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Overdiagnosis of Thyroid Cancer

Ewa Machała

Medical University in Lodz, Department of Endocrinological, General and Oncological Surgery, Lodz, Poland

E-mail address: ewamachala@o2.pl

ABSTRACT

Overdiagnosis of thyroid cancers contributes to increased incidence of thyroid cancers worldwide, which is already a serious public health problem. A great number of medical tests, helping to detect thyroid cancer, may result in an epidemic of diagnosis. A dramatic increase in the number of detected cases of thyroid cancer may be associated with a great number of neck ultrasounds, fine-needle aspirations and incidental findings during examination. Unfortunately, in response to overdiagnosis, more and more surgeries are being performed. It is important to differentiate stationary cancers from potentially aggressive diseases. Detection of cancer contributes to saving lives. However, in some instances it can be harmful, particularly if the disease is overdiagnosed. The aim of this review is to give a balanced view of thyroid cancer epidemic and controversies arising out of overdiagnosis.

***Keywords*:** thyroid cancer, papillary thyroid cancer, fine needle aspiration biopsy, throidectomy, overdiagnosis

1. INTRODUCTION

Thyroid cancer is the most common endocrine cancer. The incidence of this disease has dramatically increased worldwide and the pace of changes is more rapid than for any other type of cancer. The reasons for this phenomena still have not been fully explained. In total, (statistical data from 2015) 3.2 million people are affected by thyroid cancer [1].

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Such factors as the environment, lifestyle or radiation can predispose to its development. But can changes of these modifiable risk factors help to reduce the incidence? Despite advancement in detection methods and screening, there are still speculative controversies regarding overdiagnosis. The mortality rate due to this pathology remains relatively stable [2-4]. From the other point of view, survival period of thyroid cancer patients is so long that there is enough time to observe the disease. The mortality rate, which remains stable in spite of the rising incidence of thyroid cancer, can be associated with improved treatment methods and it would decrease more if treatment was more effective.

According to professional literature, there is an ongoing epidemic of thyroid cancer in the United States. Scientists and doctors claim however that this is not an epidemic of the disease but rather an epidemic of diagnosis [5]. According to a famous article published in "The New England Journal of Medicine" in 2016, overdiagnosis is a major drive of the thyroid cancer epidemic. Between 50 and 90% of cases of thyroid cancer in women living in high-income countries are estimated to be overdiagnosed [6].

Studies conducted in Finland and Spain revealed that the thyroid cancer mortality ratio has remained stable over the last forty years, whereas the incidence has nearly tripled [5]. This problem can be connected with overdiagnosis of papillary thyroid cancer [7,8]. It was confirmed that for above 35 years, the incidence of thyroid cancer in women was approximately 4 times higher than in men [5]. Thyroid cancer prevalence at autopsy is actually greater in men than in women [7-9], which means that the problem has existed for decades.

For some time, small papillary cancers have been more often detected. These types are the most common and indolent histological forms of thyroid cancer [10]. A rapid increase in the incidence of thyroid cancer, regarding exclusively papillary carcinoma and early-stage tumors, was accompanied by an increase in the rate of thyroidectomies. Most thyroid cancers are primarily treated with surgery, partial or total thyroidectomy, including neck lymph dissection. Overdiagnosis leads to overtreatment which involves performing thyroidectomies that do not bring clear benefits for the patient. Some findings imply that the number of detected thyroid cancers which are overdiagnosed and overtreated is growing [11].

Overdiagnoses refer to diagnoses that do harm rather than bring benefits to patients since a diagnosed condition is not a harmful form of the disease. Hence, our aim was to compare and summarise recent knowledge about overdiagnosis of thyroid cancer.

