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Endocrine related cancer review

Thyroid stimulating hormone in thyroid cancer: does it matter?

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Abstract

Differentiated thyroid cancer is the most common endocrine malignancy and the incidence is increasing rapidly worldwide. Appropriate diagnosis and post-treatment monitoring of patients with thyroid tumours is critical. Fine needle aspiration cytology remains the gold standard for diagnosing thyroid cancer and whilst there have been significant refinements to this technique, diagnostic surgery is often required for patients suspected to have malignancy. Serum thyroid stimulating hormone (TSH) is higher in patients with malignant thyroid nodules compared to those with benign disease, and TSH is proportionally increased in more aggressive tumours. Importantly, we have shown that the pre-operative serum TSH concentration independently predicts the presence of malignancy in subjects presenting with thyroid nodules. Establishing the use of TSH measurements in algorithms identifying high risk thyroid nodules in routine clinical practice represents an exciting, cost-efficient and non-invasive approach to optimise thyroid cancer diagnosis. Binding of TSH to receptors on thyrocytes stimulates a number of growth promoting pathways both in normal and malignant thyroid cells and TSH suppression with high doses of levothyroxine is routinely used following thyroidectomy in order to prevent cancer recurrence, especially in high risk tumours. This review examines the relationship between serum TSH and thyroid cancer and reflects on the clinical potential of TSH measurements in diagnosis and disease monitoring.

TSH in thyroid cancer: does it matter?

Introduction

Differentiated thyroid malignancy is the most common endocrine malignancy and over the last few decades, its incidence has increased dramatically worldwide (Kitahara and Sosa 2016; Sipos and Mazzaferri 2010). It is currently the fifth most common malignancy in women in the US and an estimated 62,000 new cases were found in North American men and women in 2015 (American Cancer Society 2015). Thyroid cancer causes more deaths than any other endocrine cancer (Monson 2000) and there will be an estimated 1,980 deaths from thyroid cancer in the US in 2016 (American Cancer Society 2016). The reasons for the observed increase in incidence have been widely debated (Wartofsky 2010) and include enhanced detection of subclinical thyroid cancer due to the growing use of diagnostic imaging as well as exposure to a number of environmental factors (Kitahara and Sosa 2016). Whilst better access to health care in countries with high socio-economic status may in part explain the rising incidence, observations of increased thyroid cancer rates in lower socio-economic countries, an increasing number of larger tumours as well as the changing thyroid cancer molecular profiles indicate that other factors are likely to be involved (Vigneri, et al. 2015). A number of disease modifiable factors including obesity have been identified as potential aetiological factors (Schmid, et al. 2015). Moreover a variety of thyroid-specific environmental carcinogens have been implicated including ionising radiation, increased dietary iodine intake and environmental pollutants (Vigneri et al. 2015). Overall, the observed changes in thyroid cancer incidence are likely due to a combination of detection bias and true increases in incidence.

Thyroid cancer often presents as a solitary nodule or as a part of a multinodular goitre. This creates an important clinical dilemma as thyroid nodules are very common occurring in 50-67% of the population and more than 90% are benign (Durante, et al. 2015; Hegedus 2004; Mazzaferri 1992; Popoveniuc and Jonklaas 2012). Detection rates of thyroid nodules are increasing due to widespread use of imaging modalities in advanced health care systems (Cramer, et al. 2010; Popoveniuc and

65 Jonklaas 2012). While incidental thyroid neoplasms have long been recognised due to their presence
66 during post-mortem examinations (Dean and Gharib 2008), there is a significant and increasing
67 clinical burden associated with detecting this disease in patients (Brito, et al. 2014), for whom the
68 differentiation between aggressive and indolent diagnoses is crucial (Cabanillas, et al. 2016a).

69 There are a number of well-established and evolving clinical tools to discern malignant from
70 benign thyroid nodules (He, et al. 2016). Most international guidelines recommend the use of a
71 combination of diagnostic tools, including measurement of thyroid stimulating hormone (TSH) to
72 assess functional thyroid status, high resolution ultrasonography (US) scanning to assess the
73 morphological characteristics of the thyroid and nodule(s), and fine needle aspiration biopsy for
74 cytological evaluation of the presence of malignancy (Hegedus, et al. 2003; Perros, et al. 2014; Pitoia
75 and Miyauchi 2015). In recent years the use of panels of molecular markers to refine the cytological
76 diagnosis of malignancy has received significant attention, although these tests are very expensive
77 and not used routinely in all centres (Xing, et al. 2013). Since most benign nodules do not require
78 further intervention it is pertinent that thyroid malignancy is diagnosed accurately and further
79 refinement of current diagnostic approaches is required.

