Occult thyroid carcinoma

Carcinoma tiroideo occulto

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SUMMARY

Some medical definitions remain the same for many years, others change due to the progress in the diagnostic tools, which are able to distinguish markers and symptoms until then undetectable. Occult thyroid carcinoma is a general term indicating clinically different situations, whereas the incidentally detected papillary thyroid microcarcinoma is the most important from the clinical point of view. It is fundamental, for therapeutic management, to determine biological parameters which would define a small group of papillary thyroid microcarcinomas with aggressive biological behaviour. The most promising genetic and molecular markers for papillary thyroid carcinoma risk stratification are discussed in this review. Preoperative evaluation of these markers, obtained through analysis of ultrasonography-guided fine needle biopsy specimens of papillary thyroid microcarcinoma, could be very valuable in guiding treatment of this type of cancer.

KEY WORDS: Thyroid • Occult carcinoma • Papillary microcarcinoma • Molecular markers • Therapeutic strategy

RIASSUNTO

Alcune definizione mediche restano invaiate nel tempo, mentre altre si modificano seguendo i progressi che consentono in campo diagnostico di definire markers e sintomi fino a quel momento non valutabili. Il carcinoma occulto della tiroide è un termine generico che indica differenti situazioni cliniche, mentre il microcarcinoma papillifero della tiroide diagnosticato incidentalmente resta l'entità clinica maggiormente significativa. È fondamentale ai fini della programmazione terapeutica la possibilità di identificare dei parametri biologici in grado di differenziare i microcarcinomi papilliferi sulla base della loro aggressività. In questa review sono stati rivisti i markers genetici e molecolari del microcarcinoma papillifero della tiroide più significativi ai fini di una loro possibile stratificazione. La valutazione preoperatoria di questi markers, ottenuti attraverso l'analisi di agobiopsie ecoguidate di microcarcinomi papilliferi, potrebbe essere utile per la pianificazione terapeutica di questo tipo di carcinoma.

PAROLE CHIAVE: *Tiroide • Carcinoma occulto • Microcarcinoma papillifero • Markers molecolari • Strategia terapeutica*

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Introduction

Papillary and follicular malignancies are well differentiated carcinomas of the thyroid gland and are among the most curable cancers [1]. Patients can be identified by using well-established prognostic parameters and therapy can follow a variety of published and regularly renewed guidelines. Treatment of thyroid cancer employs a three-tiered approach comprising surgery, iodine radiometabolic treatment and long-term thyroid-stimulating hormone suppression by exogenous administration of thyroid hormone [2]. The overall survival rate, at 10 years, for middle-aged adults with thyroid carcinomas, is about 80-95% [1]. This review focuses on one subcategory of differentiated thyroid carcinomas. "Occult thyroid carcinoma" is a general term including clinically different situations.

Classification

In the literature, there are different definitions of the term: "Occult Thyroid Carcinoma". The Merriam-Webster dictionary, in the current on-line version, explains "Occult carcinoma" as "not manifest or detectable by clinical methods alone", and *also* as "not present in macroscopic amounts" [3]. The McGraw-Hill Concise Dictionary of Modern Medicine (2002) defines "occult primary malignancy" as "unknown primary malignancy that is symptomless, which first manifests itself as metastases or secondary paraneoplastic phenomena" [4]. In 1997, Moosa and Mazzaferri defined "Occult thyroid carcinoma" as an "impalpable thyroid carcinoma that is generally smaller than 1.0 cm" [5]. A more precise definition of size is used by Stedman's Medical Dictionary (2006), where "occult papillary carcinoma of the thyroid" is described as micro-

carcinoma of the thyroid or microscopic papillary carcinoma of the thyroid, usually well encapsulated and measuring less than 5 mm in diameter [6]. A combination is used in the WHO (World Health Organization) classification system, where papillary thyroid microcarcinoma (PTMC) is defined as "papillary carcinoma measuring 1.0 cm or less in maximal diameter while other clinico-pathological features, such as metastasis to regional lymph nodes and/or distant organs as well as extrathyroid extension, are not considered" [7]. Shaha is using a broader definition of PTMC: "Traditionally, microcarcinoma was considered to be less than 1 or 1.5 cm" [8].