2. THYROID CANCERS

During the past few decades, the incidence of thyroid cancer has increased substantially in many countries. According to sourses about 23,000 new cases of thyroid cancer were estimated in 2012 among women and 70,000 among men, with an (world population) rate of 6.10/100,000 women and 1.90/100,000 men [12]. The disease can occur in any age group. However it mostly affects people above the age of 30 and in the course of time, the disease becomes significantly more and more aggressive. Post-mortem studies reveal a surprising incidence, from 0.01 to over 2.0%, including even harfour unsuspected thyroid cancer [13,14]. This high value may be a result of careful examination of the gland and regards a group of older patients who died in hospitals.

Thyroid cancers can be classified according to their histopathological characteristics. A classification of thyroid cancer is given in Table 1 and Table 2.

Table 1. Classification of thyroid cancer - WHO 2017 [16,17]

<table>
<tr><td rowspan="6">Epithelial</td><td rowspan="5">Follicular cell</td><td rowspan="4">- differentiated</td><td>Papillary

New classification: non-invasive follicular thyroid neoplasm with papillary-like nuclear features- now as a tumor</td></tr>
<tr><td>Follicular</td></tr>
<tr><td>Hurthle</td></tr>
<tr><td>Poorly differentiated</td></tr>
<tr><td>- undifferentiaded</td><td>Anaplastic</td></tr>
<tr><td>-other</td><td>Squamous cell</td></tr>
<tr><td>Other epithelial</td><td colspan="2">- Salivary gland type
- Micinous
- Sclerosing mucoepidermoid carcinoma with eosinophilia</td></tr>
<tr><td>Non-epithelial</td><td colspan="2"></td><td>- vascular
- smooth muscle
- histiocytic
- other</td></tr>
<tr><td>Secondary</td><td colspan="2"></td><td>- metastases
- other</td></tr>
</table>

The gap between the incidence and mortality rates reflect a good prognosis for most thyroid cancers.

The following factors may increase the risk of developing thyroid cancer [15]:

- **Neck irradiation** - may increase the risk of papillary and follicular thyroid cancer. Sources of radiation may include x-ray treatments, radiation therapy, exposure to radioactive iodine, exposure to ionising radiation

- **Genetic factors** - papillary carcinoma can be associated with inherited syndromes, e.g. familiar polypous polyposis, Gardner's syndrome, Cowden's disease. Medullary carcinoma is associated with the MEN syndrome.
- **Gender** - women are more prone to the disease
- **Age** - people aged 20 - 55 are most often affected
- **Family history for thyroid diseases**
- **Lifestyle factors** - diet rich in nitrates, low in iodine, lack of physical activity, smoking cigarettes, alcohol consumption
- **Obesity and diabetes**
- **Estrogen and reproductive factors**
- **Hashimoto's thyroiditis**
- **Race** - especially Asian
- **Breast cancer** - this finding continues to be examined by researchers
- **Other**