80 If malignancy is diagnosed, surgery is the primary treatment modality for differentiated
81 thyroid cancer, followed by adjuvant radioiodine ablative therapy in a significant number of patients
82 (Burns and Zeiger 2010; Perros et al. 2014; Pitoia and Miyauchi 2015). Since TSH is a growth factor
83 for thyroid cells, therapy with suppressive doses of levothyroxine is often used postoperatively and
84 this has long been known to positively affect outcomes in differentiated thyroid cancer (Mazzaferri
85 and Jhiang 1994; McLeod, et al. 2012; Pujol, et al. 1996). Current guidelines recommend the medium
86 to long term use of TSH suppression in high risk thyroid cancer but not in lower risk tumours because
87 of the health risks associated with the induction of subclinical and overt thyrotoxicosis (Perros et al.
88 2014; Pitoia and Miyauchi 2015).

The diagnosis and post-therapy monitoring of patients with thyroid nodules and cancer is important. We were the first to publish that serum TSH is raised in patients with malignant thyroid nodules compared to those with benign disease (Boelaert et al 2006), and subsequent studies have shown that pre-operative serum TSH is proportionally higher in those with more aggressive disease (Boelaert, et al. 2006; Fighera, et al. 2015; Haymart, et al. 2009; Jonklaas, et al. 2008; McLeod, et al. 2014). This review aims to explore the relationship between TSH and thyroid cancer, both before and after a diagnosis of malignancy is made.

Thyroid-stimulating hormone

Hormone structure and biochemical details

Thyroid stimulating hormone (TSH) is a two subunit glycoprotein, released from the pituitary gland in response to hypothalamic release of thyrotropin releasing hormone (TRH). The alpha subunit of the glycoprotein is similar to that of luteinising hormone (LH) and follicle-stimulating hormone (FSH), with specificity only related to the beta subunit. TSH, or thyrotropin, stimulates the thyroid to produce and secrete thyroxine (T4) and triiodothyronine (T3). The released T4 becomes effective once converted peripherally to triiodothyronine (T3) by deiodinase enzymes. The functionally active circulating hormones provide a feedback loop directly to both the hypothalamus and the pituitary suppressing further release of TSH and TRH, thereby maintaining homeostatic control of the hypothalamic-pituitary-thyroid axis (Magner 1989; Sarapura, et al. 2011; Szkudlinski, et al. 2002).

TSH function in the normal thyroid

TSH acts on thyroid cells signalling through the TSH receptor, which is found predominantly on follicular thyroid cells. TSH is a growth factor for thyrocytes, with prolonged exposure causing hyperplasia and hypertrophy (Sarapura et al. 2011). Stimulation of the TSH receptor causes activation of the adenylate cyclase pathway, resulting in alterations in cell-cycle proteins causing changes in thyroid gland growth and cell morphology, as well as the production of thyroid hormones. The effects of TSH can be broadly summarised as follows: synthesis of thyroid hormones, thyroid gland growth, changes in thyrocyte morphology, regulation of post-transcriptional activation of the sodium iodide symporter (NIS) and modulating extra-thyroidal effects (Sarapura et al. 2011).

Diagnosing thyroid malignancy

Types of thyroid cancer

Thyroid cancers arise from thyroid follicular cells or parafollicular cells. Differentiated thyroid cancer (DTC) includes two subtypes, papillary and follicular cancers, both of which arise from

follicular cells and together make up 90% of thyroid cancers. Papillary thyroid cancers are the most common and represent 85% of all thyroid malignancies. Medullary thyroid cancers account for 3-4% of all thyroid cancers and 80% arise from sporadic mutations, whereas the remainder are hereditary, usually as part of multiple endocrine neoplasia syndromes. Finally, thyroid cancers can be undifferentiated, referred to as anaplastic thyroid cancers, and these tumours have the most aggressive phenotype and the worst prognosis with median survival rates of 3-7 months (Cabanillas, et al. 2016b).