From the previous paragraph, it is clear that the term occult thyroid carcinoma and papillary microcarcinoma could be considered synonyms in the majority of clinical situations. Nevertheless, there are some mismatching situations. For a better understanding, we can divide the term "occult thyroid carcinoma" into four different categories. The first group comprises patients with thyroid carcinoma or microcarcinoma incidentally found in the thyroid gland after total thyroidectomy for benign disease [9-11] or at autopsy [12-19]. In the second group there are patients with incidentally detected PTMC on imaging studies, mainly ultrasonography, and evaluated by fine needle aspiration biopsy (FNAB). The third group are patients with clinically apparent metastases of thyroid carcinoma, where the primary tumour is not detectable before surgery and microscopic tumour – microcarcinoma is found in the final histological specimen. The fourth group covers patients with thyroid cancer localized in ectopic thyroid tissue with clinical symptoms or with apparent metastases.

Thyroid gland embryology

The primordial thyroid gland is the first identifiable, approximately on the 24th day of gestation, beginning as an endodermal invagination, a proliferation of endodermal epithelial cells on the median surface of the developing pharyngeal floor. The thyroid gland originates between the first and second pharyngeal (branchial) pouches. The area is known as the foramen caecum and lies where the midline intersects the *sulcus terminalis*, which divides the tongue into anterior two thirds (oral part) and posterior one third (pharyngeal part). The thyroid diverticulum begins its descent through the tongue carrying with it the thyroglossal duct and, during the fifth and sixth weeks, the path of descent carries the developing gland anterior to the hyoid bone and the larynx. At the same time, the gland becomes bi-lobed, medially connecting with the isthmus and the superior part of the thyroglossal duct degenerates. During the seventh week, the descent of the thyroid continues and it reaches its final position, level under the cricoid cartilage anteriorly to the trachea. The distal part of the thyroglossal duct degenerates, but may remain as a pyramidal lobe [20]. Thyroid hormones start to be secreted during the twelfth week of development. Para-folicular cells originate in the neural crest region and infiltrate the ultimobranchial body which arises from the fifth pharyngeal pouch. Ultimobranchial body then fuses with the thyroid beyond the anterior part of the neck during the process of descent and the cells disseminate into the thyroid and differentiate into calcitonin-producing C cells [21].

Thyroid carcinoma in ectopic thyroid tissue

Failure of migration can result in ectopic thyroid tissue being differentiated anywhere along the thyroglossal tract. It has been found in a variety of sites ranging from the base of the tongue to the neck, and has also been found in the trachea, oesophagus [22], mediastinum [23] and associated with the heart's descent [24 25]. The majority of ectopias are manifested as simple thyroglossal duct cysts in conjunction with a normally developed thyroid gland [26]. The most frequent remnant is the caudal part of the track-pyramidal lobe, present in 30-50% of patients [21 24].

Complete arrest of the descent of the developing thyroid, resulting in the presence of thyroid tissue at the tongue base, is known as lingual thyroid. Carcinoma arising in a lingual thyroid is very unusual [26] and, in contrast to other localizations, the follicular type is predominantly reported. Less differentiated (medullary) or undifferentiated (anaplastic) carcinomas in the lingual thyroid have not been reported in the literature. The explanation for medullary carcinoma can be found in embryology. The C-cells migrate independently and fuse with the thyroid after its complete descent from the foramen caecum. Clinical symptoms occur mainly on account of a mass effect and include dysphonia, dyspnoea, dysphagia or a foreign body sensation, rarely hemoptysis. Due to the fact that lingual thyroid carcinoma is an extremely rare entity, there is no general consensus regarding the most appropriate therapeutic strategy in the literature. Surgery is the treatment of choice, usually peroral resection, which could be combined with an external approach – lateral pharyngotomy or transhyoid incision. A neck dissection would only be indicated if metastatic nodules are noted. If there are positive margins, or more advanced disease is present, adjuvant radiometabolic treatment should be given [26].

