Abstract

Background. Ultrasound and ultrasound-guided fine-needle aspiration biopsy have been shown to be sensitive techniques for monitoring patients for recurrent differentiated thyroid carcinoma in the thyroid bed and regional lymph nodes after total thyroidectomy. However, the role of ultrasound and ultrasound-guided fine-needle aspiration biopsy in the confirmation of differentiated thyroid cancer recurrence has not been differentiated for thyroid bed and regional lymph nodes and for assessing clinical behaviour adequately. Objective. The aim of the study was to evaluate the significance of ultrasound examination and ultrasound-guided fine-needle aspiration biopsy for the diagnosis of recurrent thyroid cancer. Patients and methods. During 1998–2002, due to suspicion of recurrence of thyroid cancer, 131 ultrasound-guided fine-needle aspiration biopsies were performed on 85 patients: 75 biopsies of regional lymph nodes and 56 biopsies of thyroid bed. All biopsies were performed on nonpalpable lesions (less than 1.5 cm in diameter). Results. Fifty-six ultrasound-guided fine-needle aspiration biopsies of thyroid bed tissue under suspicion of malignancy were performed. Twenty patients underwent surgery. In 16 cases, the cytological diagnosis of thyroid cancer was confirmed by postoperative histological examination. Seventy-five ultrasound-guided fine-needle aspiration biopsies of regional lymph nodes under suspicion of malignancy were performed; 18 patients underwent surgery for regional lymph nodes. In 18 cases, the cytological diagnosis of metastatic thyroid cancer was confirmed by postoperative histological examination. Conclusions. Ultrasound and ultrasound-guided fine-needle aspiration biopsy is a valuable and relevant method for the early diagnosis and reliable follow-up of small recurrent differentiated thyroid cancer at thyroid bed and regional lymph nodes and allows assessing their cytomorphological nature and establishing their precise localisation. Ultrasound-guided fine-needle aspiration biopsy offers favourable conditions for choosing the optimal management strategy. Small thyroid cancer with invasion outside the thyroid capsule pT4 is more inclined to metastasize to regional lymph nodes than large thyroid cancer (diameter more than 4 cm) without external invasion pT3 (TNM staging 5th edition). Papillary thyroid cancer metastasizes to regional lymph nodes later than medullary thyroid cancer. Most cases of recurrence of thyroid cancer were diagnosed during the first two years after thyroidectomy.
Keywords:
differentiated thyroid cancer, thyroid bed, regional lymph nodes, ultrasound, ultrasound-guided fine-needle aspiration biopsy

Background
Thyroid cancer accounts for 0.8% of all well-differentiated forms of cancer [1]. Differentiated thyroid cancer is divided into papillary and follicular carcinomas. The 10-year survival in papillary and follicular thyroid cancer is 90–93% and 85% respectively [2–4]. Thyroid cancer is a unique type of malignant cancer because even with distant metastases it may have a better prognosis than other types of malignancies [5]. However, cancer recurrence in thyroid bed and/or in regional lymph nodes is associated with increased mortality [6]. In order to achieve a successful treatment of thyroid cancer, early detection of regional lymph node metastases and tumour in the thyroid bed is crucial. Early detection of thyroid cancer recurrence is an important survival prognostic criterion [7]. Clinical recurrence after a radical operation of differentiated thyroid cancer occurs in 5–20% of cases [6, 8]. In recent years, the importance of ultrasound examination in the early diagnosis of thyroid cancer recurrence has increased significantly. Patients who suffer from low risk papillary and follicular thyroid cancer and have undergone thyroidectomy or I131 ablation are recommended to be followed up by measuring serum thyroglobulin, performing neck ultrasound and chest X-ray [9]. Neck ultrasound is an accurate diagnostic method used to determine thyroid cancer recurrence in thyroid bed and regional lymph nodes. Local tumour changes in the thyroid bed after thyroidectomy and metastases of lymph nodes have their specific echogenic signs. Using the ultrasound technique, it is possible both to detect malignant tumours in thyroid bed and perform ultrasound guided fine needle aspiration biopsy thereby identifying reoccurrence of the disease or finding residual malignant tumours in the thyroid bed and regional cervical lymph nodes before the operation. However, the role of ultrasound and ultrasound-guided fine-needle aspiration biopsy in the confirmation of differentiated thyroid cancer recurrence has not been adequately addressed. During the last decades, all attention in differentiated thyroid cancer monitoring was dedicated to only two diagnostic methods – measurement of serum thyroglobulin level and I131 scintigraphy.