Current diagnostic approaches and limitations

Guidelines recommend that patients suspected to have thyroid malignancy are assessed by a physician with a specialist interest in thyroid cancer care, and who is a regular member of the multi-disciplinary team (Perros et al. 2014). It is paramount to perform a full clinical assessment which includes taking a personal and family history as well as careful clinical examination (Hegedus 2004; Hegedus et al. 2003; Perros et al. 2014; Pitoia and Miyauchi 2015). In many cases, however, thyroid glands harboring malignancy are clinically indistinguishable from those that do not and there is substantial variation among practitioners in evaluating nodules. Features suggestive of malignancy include the presence of firm, fixed thyroid lumps, vocal cord palsy, a positive family history, rapid nodule growth and being at the extremities of age (>60 years or <20 years) (Hegedus et al. 2003). Table 1 displays clinical characteristics associated with an increased risk of malignancy.

The serum TSH concentration is routinely measured to exclude the presence of a toxic nodule causing subclinical or overt hyperthyroidism in all patients (Hegedus et al. 2003; Perros et al. 2014; Pitoia and Miyauchi 2015). If the TSH is below the laboratory reference range, assays for free triiodothyronine (fT3) and free thyroxine (fT4) are required in order to exclude overt hyperthyroidism (raised free T4 and free T3) or “T3-toxicosis” (raised serum free T3 alone). Similarly, if TSH is raised then overt hypothyroidism must be excluded (this being indicated by low fT4 with a raised TSH concentration). Although virtually all patients with thyroid carcinoma are euthyroid, the

147 presence of a suppressed serum thyrotrophin (TSH) level (generally indicative of subclinical or overt
148 thyrotoxicosis) does not rule out the presence of malignancy (Hegedus 2004; Hegedus et al. 2003;
149 Perros et al. 2014; Pitoia and Miyauchi 2015). Measurement of serum thyroglobulin is of little value
150 in the initial diagnosis of thyroid cancer whereas this remains an important tumor marker in the
151 follow-up of patients with thyroid cancer (Perros et al. 2014; Pitoia and Miyauchi 2015).
152 Measurements of basal plasma calcitonin and carcino-embryonic antigen (CEA) are useful if
153 medullary carcinoma is suspected but do not form part of the routine evaluation of thyroid nodules
154 (Perros et al. 2014).

155 Thyroid ultrasonography is an extremely sensitive tool for the diagnosis of thyroid nodules
156 and may be specific in diagnosing papillary thyroid cancer (Cesur, et al. 2006; Hambly, et al. 2011).
157 Moreover this imaging modality aids the decision-making processes of which nodules to target for
158 fine needle aspiration biopsy (FNAB) and increases the diagnostic yield of thyroid cell sampling
159 (American Cancer Society 2015; Perros et al. 2014; Pitoia and Miyauchi 2015). Multiple studies have
160 confirmed typical sonographic features associated with increased risks of malignancy (Table
161 2(Frates, et al. 2005; Hambly et al. 2011; Lee, et al. 2011)) and current guidelines now recommend
162 the use of a combination of these features in algorithms predicting the likelihood of thyroid
163 malignancy as well as the selection of nodules requiring (FNAB) (Haugen, et al. 2015; Perros et al.
164 2014; Pitoia and Miyauchi 2015). High resolution ultrasonography by an experienced operator is
165 highly recommended in the initial evaluation of patients with thyroid nodules.

166 Fine needle aspiration cytology remains the gold standard to confirm absence or presence of
167 thyroid malignancy. The results can confirm that a nodule is benign, triage patients requiring
168 diagnostic surgery or confirm a diagnosis of malignancy enabling one step therapeutic surgery
169 (Perros et al. 2014; Pitoia and Miyauchi 2015). In the UK, cytology results are reported using the THY
170 classification (The Royal College of Pathologists 2009) whereas in the US the Bethesda scoring
171 system (Bongiovanni, et al. 2012) is employed. Despite accuracy of diagnosis in the majority of
172 thyroid nodules, FNAC has drawbacks including the sometimes high rate of insufficient/inadequate

samples, the inability to distinguish between benign and malignant follicular lesions and difficulties in detecting follicular variant papillary carcinomas (Rago, et al. 2007; Sangalli, et al. 2006).

Indeterminate or suspicious thyroid lesions represent 10-26% of nodules evaluated cytologically. These nodules usually require diagnostic surgery and a median 34% of patients with indeterminate nodules have thyroid malignancy (Xing et al. 2013). In order to avoid unnecessary thyroidectomy, a number of centres use gene expression classifiers or mutation analysis panels to further refine the cytological diagnosis. These diagnostic tools however are very expensive and only routinely available in a limited number of centers world-wide (Bernet, et al. 2014; Pitoia and Miyauchi 2015). Whilst there have been significant advances in our current diagnostic approaches for thyroid cancer, further cost-efficient and easily applicable approaches are needed to allow informed decision making for both physicians and patients when evaluating the likelihood of malignancy in thyroid nodules.