Persistence of the thyroglossal duct with cyst formation is the most common congenital cervical abnormality. It may be located anywhere from the thyroid cartilage up to the base of the tongue, but approximately 50% of these cystic masses are located at, or just below, the level of the hyoid bone. The incidence of carcinoma arising in the thyroglossal duct cyst is reported to be about 1.3% in the adult population, with papillary thyroid carcinoma (PTC) comprising the majority of cases [27]. Also mixed papillary-follicular, squamous cell carcinoma or Hürthle cell carcinoma may be found [28]. Choice of therapy must be based upon the patient's age and the size and extent

of the tumour. The treatment of choice for thyroglossal duct cyst with microscopic focus of papillary carcinoma (TDCC), without cyst wall invasion, is surgical excision via a Sistrunk procedure [29], first described in 1920 [30]. The key elements are removal of the central portion of the hyoid bone and excision of any proximal thyroglossal duct. In other situations, removal of all thyroid tissue, followed by radiometabolic treatment should be performed [28 31]. Nevertheless, opinions differ as to whether thyroidectomy and neck dissection should be performed since carcinoma is found in approximately 25-40% of thyroid glands and about 10% metastasize to cervical lymph nodes [32]. Moreover, Hartl et al. [33] recently reported a high rate of multifocality and lymph node metastases. They found foci of carcinoma in thyroid lobes in 56% of patients and 75% had lymph node metastases, in both central and lateral compartments [33]. However, overall prognosis is favourable for the majority of patients [31 32].

In very rare circumstances, thyroid tissue may be found below the diaphragm. It could be associated with the gastro-intestinal tract [20], but more often it is described as a *struma ovarii*. *Struma ovarii* is a monodermal highly specialized ovarian teratoma, which is composed predominantly of biologically active thyroid tissue (more than 50% of thyroid tissue in tumour mass) [34 35]. It was described for the first time in 1889 [36]. This thyroid tissue is derived from an ovarian germ cell tumour [20] and exhibits the same histological, physiological and pharmacological features as cervical thyroid tissue. Only 3-5% of these cases are classified as malignant. Although the most prevalent histological type is follicular carcinoma, papillary, mixed follicular-papillary or a follicular variant of papillary carcinoma have also been reported. Metastatic disease is extremely rare. Metastases are predominantly found in the peritoneum, mesentery and omentum. Primary carcinoma of the thyroid must be excluded. The therapeutic schema is not well defined, metastases can accumulate radioiodine, and thus, total thyroidectomy is usually part of a complex surgical therapeutic approach followed by radioiodine ablation and thyroid-stimulating hormone (TSH) suppression. Furthermore, thyroglobulin levels can be monitored as a tumour marker for recurrence.

Occult thyroid carcinoma

Some medical definitions remain unchanged for many years, others are changed due to the progress in the diagnostic tools, which are able to distinguish markers and symptoms, until then undetectable. The term "Occult thyroid carcinoma" was used, for the first time, in the middle of the last century [37]. It defined thyroid cancer, with or without local metastases, which was identified after final histology [38]. This situation has radically changed in the last 10-15 years, since when ultrasonography (US) has become a routine investigation in the care of patients with thyroid diseases and is now a gold standard both in the diagnostic process and follow-up. US allows detection of very small nodules (up to 3 mm) and US guided FNAB can be, with high sensitivity, helpful in defining the biological behaviour of the nodule [39-41].

Incidentally detected thyroid carcinoma

The first papers reporting thyroid cancer, usually found at autopsy date back to the middle of the last century. The patients did not have any clinical symptoms during their lives [13]. The same methodology has been updated since then in several autopsy studies across the world [12 14-19 42-50] and autopsy prevalence of thyroid carcinoma (or microcarcinoma) has been reported ranging from 0.01% in USA [16] to 35.6% in Finland [15]. This enormous difference might be explained by genetic factors, environmental factors and methods used for histological examination.