Objectives
The aim of this study was to evaluate the significance of ultrasound examination and ultrasound-guided fine-needle aspiration biopsy for the diagnosis of recurrent differentiated thyroid cancer at thyroid bed and regional lymph nodes, and to assess the clinical course of differentiated thyroid cancer recurrence.

Materials and methods
The study was performed during 1998–2002 at the Department of Interventional Sonoscopy and Ultrasound Diagnostics of Institute of Oncology, Vilnius University. The following study inclusion criteria for the patients undergoing ultrasound examination with suspected thyroid cancer recurrence were used: patients after thyroidectomy for thyroid cancer, specific echogenic signs of malignancy in thyroid bed and/or regional cervical lymph nodes at ultrasound examination, changes in thyroid bed and regional cervical lymph nodes not palpable (diameter < 1.5 cm). The mean age of patients was 54.67 ± 12.89 years (mean ± standard deviation); 56 female and 29 male patients were investigated. All patients suffering from papillary and follicular thyroid cancer underwent thyroidectomy and I131 ablation. Ultrasound examination was performed using the Voluson 730 (Kretztechnik AG) ultrasound system with an SP 6–12 wide band linear probe. No special needle guide probes were used. Biopsy was performed using 21-gauge, 4.0 cm length needles; 20 ml syringes were used for aspiration. Aspiration biopsy material from thyroid bed and regional cervical lymph nodes was prepared for cytology examination by the conventional blood smear preparation method. Slides where air-dried and stained by the Giemsa staining method. The adequacy of the aspirate was evaluated by a cytopathologist according to its cellular composition quality and in correlation with clinical data. Cytological results of fine needle aspiration biopsy from thyroid bed and regional cervical lymph nodes were divided into the following groups: noninformative specimen, benign changes, suspicion of cancer and malignant changes. All cytological and postoperative histological examinations where performed at the National Center of Pathology. All patients undergoing operation and I131 ablation were treated at the Institute of Oncology, Vilnius University. 131 ultrasound-guided fine-needle aspiration biopsies were performed for 85 patients with suspected thyroid cancer recurrence (75 biopsies of cervical regional lymph nodes and 56 biopsies of thyroid bed).
Statistical data processing
Measurements of continual variables are presented as mean ± standard deviation (M ± SD). To compare continual variables, two-sided Student’s t test for independent samples was used. The margin of statistical significance was p < 0.05. Categorical data were evaluated by the chi-square test or exact two-tailed Fisher’s test.

Results
In order to evaluate the influence of patient’s age on the possibility of developing differentiated thyroid cancer recurrence, patients were divided into two groups: patients under 45 years, and 45 years or older. The mean age of patients aged under 45 years and diagnosed with cancer in thyroid bed and/or regional cervical lymph nodes was 38 ± 7.87 (mean ± standard deviation). The mean age of patients aged 45 years or older and diagnosed with cancer in thyroid bed and/or regional cervical lymph nodes was 57 ± 9.34 (mean ± standard deviation). There was no statistically significant difference in malignant disease recurrence between the two age groups (p = 0.43). Recurrence of the thyroid cancer (papillary and follicular) was suspected in thyroid bed location in 45 (80.3%) patients and regional cervical lymph nodes in 64 (85.3%) of all the study cohort. Signs of disease recurrence in the thyroid bed two years after thyroidectomy were observed in 30.4% and disease recurrence in regional cervical lymph nodes in 37.3% of patients. The smallest and the greatest diameter of tumour of the thyroid bed was 0.4 and 1.5 cm, respectively, the mean diameter being 0.99 ± 0.36 cm. In 30 cases, the diameter of tumour in the thyroid bed was smaller than 1.0 cm. There was no statistically significant difference between different size groups of thyroid bed tumours in the histological type of primary tumour and tumour extracapsular extension (primary tumour, pT, was assessed using TNM classification, 5th ed., 2002) were observed. There was no statistically significant difference in the time of recurrence between primary tumour with or without extracapsular extension. According to our data, tumours with extracapsular extension pT4 (primary tumour assessed using TNM classification, 5th ed., 2002) are statistically significantly more prone to metastasize to regional cervical lymph nodes earlier than big (> 4 cm) tumours with no extracapsular invasion (pT3) (p = 0.023 using two-sided Student’s t test). Papillary tumours gave regional cervical metastases significantly later than medullary tumours (p = 0.049, using Student’s t test). No other differences among different histological forms regarding the time of metastasis were observed.

