THYROID NODULARITY – TRUE EPIDEMIC OR IMPROVED DIAGNOSTICS

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SUMMARY – The incidence of thyroid nodules has been rising steadily during the last 30 years, since the introduction of new diagnostic methods such as ultrasonography and computerized tomography, thus posing a real challenge in determining the best approach strategy for treatment of this new 'epidemic'. We analyzed and compared data from several studies showing the prevalence of thyroid nodules on autopsy, palpation and ultrasonography to be 13%-60%, 0.5%-6.5% and 13.4%-46%, respectively. This demonstrates that thyroid ultrasonography is a very sensitive and accurate diagnostic tool the use of which, however, entails an increased number of incidentally discovered thyroid nodules without clinical significance. Therefore, ultrasonography of the thyroid should not be performed without clinical indication determined by thyroid specialist.

Key words: *Thyroid nodule – history; Thyroid nodule – pathology; Thyroid nodule – therapy; Thyroid nodule – ultrasonography; Tomography, x-ray computed*

Introduction

Thyroid nodule can be defined as an area within the thyroid gland that is distinct from the surrounding thyroid parenchyma on palpation and/or ultrasonography[1]. It usually is not caused by a single disease but is a clinical manifestation of many different thyroid diseases. Thyroid nodules are the most common thyroid disease. The prevalence of clinically detectable thyroid nodules is around 3% in the general population, while the incidence is 0.1%[2]. Thyroid nodules are usually benign[3,4]. However, the risk of thyroid cancer in a nodule is around 5%[5] and cannot be considered negligible.

The factors that influence the incidence of thyroid nodules include age and sex, iodine intake and exposure to radiation. Thyroid nodules are up to five times more frequent in women than in men. It is also known that the prevalence of thyroid nodules increases with age[2,6-9]. Even small differences in the levels of iodine intake can have profound effect on the occurrence of thyroid abnormalities. It has been proven that nodular thyroid disease, especially multinodular toxic goiter, is more frequent in iodine deficient regions[10], pointing to the level of dietary iodine as an important etiologic factor in the development of thyroid autonomy. In addition, a significant linear radiation dose response has been reported for thyroid nodules including malignant tumors and benign nodules[11]. The sources of ionizing radiation may be atomic bomb, nuclear accidents, radiotherapy, etc. Young age at exposure is a primary risk for cancer after radiation exposure because the thyroid gland of children is especially vulnerable to the carcinogenic action of ionizing radiation.

Clinical evaluation of patients with thyroid nodules includes palpation, serum thyroid-stimulating hormone (TSH), thyroid ultrasonography (US), thyroid scintigraphy, and fine needle aspiration biopsy (FNA), which is currently considered the most accu-

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Table 1. Prevalence of thyroid nodules on autopsy

Country	Prevalence of nodules	Author(s)
USA	13% (soldiers aged 18-39)	Oertel and Klinck, 1965[16]
Hungary (Szolnok, Budapest)	27.1% Iodine sufficiency 44.6% Iodine deficiency	Kovacs *et al.*, 2005[17]
USA	50.5%	Mortensen *et al.*, 1955 (Mayo Clinic)[18]
Belarus	60%	Furmanchuk *et al.*, 1993[19]

rate diagnostic method to differentiate benign from malignant thyroid nodules[1,12-15]. Since the introduction of new diagnostic methods such as US and computerized tomography (CT), there has been a steady rise in the incidence of thyroid nodules in the past thirty years. This rising tendency is the result of incidental detection of nodules smaller than 1 cm, detection of clinically non-significant nodules on routine neck US or non-thyroid diagnostic tests like US of parathyroid glands, cervical lymph nodes or salivary glands, Doppler assessment of carotid arteries, and neck or chest CT or magnetic resonance imaging (MRI) and positron emission tomography (PET). These nodules, appropriately named incidentalomas, present a real challenge to all thyroid specialists in determining the best approach strategy for their treatment.