Probably the most important factor is genetic predisposition, which is supported by the fact that the prevalence in the Japanese population exposed to the radiation during the bomb attack on Hiroshima and Nagasaki (11.3-28.4%) [12 14 16] and in the Japanese population staying in Hawaii, without the radiation exposure (24%) [16 19], is similar. In the literature, several critical genetic alterations, associated with development of specific thyroid tumour types, have been described. The three types of genetic alteration in the Mitogen-activated Protein Kinase (MAPK) pathway, including *RET* rearrangement and *Ras* and *BRAF* mutation, are present in approximately 70% of PTCs [51]. The MAPK pathway is activated by signals from a variety of cell surface receptors and growth factors [52]. All of them are sufficient to trigger PTC tumourigenesis, but from numerous clinico-pathological and molecular studies, it is obvious that *BRAF* mutation plays a fundamental role in progression, invasiveness and recurrence of PTC. *BRAF* mutation is also associated with overexpression of the Vascular Endothelial Growth Factor (VEGF) [53], which is a strong angiogenic protumour molecule that plays a critical role in human cancer progression and invasion [54]. The explanation for this proangiogenic *BRAF* – VEGF association is in the unique molecular mechanism, when *BRAF* mutation promotes VEGF overexpression and inhibition of Tissue Inhibitor of Metalloproteinases-3 (TIMP3) [51]. TIMP3 is the tumour inhibitor, which suppresses tumour growth, angiogenesis, invasion and metastasis by preventing the interstitial matrix destruction promoted by matrix metalloproteinase 3 (MMP-3) [55]. Moreover, *BRAF* mutation, in the primary PTC, is associated with loss of radioiodine avidity in the recurrent tumour [56].

Recently, Gudmundsson et al. [57] published the results of a genome-wide association study, which involved more than 37,000 individuals of European descent and reported that a common variation on 9q22.33 and 14q13.3 predis-

poses to thyroid cancer. Individuals who are homozygous for both variants have an estimated risk of thyroid cancer 5.7-fold greater than non-carriers.

Iodine intake is mentioned as an important environmental factor. A wide range of variants has been found in different parts of the world. In areas with sufficient iodine intake, the incidence of thyroid cancer is higher and a predominance of papillary carcinoma has been mentioned. Iodine-dependent areas represent an increased prevalence of goitre and thyroid nodules and follicular and anaplastic cancers would be more prevalent [58]. On the other hand, in 2005, Kovacs et al. [43] published results of a study, where consecutive series of autopsies were performed in Hungary in two areas with different iodine uptake [59]. They concluded, that the prevalence of microcarcinomas was not related to iodine intake, because from 222 thyroids examined in an iodine deficient group and from 221 thyroids in an iodine sufficient group, the prevalence was only 4.74%, with respect to 4.52% [43].

The next important and, in extreme situations, the most important factor, is exposure to radiation. The thyroid gland is highly sensitive to radiation-induced oncogenesis and both types of radiation, external or internal (delivered from radioiodine), are the most prominent factors in the development of thyroid cancer [60]. The most vulnerable is the thyroid gland in children, which was clearly documented in Belarus, in connection with the Chernobyl accident. The incidence of thyroid cancer, in children, was less than 1 per million, per year, before the accident, but after the accident increased, in certain areas, to 100 cases per million per year. Surprisingly, in the Chernobyl region, a big difference was found in children, exposed to radiation in the age group younger than 3 years and those exposed before birth (*in utero*), born after the accident. Fifteen years after the accident, in the first group, 33 cases of thyroid cancer were found (out of 9472 children), compared to no cases in the group exposed *in utero* (out of 12129 children) [61].

Within the context of radiation, it is necessary to mention that there is an increased risk in patients with a history of benign thyroid disease (thyroid nodules, Grave´s disease, hyperthyroidism) and external radiation to the neck area and, indeed, very young oncologic patients, after radiation therapy [11 62-65].

Methods used for histological examination of the thyroid glands differed in the studies [12 14-19 42-50]. While formalin fixation and 3 mm slices of the gland were used in all studies, only some Authors examined all slides microscopically. Others embedded only macroscopically suspected. Meta-analysis [43] of the prevalence of thyroid microcarcinomas (or occult thyroid carcinoma) found 13.19% of the microcarcinomas in the first group and 10.20% in the second. Moreover, Sampson et al. [42] published a study focusing on more than 140 papillary microcarcinomas less than 1 mm in maximum dimension. Thus the prevalence of papillary microcarcinoma in autopsies, if sectioned thinly enough, could be even higher than data published to date.