Serum TSH in the diagnosis of thyroid cancer

TSH and promotion of thyroid cancer growth

Several studies including two large meta-analyses (McLeod et al. 2012; Zheng, et al. 2016) have confirmed that higher serum TSH is associated with an increased risk of differentiated thyroid cancer. Table 3 demonstrates a range of original research studies investigating the link between serum TSH concentrations and differentiated thyroid cancer. Importantly, several studies have shown higher TSH to predict thyroid malignancy, independent of other risk factors including patients' age and gender as well as a positive family history (Kim, et al. 2013; McLeod et al. 2012). The first study was performed by our group, and demonstrated an increase in risk of diagnosis of malignancy in parallel with an increase in serum TSH (Boelaert et al. 2006). The lowest risk of thyroid cancer diagnosis was in those with a TSH below the lower limit of the reference range (<0.4 mIU/l). There was a significant cut off at serum TSH of 0.9mIU/l, with an increased risk of cancer diagnosis in those with serum TSH concentrations above this. The highest risk of cancer diagnosis was in the

group with subclinical hypothyroidism who had serum TSH >5.5. mIU/l. Importantly we found that, even within the normal range, higher TSH concentrations correlate with a higher risk of DTC and this was subsequently confirmed by others (Haymart, et al. 2008).

Higher pre-operative serum TSH concentrations have also been associated with more advanced cancer stage at diagnosis. Mean serum TSH levels were higher in those with stage III and IV disease and in those with larger tumours or in cancers associated with lymph node metastases (Fiore, et al. 2009; Haymart et al. 2008; Shi, et al. 2016). A meta-analysis of 28 studies, analysing 42,032 control subjects and 5,786 patients with thyroid cancers has confirmed that higher pre-operative TSH levels are associated with increased risk of thyroid malignancy as well as a correlation with higher disease grade (McLeod et al. 2012). A more recent meta-analysis of 56 studies encompassing 20,227 thyroid cancer cases and 50,003 controls with benign thyroid nodules has confirmed that higher serum TSH level were significantly associated with thyroid cancer size and with the presence of lymph node metastasis (Zheng et al. 2016). These findings are consistent with serum TSH having a role in the promotion of thyroid tumour growth and agressiveness.

Indeed TSH is a known growth factor for thyroid nodules and suppression of serum TSH concentrations by administering exogenous thyroid hormone may inhibit the growth of established nodules as well as the development of new nodules (Papini, et al. 1998). Benign and malignant thyroid tumours express functional TSH receptors on the plasma membrane (Ichikawa, et al. 1976) and TSH increases adenylate cyclase activity leading to cAMP production and cell growth through stimulation of these receptors in vitro (Carayon, et al. 1980). Importantly the expression of TSH receptors in DTC has been associated with an improved prognosis (Shi, et al. 1993). Differentiated thyroid cancers usually retain responsiveness to TSH and suppressive doses of levothyroxine can be used to inhibit the progression of metastatic thyroid cancer (Simpson, et al. 1988) as well as decrease rates of recurrence in patients treated with surgery or radioactive iodine (Biondi, et al. 2005; McGriff, et al. 2002), in keeping with TSH's tropic effect on thyroid tissue promoting neoplasia and carcinogenesis.

TSH and the initiation of thyroid cancer

It has been demonstrated that even in patients who do not present with thyroid nodules, higher serum TSH concentrations are associated with increased risks of thyroid malignancy. In a large sample drawn from the general population TSH levels were significantly higher in patients with DTC when compared with the control group. Among 1,548 controls, 606 subjects had thyroid nodules detected on ultrasound. Further subgroup analysis demonstrated that control subjects without detectable thyroid nodules had proportionally higher risks of DTC as TSH concentration rose, suggesting a role for TSH in the generation of thyroid cancer. This study did not indicate a relationship between higher serum TSH concentrations and more advanced thyroid cancer in contrast with others (Fiore et al. 2009; Haymart et al. 2008; McLeod et al. 2012; Zheng et al. 2016).