Discussion
Scientific data regarding the clinical importance and follow-up strategy of differentiated thyroid cancer recurrence in regional lymph nodes are inconclusive [7]. The follow-up of thyroid cancer patients should be performed by an interdisciplinary team [7]. Using this approach, one can expect optimal treatment results. Following surgical removal of differentiated thyroid tumour, it is recommended to perform neck ultrasound examination after 6 and 12 months and every 3–5 years subsequently [10]. Previously there have been recommendations to perform neck ultrasound examination for recurrent differentiated thyroid cancer [11]. Data provided by ultrasound examination are very important, however, they do not give information enough to establish the diagnosis of thyroid cancer recurrence in thyroid bed and regional cervical lymph nodes. A variety of echogenic signs helps to suspect recurrence of a malignant disease in the thyroid bed, however, the morphologic features can only be
defined by cytopathological examination. Therefore, ultrasound-guided fine-needle aspiration biopsy should be performed, if there is any suspicion of cancer recurrence. Published data show that ultrasound examination with ultrasound-guided fine-needle aspiration biopsy is more sensitive than palpation and radionuclide scintigraphy in diagnosing the recurrence of differentiated thyroid cancer [12]. Conventional aspiration biopsy (aspiration biopsy performed using palpation) for diagnosing thyroid cancer recurrence is limited by postoperative fibrosis, especially if the lesion under scrutiny is small. Using ultrasound guidance for aspiration biopsy, it is possible to avoid complications such as injury to the common carotid artery, internal jugular vein, trunk of vagus nerve, trachea and esophagus. It is more difficult to avoid complications performing conventional fine needle aspiration biopsy. In our study, all cases of malignant disease recurrence were in the preclinical stage. Therefore, on evaluating our data we support the opinion that the use of ultrasound examination for long-term follow-up of differentiated thyroid tumour is necessary [4]. Ultrasound examination and ultrasound-guided fine-needle aspiration biopsy facilitate not only detection of disease recurrence in thyroid bed, but also evaluation of its morphological features. This is important both in the case of malignant tumour and benign lesion (e.g., residual thyroid tissue). Treatment considerations depend on the histological form of cancer. In over 50% of cases where ultrasound-guided fine-needle aspiration biopsy and cytological examination show recurrence of differentiated thyroid cancer in thyroid bed or regional lymph nodes, scintigraphy and measurement of thyroglobulin level in the serum fail to show the recurrence of the disease [13]. Before choosing an appropriate treatment for thyroid cancer, it is necessary to look for a metastatic disease in regional cervical lymph nodes. Because of their anatomic position, enlarged cervical lymph nodes are not easily palpable, especially when they are small and located behind sternocleidomastoid muscles, deep in the paratracheal region, or behind a carotid artery or jugular vein. Moreover, because of their biological behaviour, radiiodine does not accumulate in these nodes [14]. Ultrasound examination of neck lymph nodes and ultrasound-guided fine-needle aspiration biopsy not only facilitate detection of metastatic cervical lymph nodes, but also help accurately determine their location. Papillary and follicular thyroid cancer rarely metastasize to level I cervical lymph nodes, level II is affected in 52% of cases, level III in 57%, level IV in 49% and level V in 41% [15]. Knowledge of metastatic lymph node location is crucial when decision about the extent of the operation is made (selective lymphadenectomy, radical lymphadenectomy). Ultrasound-guided fine-needle aspiration biopsy helps detecting a precise location of thyroid cancer recurrence and evaluating its morphological background, providing the possibility to accommodate an optimal treatment method. The time of the disease recurrence in thyroid bed and cervical lymph nodes after the first operation is presented in Figures 1 and 2. These figures show that the majority of thyroid cancers recur within two years after thyroidectomy. However, a considerable number of cases recur 8–10 years following the primary treatment. Therefore, according to the data of our study we support the use of ultrasound examination for the long term follow-up of differentiated thyroid cancer patients [4, 16]. The results of our study showed that thyroid cancer recurrence rate in two age groups (under 45 and 45 years or older) was not significantly different (p = 0.43). This discrepancy (age is known to be one of the major risk factors of differentiated thyroid cancer) could be explained by the study design and the patient