Papillary thyroid carcinoma *versus* microcarcinoma

The incidence of thyroid cancer is increasing, while the incidence of many head and neck cancers is decreasing [66 67]. But, as epidemiological studies and stable overall mortality for this type of cancer have revealed, it is predominantly due to the increased detection of small cancers – microcarcinomas, which is the result of the use of precise imaging studies – magnetic resonance imaging (MRI) and, US [66]. The more frequent detection of occult thyroid carcinoma is the main reason for changes in the ratio in the prevalence of papillary and follicular thyroid carcinoma in Western countries and in Japan. In both regions, the percentage of papillary thyroid carcinoma is increasing, from 78.4% thirty years ago [68] to 93%, registered by the Japanese Society of Thyroid Surgeons (JSTS), in 2004. A similar situation has been reported in Western countries, where, in 2002, papillary carcinoma comprised 85.3% [69 70]. The second reason for the increasing prevalence of papillary thyroid carcinoma, mentioned by Ito & Miyouchi [69], could be the previous classification of the follicular variant of papillary carcinoma as a follicular carcinoma.

The prevalence of incidentally detected PTMC found at autopsy and from clinical studies was 100-1000-fold higher than the incidence of clinical cancer [43 69]. This finding strongly suggests that most papillary microcarcinomas remain latent and do not become clinically apparent. Therefore, there is considerable doubt as to whether all PTMC should be treated surgically, immediately after diagnosis, although it is also true that PTMC is frequently multicentric and metastasizes to the lymph nodes [69]. PTMC is not a uniform category. Fundamental, for future clinical work, is to determine the clinical and especially the molecular parameters which would define a small group of PTMC with an aggressive biological behaviour [71].

Roti et al. [9] attempted to identify clinical characteristics differentiating incidental PTMC and suspected clinical carcinoma. There were no clinical differences, except for the size of the tumour. None of the patients with a cancer < 8 mm had distant metastases [9 72].

One of the most interesting molecular markers for determining the biological behaviour of the papillary microcarcinoma could be Cyclin D1, the overexpression of which has been associated with 93.3% of clinical PTC, but only 12.5% of asymptomatic PTMC ($p = 0.0001$) [73]. Also Khoo et al. [74] found that Cyclin D1 protein is greatly overexpressed in metastasizing PTMC (90.9%), but only in 8% of nonmetastasizing PTMCs ($p < 0.001$). These Authors did not find any increase in the Cyclin D1 gene. They concluded that Cyclin D1 overexpression was asso-

ciated with metastasizing PTMC and Cyclin D1 immunohistochemistry might be a valuable tool in predicting the metastatic potential [74].

Activation of the signalling pathways (Wnt / b-catenin) through Cyclin D1 up-regulation, at an early stage of thyroid carcinogenesis, may promote tumour growth and metastatic potential in PTMC. Cyclin D1 expression was significantly associated with tumour size, aggressive growth and metastases to lymph nodes [75 76].

Ito et al. [77] demonstrated that increased expression of Cyclin D1 protein is associated with overexpression of other cell proliferating markers, such as pRb (retinoblastoma gene product) and Ki-67 as well as with decreased expression of p27 (p27 is a tumour suppressor protein and acts as an inhibitor of Cyclin Dependent Kinases 2 (Cdk2) activity, it is also required early in the cell cycle for the assembly of Cyclin D1/Cdk4 complexes) in patients with clinically apparent metastasis of PTMC compared to patients without metastases or patients with occult metastases.

Cyclin D1 protein overexpression was frequently demonstrated in clinically apparent well differentiated papillary carcinoma [78], but is also associated with more aggressive types of thyroid carcinomas (tall cell variant, anaplastic, etc.) [79] and with tumours of patients under 40 years of age [80].

Protein S100A4 has been mentioned with regard to the metastatic potential of papillary microcarcinoma. Its positivity, in immunohistochemistry, was significantly associated with macrometastasis and lateral node metastases [81 82]. S100A4 is member of the S100 calcium-binding proteins that regulate intracellular processes such as cell growth, motility, cell cycle, transcription and differentiation. Its capacity to promote invasion and metastasis of many human malignancies has also been identified [83-87].

