repeated US examinations that allow detection of any significant increase in the lesion’s size and analysis of the lesion’s relationship with the thyroid capsule as well as evaluation of lymph nodes in the neck (30).

The proper selection of lesions for biopsy is one of the important components influencing the effectiveness of this examination. Another is an epidemiological situation of examined populations which affect the incidences of follicular lesions (follicular adenomas and carcinomas as well as hyperplastic nodules in nodular goitre) and papillary cancers (15, 16). In the areas of long-term iodine deficiency, the consideration of ‘follicular neoplasms/tumours’ results as an indicator of malignancy yields a significant increase in FP results. This cytological outcome corresponds more frequently to non-neoplastic hyperplastic nodules or follicular
adenoma than to thyroid cancers. This is the reason for low positive predictive value of FNAB in the first version of our analysis. Interestingly, if follicular neoplasm/tumour in cytological outcome was assumed as a negative result with respect to cancer diagnosis it would cause a twofold increase in the number of undiagnosed cancers >10 mm and only 15% increase in the case of infracentimetric cancers. Thus, it seems that in the regions of similar epidemiological situation, in patients with such cytological outcome the surgical treatment may be postponed only in the case of small lesions.

The epidemiological differences also influence the distribution of cytological and histopathological results between particular categories (15, 16, 19, 31). The high prevalence of non-neoplastic endemic nodular goitre leads to the dominance of benign lesions between the categories of FNAB outcomes. In our data, the suspicious or malignant lesions constitute slightly above 5% of all cytological outcomes while in areas of a long-term normal iodine supply this percentage reaches 20–30% (22, 23). Reports from Korea and the USA, where iodine supply is high, show that malignant neoplasms are found in over 10% of cytologically examined small lesions (13, 22, 23). Moreover, in endemic or post-endemic areas the rate of malignant lesions in post-operative histopathological examination is relatively low. In our material, such rate was only 7% while in areas of high iodine supply it is several times higher. This difference results from a high number of patients in iodine-deficient areas who are referred to a surgeon not because of the suspicious FNAB outcome – only 17% of the patients in our series – but because of large multinodular goitre, notwithstanding the benign outcome of FNAB.

Our data showed that the rate of non-diagnostic aspirates in the case of small lesions was not higher than in the case of larger lesions. Similar results were observed by Accurso et al. (2005), Nam-Gong et al. (2004) and Papini et al. (2002) (13, 14, 32). According to their and our observations, small lesions of mixed (cystic solid) or heterogeneous echostructure are less frequent, and in this case higher rates of non-diagnostic specimens are observed (14). However, the data on the efficacy of FNAB in obtaining diagnostic cellular material from small thyroid lesions are equivocal. Some reports suggest that the smaller the size of aspirated lesion the higher the rate of inadequate specimens (24, 27, 33). Other reports from Japan and Korea suggest that if the staff performing FNAB of the thyroid is experienced enough, it is possible to aspirate reliably even very small lesions – with diameters of 2–3 mm (13, 34). In these Asian countries, specialists more often diagnose very small thyroid lesions which – because of the specific epidemiological situation – less frequently coexist with other larger lesions but are microcarcinomas more frequently than in the countries with low iodine supply.

The differences described above in epidemiological situations of examined populations result in significant differences in the reported data on FP and FN results, as well as sensitivity (from 65 to 99%) and specificity (from 72 to 100%) of thyroid FNAB (30, 35–40).

In conclusion, in endemic or post-endemic areas the percentage of revealed carcinomas through aspiration of small lesions does not appear to be lower than that observed when larger nodules are biopsied, in spite of the fact that the efficiency of US selection of small lesions for FNAB is inferior to that of large lesions. In such regions, extrathyroidal extension is present in nearly 30% of microcarcinomas confirmed by post-operative histopathological examination. Thus, in endemic or post-endemic areas, more powerful and rigorous criteria for selection of small lesions for FNAB are needed that would allow optimization of the number of performed biopsies in relation to the revealed number of clinically invasive thyroid microcancers. Moreover, it is particularly indicated to follow up small thyroid lesions with repeated US examinations in endemic and post-endemic regions.

In regions of recently normalized iodine supply, the risk of cancer – if follicular neoplasm has been discovered through FNAB – is lower than in the case of other suspected lesions, but in the patients with such cytological outcome the surgical treatment may be postponed only in the case of small lesions. In fact, the diagnosis of follicular neoplasm in small lesions is related to a rather low risk of malignancy.

Declaration of interest

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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