Prevalence of Thyroid Nodules – Autopsy Data

The 'real' prevalence of thyroid nodules can be accurately verified only with data obtained on autopsy. Relevant studies assessing thyroid nodularity on autopsy were conducted in the past and concluded that 20%-60% of the general population with no previously recorded thyroid abnormalities had nodular thyroid disease (Table 1). The prevalence depended on age, sex and dietary iodine, as stated above.

Methods of Detection

Thyroid nodules are usually detected on neck palpation or US. Thyroid palpation is still considered a routine method of nodular thyroid disease detection. However, even the most experienced physician cannot detect thyroid nodules of less than 1 cm in diameter, which obviously limits the method reliability. Historically, until some thirty years ago, thyroid palpation was a standard method of evaluation, but was supplanted by US as a significantly more sensitive technique. In the studies we reviewed, the prevalence of nodular thyroid disease varied between 0.5% and 6% (Table 2); however, not all of these studies were conducted on randomized populations, so lower and higher values were expected in younger and older populations, respectively.

Ultrasonography was introduced as a method of thyroid imaging in 1967 by Fujimoto[24], having dramatically changed diagnostic work-up and management of patients with thyroid disorders, in the last 20 years in particular. It is a reliable and noninvasive method to detect thyroid lesions and to distinguish solid from cystic lesions[25]. Currently, US can detect thyroid lesions as small as 2 mm, which makes it the most accurate imaging technique for the detection of thyroid nodules. This procedure is mandatory when a

Table 2. Prevalence of palpable thyroid nodules

Country	Prevalence of nodules	Author(s)
USA (Salt Lake City)	0.46% (schoolchildren) 2.3% (young adults)	Rallison *et al.*, 1991[20]
England (Wickham)	3.2%	Tunbridge *et al.*, 1977[2]
USA (Massachusetts)	4.2%	Vander *et al.*, 1968[21]
Italy (Sicily)	5.1%	Belfiore *et al.*, 1987[22]
Denmark	6.5% (middle age women)	Christensen *et al.*, 1984[23]

Table 3. Prevalence of thyroid nodules on ultrasonography

Country	Prevalence of nodules	Author(s)
USA (Stanford)	13.4%	Caroll, 1982[26]
Italy (Pescopagano)	17% (age ≥15)	Aghini-Lombardi *et al.*, 1999[29]
Japan (Tokushima)	19.7%	Miki et al., 1993[27]
Finland (Hyvinkaa)	21.3%	Brander *et al.*, 1991[28]
Germany	23.4% (age 18-65)	Reiners *et al.*, 2004[7]
Denmark Copenhagen)	31.3% (age 41-71)	Knudsen *et al.*, 2000[30]
Italy (Palermo)	33.1%	Bartolotta *et al.*, 2006[31]
USA (San Francisco)	40% (patients with hyperparathyroidism)	Stark *et al.*, 1983[32]
USA	46%	Horlocker *et al.*,1985[6]

Most of these countries were iodine sufficient at the time of the respective study, and only Italy and Germany were mildly iodine deficient.

nodule is discovered on palpation. US is also used as a guide to FNA biopsy.

In the past 25 years, a number of studies assessing the prevalence of thyroid nodules have been conducted in various countries and in various populations all over the world. In these studies, the prevalence ranged from 13.4% to 46% (Table 3). Probably the most extensive prospective study was performed by Reiners *et al.*, which included almost 100,000 employees of various companies throughout Germany and yielded very comprehensive data on thyroid nodule prevalence according to age and sex[7].