![Fig. 1. Time of recurrence in thyroid bed after thyroidectomy](image-url)
Recurrence of differentiated thyroid cancer: significance of ultrasound examination and ultrasound-guided fine-needle aspiration biopsy

Inclusion and exclusion criteria. Our data indicated that papillary and medullary cancers were prevailing cancers of thyroid bed. In general, medullary thyroid cancer accounts only for 5–10% [17, 18] and differentiated thyroid cancer for 90% of all thyroid malignancies [17], whereas in our study we found a higher recurrence rate of the medullary histological form in comparison with the differentiated one. Thyroid cancer recurrence was never suggested by serum thyroglobulin level for any of our study patients. Spencer et al. state, that there is no “normal” thyroglobulin value after thyroidectomy [19]. Every patient suffering from differentiated thyroid cancer has an individual level of serum thyroglobulin, depending on a variety of factors: thyroid tissue (residual or malignant), the level of thyrotropic hormone stimulation, surgical injury level, biopsy or inflammatory changes (thyroiditis), serum thyroglobulin antigen level, the extent of malignant changes, etc. [11, 19]. For example, thyroglobulin level may be elevated for 3 weeks after biopsy [11, 19]. Our opinion is that recurrence of the malignant disease could not be detected in the group of our study patients suffering from differentiated thyroid cancer by serum thyroglobulin level because of the size of the tumour – only patients with non-palpable tumours (diameter less than 1.5 cm) were included into the study. Moreover, this method does not allow to distinguish residual thyroid tissue in the thyroid bed from malignant changes [20]. A great number of differentiated thyroid cancer recurrences have a clinically and biochemically silent course [11]. Combination of three diagnostic methods (measurement of serum thyroglobulin level, ultrasound examination and ultrasound guided fine needle aspiration biopsy of thyroid bed and regional cervical lymph nodes and $^{131}$I scintigraphy) provides excellent follow-up results and facilitates application of an optimal treatment method. Ultrasound examination and ultrasound-guided fine-needle aspiration biopsy are a safe, not expensive diagnostic method of thyroid cancer recurrence, which requires no extra preparation, but does require special skills of the investigator.

Conclusions

Ultrasound and ultrasound-guided fine-needle aspiration biopsy are valuable and relevant methods for the early diagnosis and reliable follow-up of small recurrent differentiated thyroid cancer at thyroid bed and regional lymph nodes, which allow to assess their cytomorphological nature and establish precise localisation. Ultrasound-guided fine-needle aspiration biopsy provides favourable conditions for choosing an optimal management strategy. Small thyroid cancer with invasion outside thyroid capsule pT4 (TNM staging 5th edition) is more inclined to metastasize to regional lymph nodes than large thyroid cancer (diameter more than 4 cm) without external invasion pT3 (TNM staging 5th edition). Papillary thyroid cancer metastasizes to regional lymph nodes later than does medullary thyroid cancer. Most cases of thyroid cancer recurrence were diagnosed during the first two years after thyroidectomy.

References

2. Lundgren CI, Hall P, Ekbom A, et al. Incidence and
survival of Swedish patients with differentiated thyroid cancer. Int J Cancer. 2003; 106: 569–73.


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DIFERENCIUOTO SKYDLIAUKĖS VĖŽIO ATKRYTIS: ULTRAGARSINO TYRIMO BEI ULTRAGARSU KONTROLIUOJAMOS ASPIRACINĖS BIOPSIJOS PLONA ADATA REIKŠMĖ DIAGNOZUOJANT LIGOS ATKRYTĮ
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Santrauka

Raktažodžiai: skydliaukės vėžys, skydliaukės guolis, sritiniai kaklo limfmazgius, ultragarsinis tyrimas, ultragarsu kontroliuojama aspiracinė biopsija plona adata