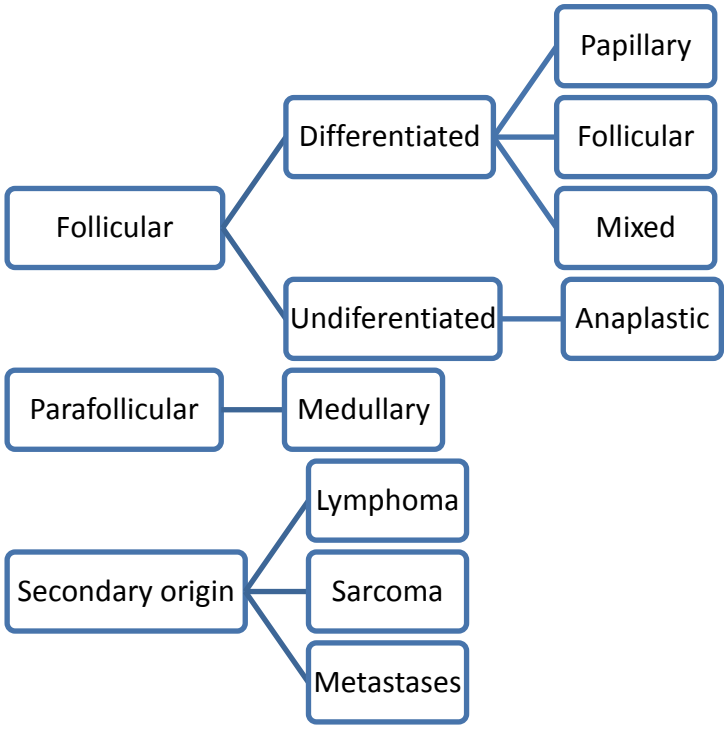

Table 2. Classification of thyroid cancer

Papillary microcarcinoma is a type of papillary thyroid cancer. Its diameter is usually less or equal to 1 cm. Its increased incidence was described in autopsy series [7] but also in retrospective surgical studies.

Most thyroid carcinomas are recognized because of a positive or suspicious FNA done for a clinical or sonographical detection of a thyroid nodule, either single or in "multinodular" goiter [18]. Biopsy and ultrasonography constitute basic and most useful examinations. TSH

and fT4 are usually measured to verify the metabolic status. Anti-TPO and TG antibodies may be useful in helping to differentiate thyroiditis. Isotope scans have a limited role in initial diagnosis.

Typical features of ultrasoud scanning such as: microcalcifications, irregular margins, hypoechogeneicity, intranodular blood vessels and round shape can indicate malignancy. They are indications for FNA. Also thyroid elastosonography is a promising tool to differentiate benign and malignant nodules.

Total thyroidectomy is performed in 85% of patients with thyroid cancer [2]. Patients who undergo total thyroidectomy are at risk for complications: permanent hypoparathyroidism, vocal cord paralysis. Additionally, they will definitely need supplementation with thyroid hormone and monitoring. Patients with histopathologically diagnosed cancer will receive radiation treatment, most often with application of radioactive iodine [2].

A prognosis depends mainly on the type of cancer and cancer stage and is better in younger than older people [19]. Table 3 presents this relationship.

Table 3. Prognosis of different types of thyroid cancer [19]

Cancer type	For 5-year survival				For 10-year survival
	Stage I	Stage II	Stage III	Stage IV	
Papillary	100%	100%	93%	51%	93%
Follicular	100%	100%	71%	50%	85%
Medullary	100%	98%	81%	28%	75%
Anaplastic	-			7%	No data

3. ROLE OF FINE NEEDLE ASPIRATION BIOPSY AND BETHESDA CLASSIFICATION IN DIAGNOSTIC PROCESS

Fine needle aspiration (FNA) biopsy plays an essential role in the diagnostic process of patients with thyroid nodules. FNA biopsy, involving a collection of thyroid tissue, is used for differentiating thyroid cancers from benign thyroid nodules. This is an important and widely applied method which can help to reduce the rate of unnecessary surgeries, but also can triage patients with diagnosed cancer for operation. Besides, it is a simple, safe as cost-effective method. Published studies reveal that the percentage of malignant operated nodules increased up to 50 %. Before a routine use of FNA, it had been around 14 % [20,21].

During the National Cancer Institute Thyroid Fine Needle Aspiration State of the Science Conference, held in 2007, the terminology as well as morphological criteria for the evaluation of FNA's preparations of thyroid were defined and formed a framework for the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC). The main aim was to

discuss and try to solve the problem of confusing reporting terminologies used for thyroid FNA. The TBSRTC consisted and consist until now of 6 diagnostic categories with defined implied risk of malignancy and algorithm of clinical management [22]. It was published in 2010 and greatly influenced clinical practice. The terms and definitions have been adopted successfully. Until today, it has facilitated communication among cytopathologists, endocrinologists, surgeons, radiologists and other health care specialists. The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) established a category-based reporting system for FNA materials.