As already pointed out, genetic alterations associated with MAPK pathway are frequently detected in PTC. Although the overall prevalence of BRAF mutation in PTC is relatively high (approximately 45% on average), the prevalence in PTMC is much lower, as documented in studies from many parts of the world [88-91]. The only exception are studies from Korea, in which an unusually high prevalence of BRAF has been reported in both PTC (80-90%) [92-94] and PTMC (65%) [95]. A relatively low prevalence of BRAF, in PTMC, seems to be feasible for a new risk stratification of PTMC. BRAF mutation detected by means of FNAB [94 96] could be the parameter of choice for the selection of patients for the appropriate extent of surgical and medical treatments [97].

Therapeutic strategy

Incidentally detected PTMC is clinically the most important subcategory of the term "Occult thyroid carcinoma". The incidence of PTMC is increasing because of the routine use of imaging methods, in combination with FNAB. The majority of these patients do extremely well with appropriate limited surgery and close follow-up [98]. The impact of medical and surgical interventions on the survival of patients with PTMC was evaluated by Lin et al. [99]. Overall actuarial survival rates, at 10 and 15 years, were 96.6% and 96.3%, respectively. Increasing age was the only statistically important predictor for disease-specific survival ($p = 0.001$). Neither the type of surgery (total thyroidectomy, near-total/subtotal thyroidectomy or lobectomy), nor the radiometabolic treatment has any impact on excellent prognosis of patients with PTMC. The Authors conclude, that patients lacking evidence of metastatic disease may undergo lobectomy alone [99]. The concept of limited surgery is supported also by many other Authors [2 99 100]. Bilimoria et al. [100] analysed almost 40,000 patients from the National Cancer Data Base with papillary thyroid carcinoma and concluded that the treatment of choice for patients with a tumour less than 1 cm is thyroid lobectomy [100].

Some Authors are of the opinion, that surgery, even if limited, may not be the first step of treatment [69]. Ito et al. [101] selected low-risk patients with PTMC and, during 5 years' follow-up, only 6.7% of these patients were confirmed as showing an increase in size at US compared to baseline findings. None developed additional distant metastasis or died of thyroid carcinoma. The Authors conclude that surgical treatment after the appearance of carcinoma progression is not late [101].

On the other hand, PTMC is often multifocal; the range of multiple non-contiguous tumour foci is between 18 and 87%, depending upon the technique used for the pathological analysis [102]. The genetic studies, which compared the specific patterns of monoclonal X-chromosome inactivation [102] and distribution of BRAF mutation [103] demonstrated that the individual tumour foci often arise as independent tumours and, indeed, that they can grow and spread.

Conclusions

PTMC is not a uniform category. Fundamental for future clinical purposes is to determine clinical and especially molecular parameters which would define small groups of PTMC with aggressive biological behaviour. The clinical classification systems for high-risk papillary carcinoma patients, such as the UICC/AJCC TNM staging system [7], or AMES [104], or AGES [105], or MACIS [106], were proposed to stratify the risk based on different clinical parameters, but these are not helpful for PTMC. The most promising genetic and molecular markers for PTMC risk stratification have been discussed in this review. Preoperative information regarding *BRAF* mutation status, overexpression of protein S100A4 or Cyclin D1, obtained by analysis of FNAB specimens of PTMC, could be extremely valuable

in determining the choice of therapeutic management of this cancer. It could help to assess the extent of initial surgical treatment and the need for radioiodine ablation. In some cases, patients for whom only follow-up was indicated, could be defined thanks to these genetic and molecular markers.

Abbreviations

PTMC: papillary thyroid microcarcinoma
PTC: papillary thyroid carcinoma
WHO: World Health Organization
FNAB: fine-needle aspiration biopsy
UICC: Union Internacional Contra la Cancrum or International Union Against Cancer
AJCC: American Joint Committee on Cancer
AMES: age, metastases, extent and size
AGES: age, grade, extent, and size
MACIS: metastases, age, completeness of excision, invasiveness, size
TDCC: thyroglossal duct cyst papillary carcinoma
MAPK: mitogen-activated protein kinase
VEGF: vascular endothelial growth factor
pRb: retinoblastoma gene product
MRI: magnetic resonance imaging
US: ultrasonography

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