Discussion

Data collected from these studies show great disparity between the prevalence of palpable thyroid nodules and real prevalence found on autopsy. On the other hand, the prevalence of nodules discovered on US was in line with autopsy data, demonstrating that US is a very sensitive and accurate diagnostic tool for thyroid gland examination, whereas palpation is limited by the experience of the examiner and difficult detection of small nodules. However, the widespread use of US and other new diagnostic methods entails an increase in the number of incidentally discovered nodules without clinical significance, posing a problem of how to manage these new 'patients'. Fortunately, the majority of thyroid nodules are benign and only a small percentage require surgical treatment. What is more important, most benign thyroid nodules are asymptomatic, nontoxic and slow-growing and require only simple follow-up[33].

However, as mentioned above, around 5% of thyroid nodules are or will become malignant. Clinically apparent thyroid cancer is a relatively uncommon malignancy with a prevalence of 0.1% and even lower mortality[34,35], but its incidence has been increasing steadily over the past 30 years[9]. This phenomenon can also be mainly ascribed to the introduction of new diagnostic methods, US in particular, since the pool of so-called 'occult thyroid cancers' is substantial, i.e. 5% to 36% in autopsy studies in various countries[36-38]. These data demonstrate that thyroid cancer is actually much more common than suggested by clinical studies, and that the majority of clinically unapparent cancers would remain 'silent' throughout the patient's life[39].

Considering these facts, what should be our approach to thyroid nodules and their potential malignant transformation? Current guidelines for the management of thyroid nodules issued by the American and European thyroid associations clearly state that US screening of the general population for thyroid nodules is not recommended. These guidelines also recommend to perform US-guided FNA on all palpable and non-palpable thyroid nodules with a cut-off value of 1-1.5 cm[1,12-14,40,41]. FNA of nodules smaller than this cut-off value is recommended only in nodules with suspect US characteristics (hypoechoic, solid, irregular margins, intranodular vascular pattern, microcalcifications). In case of multinodular goiter, FNA is recommended in dominant nodules and nodules with previously mentioned suspect characteristics. This approach could, however, further increase the detection rate of thyroid cancer by detecting small, clinically

unapparent occult thyroid cancers[27], while the benefit for these patients would be dubious.

Conclusion

Thyroid nodules are discovered at an ever increasing rate since the introduction of modern diagnostic tools like CT, MRI, PET scans and US in particular, which is becoming an extension of physical examination of the thyroid. Since the pool of non-palpable, clinically non-significant thyroid nodules is huge, this increase could actually be expected and there has been no evidence of true increase of thyroid nodularity. The risk of malignancy should not be ignored since an estimated 5% of all nodules are malignant; however, the majority of these malignancies have little biological significance. Therefore, US of the thyroid should not be performed without clinical indication determined by thyroid specialist.

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Sažetak

ČVOROVI ŠTITNE ŽLIJEZDE – STVARNA EPIDEMIJA ILI POBOLJŠANA DIJAGNOSTIKA

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Incidencija čvorova štitne žlijezde u stalnom je porastu posljednjih 30 godina, od uvođenja novih dijagnostičkih metoda poput ultrazvuka i kompjutorizirane tomografije, što predstavlja pravi izazov pri određivanju najboljeg pristupa u liječenju ove nove 'epidemije'. Analizirali smo i usporedili podatke iz nekoliko istraživanja koja navode učestalost čvorova štitne žlijezde utvrđenih na autopsiji, palpacijom i ultrazvukom od 13%-60%, 0,5%-6,5%, odnosno 13,4%-46%. To pokazuje kako je ultrazvuk vrlo osjetljiva i točna dijagnostička metoda, međutim, njegova primjena dovodi do sve većeg broja slučajno otkrivenih, klinički neznačajnih čvorova štitnjače. Stoga ultrazvuk štitnjače ne treba primjenjivati bez kliničke indikacije koju je postavio specijalist za štitnu žlijezdu.

Ključne riječi: *Čvor štitne žlijezde – anamneza; Čvor štitne žlijezde – patologija; Čvor štitne žlijezde – terapija; Čvor štitne žlijezde – ultrazvuk; Tomografija, kompjutorizirani rtg*