During the symposium "The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC): Past, Present, and Future", held as part of the 2016 International Congress of Cytology in Yokohama in Japan, new categories were presented, summarized, and recommended [22].

According to the TBSRTC 2017 revision, every report should be classified into one of six diagnostic categories:

I - non-diagnostic or unsatisfactory
II - benign
III - atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS)
IV - follicular neoplasm or suspicious for a follicular neoplasm
V - suspicious for malignancy
VI - malignant

The 2017 revision of the Bethesda System was simultaneously published in *Thyroid* (2017; 27: 1341-1346) and the *Journal of the American Society of Cytopathology* (2017; 6: 217-222) [23,24].

New advances in pathomorphology (e.g. wider application of molecular testing) and therapy of thyroid pathologies led to changes. To put it briefly, new guidelines for treating thyroid pathologies and reclassification of non-invasive follicular variant of papillary thyroid carcinoma to other category were main factors [25-27].

Fine needle aspiration biopsy (FNAB) plays a crucial role in the diagnosis of thyroid lesions. The choice of further therapeutic strategy largely depends on its result. It is crucial to be knowledgeable of the risk of malignancy in each diagnostic class in a population. Prognosis depends mainly on the type of cancer and stage of the disease.

The rising incidence of thyroid cancer may represent an actual increase in the detection of clinically occult thyroid "incidentalomas", accompanied by an increase use of ultrasonography and fine needle aspiration (FNA) [28].

4. FACTORS LEADING TO INCREASED DETECTION OF THYROID CANCER

Changes in pathological practice play an important role. In compliance with current procedures, a thyroid specimen is examined, which increases chances for identification of small lesions and microcancers [29]. The trend of "overclassification" of thyroid nodules and classifying them into the cancer group encourage scientific community to make an effort to reduce the number of unnecessary aggressive treatments. Some authors imply that

ncapsulated noninvasive follicular variants of papillary thyroid carcinoma (FVPTC) have been recently classified as benign tumours. They were renamed as "noninvasive follicular thyroid neoplasms with papillary-like nuclear features" (NIFTP) to reduce overdiagnosis and overtreatment [29].

The thyroid cancer incidence has dramatically increased after an implementation (in some countries) of routine screening in healthy people. Studies confirmed that the thyroid cancer incidence is increased in communities with higher household income, education, and health insurance coverage [30]. There are some data that thyroid cancer detection is strongly related to medical care the individual is provided with. In people who enjoy good quality health care more small cancers are detected and more thyroid cancers are identified in total [31].

Advanced diagnostic imaging examinations, such as computed tomography (CT), magnetic resonance imaging (MRI), ultrasound, or advances in nuclear medicine, including positron emission tomography (PET) are important diagnostic tools and additional help in diagnostics. Increased use of imaging examinations supposedly contributed to identification of a greater number of clinically occult thyroid diseases.

Most commonly, an ultrasound is performed to confirm the presence of a nodule and assess the status of the whole gland.

With regards to non-malignant thyroid diseases, such as hyperthyroidism or suspected benign thyroid nodules, surgical treatment is implemented these days more frequently than before [32]. An increased number of thyroidectomies will result in more specimens being examined for carcinoma, possibly another contributing factor for increased detection. In a retrospective study, patients who had undergone total thyroidectomy for hyperthyroidism, incidental papillary thyroid microcarcinomas were found in 28% of the euthyroid goiter group and 26% in patients with Graves' disease [33].

5. OVERDIAGNOSIS OF THYROID CANCER

According to literature, most thyroid cancers are treated by total thyroidectomy which is performed for 85 % of diagnosed patients [2]. These people are at risk of intra-operative as well as postoperative complications: including permanent hypoparathyroidism or vocal cord paralysis. Such patients will also need lifelong supplementation of thyroid hormones and surgical, endocrinological monitoring. Some of them will receive radiation treatment which can increase the risk of other cancers.

Three mechanisms explaining an increase in the incidence of thyroid cancer were described [2]:

1) Opportunistic screening - physical check-up of asymptomatic patients
2) Diagnostics cascade - performing various tests for evaluation of diagnosis
3) Incidental findings - accidental detection of thyroid abnormalities on radiological examinations for other purposes.

Some studies reveal that a large number of thyroid cancer cases was due to an increased incidence of papillary carcinoma and early stage tumors [11]. This resulted in a three up to four- fold increase in the number of thyroidectomies [11].

Between 45 % and 70 % of thyroid cancer cases can be overdiagnosed in France, the United Kingdom, the US [34]. The rate of total thyroidectomies or lobectomies increased from 31 % to 44 % [11,35-37].

The increase in the incidence of thyroid cancer is largely due to a rising incidence of papillary thyroid cancer. This change is characterized with slow growth and low potential for recurrence or mortality. However, there are not many data regarding the survival of patients who have never received treatment. According to studies, it is clear that more tumors are being detected due to increased performance of ultrasound-guided fine-needle aspirate biopsy. Ultrasound enables to recognie smaller lesions - variants of papillary cancers. This can be also treated as overdiagnosis if it is not proven in histopathology [38]. Some authors suggest that in the case of minimally invasive tumors, such as follicular carcinoma and encapsulated follicular variant of papillary thyroid carcinoma (EFVPTC), a simple excision of the lesion is considered if there is no doubt with regards to diagnosis [38,39]. Follicular variant of papillary thyroid carcinoma (FVPTC) is a challenging and controversial diagnosis. Reclassification can affect more than 45,000 patients worldwide each year and result in reduction of negative consequences associated with the diagnosis of cancer such as psychological burden, medical overtreatment and expense. According to literature, only 2 (0.6%) of 352 well-documented non-invasive encapsulated/well-circumscribed FVPTCs recurred [29,40-43]. If the diagnosis of noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) is made on the basis of a careful histopathological analysis, the recurrence rate of the tumor will beless than 1% within the first 15 years [29].

Genetic factors are important. Thus, they should be considered. They shed light on prognostic capacities. BRAF, RAS, TERT promoter mutations, occurring in papillary cancers on their own, do not significantly affect mortality. If the TERT promoter contains a mutation accompanied by BRAF and RAS mutations, it is highly probable that mortality due to thyroid cancer will be higher Introduction of molecular diagnostics into everyday clinical practice is still a great challenge [41-43].

6. CONCLUSIONS

The increase in overdiagnosis of thyroid cancer is already a serious public health concern. It is important to gain more research evidence in order to evaluate the best approach, to be able to differentiate stationary cancers from potentially aggressive diseases and to avoid unnecessary harm to patients. Professional literature confirms that the problem of overdiagnosis and overtreatment in papillary thyroid cancer has arisen. It is necessary to perform more randomized clinical trials on an alternative approach—active surveillance of incidentally identified, asymptomatic, small papillary thyroid cancers [2]. Reclassification of the conditions, i.e. classifying them into other categories than cancer should be carefully considered. In highly developed countries, where patients are provided with good access to diagnostic tests such as ultrasound, CT, MRI and possibility to enjoy routine cancer surveillance, the incidence of thyroid cancer is higher. Since ultrasounds became available, small-sized thyroid nodules are being increasingly discovered through imaging examinations, even unintentionally. Each patient with suspicion of cancer should be individually, more closely examined with consideration given to risk factors. It cannot be excluded that unfavorable trends regarding risk factors for thyroid cancer lead to overdiagnosis.

If we follow these patterns, we will be more able to tell which conditions might be real and which can be identified as subclinical diseases [2].

Concluding, overdiagnosis can lead to overtreatment. Many patients undergoing surgery and often receiving radioactive iodine as part of their cancer therapy may never have developed the clinical disease. Thus, we need to develop better tools for improve detection of small cancers that really need treatment.

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