Evidence for a role of TSH in the development of thyroid tumours comes from studies of the $TR\beta^{PV/PV}$ mouse which has a dominant negative mutant thyroid hormone nuclear receptor gene inserted in the TRβ locus. This mouse model has disrupted pituitary-thyroid axis signalling resulting in raised serum TSH concentrations and the rapid development of metastatic thyroid cancer (Suzuki, et al. 2002). Crossing of this model with TSH receptor gene knockout mice ($TSHR^{-/-}$) resulted in impaired thyroid growth and no occurrences of thyroid cancer, consistent with a role for TSH in thyroid tumourigenesis (Lu, et al. 2010).

Serum TSH and thyroid autoimmunity

Several studies have indicated an association between thyroid autoimmunity and thyroid malignancy (Boelaert 2009; Haymart et al. 2008; McLeod et al. 2012). There is an increased incidence of thyroid cancer in patients with Hashimoto's disease. Our previous study (Boelaert et al. 2006) demonstrated that although raised thyroid peroxidase (TPO) levels did not independently predict malignancy, patients with cancer had significantly higher levels of TPO antibody than patients with benign disease. Fiore et al. (Fiore et al. 2009) demonstrated that TSH was higher in patients independent of whether they had raised TPO antibodies or not, and that there was no difference in rates of thyroid carcinoma between the autoimmune thyroid disease population and

antibody negative patients. Haymart et al. (Haymart et al. 2008) observed the debate about association of thyroid cancer with both Hashimoto's disease and Graves' disease. They suggest that as Hashimoto's disease often progresses to hypothyroidism resulting in elevated TSH concentrations, and because Graves' disease is associated with TSH receptor stimulation, which is associated with thyroid cancer (Mazzaferri 2000), it follows that TSH receptor activation is the link between thyroid cancer and thyroid autoimmune disease. More recently, a study directed at assessment of anti-thyroglobulin antibody (TgAb) measured pre-operative levels in differentiated thyroid cancer patients and concluded that TgAb was not an independent predictor of DTC prognosis, once adjusted for age and gender (McLeod et al. 2014); they noted that TgAb may be raised in autoimmunity and in patients exhibiting an immune response to the tumour, and may not be a true representation of thyroid autoimmune disease. Figure 1 summarises the potential effects of TSH as a tumour initiator, cancer promoter or in relation to thyroid auto-immunity.

Aetiology of raised serum TSH concentrations in thyroid cancer

There is no consensus on why serum TSH is raised in differentiated thyroid cancer nor do we fully understand the cause and effect relationship (Boelaert 2009). Iodine deficiency causes a consequent rise in serum TSH concentrations and chronic iodine deficiency is a well-established risk factor for the development of goitre and follicular thyroid cancer (Feldt-Rasmussen 2001; Lind, et al. 1998; Nagataki and Nystrom 2002). However, a causal role for TSH in the initiation of thyroid cancer has not been exclusively demonstrated and it remains unclear if serum TSH concentrations are higher as a consequence of the presence of thyroid malignancy.

A further potential explanation is that patients with lower serum TSH concentrations already have or are progressing towards development of autonomously functioning thyroid nodules, which are less likely to be malignant (Hegedus 2004; Hegedus et al. 2003; Mann, et al. 1988). Fiore et al demonstrated significant age-dependent development of thyroid autonomy (serum TSH<0.4 mIU/l) in patients with benign thyroid disease but this was less evident in those with papillary thyroid cancer and in patients with multinodular goitre. The frequency of thyroid autonomy was higher and

the risk of papillary thyroid cancer was lower than in those with solitary nodules, consistent with a protective effect of lower serum TSH concentrations on thyroid cancer development or progression (Boelaert 2009; Fiore et al. 2009).

Serum TSH and papillary microcarcinoma

Papillary microcarcinomas, defined as thyroid cancer <10mm in diameter, are increasing dramatically in frequency, and distinguishing those that proliferate and progress aggressively from small indolent tumours is difficult. The increased incidence is partly due to the finding of incidentalomas on routine imaging as well as on histopathological examination of thyroid specimens removed for reasons not associated with the suspicion of malignancy (Roti, et al. 2008). Current guidelines do not recommend completion thyroidectomy nor the administration of radioiodine routinely for these tumours. A more conservative approach for their management has been recommended, and for low risk patients, who have isolated and intrathryoidal tumours, without nodal metastases, lobectomy is sufficient (Haugen et al. 2015; Pacini, et al. 2012; Perros et al. 2014). In those with evidence of metastases, a positive family history, previous radiation to the head and neck or in subjects older than 45 years, total thyroidectomy and radioiodine ablation may be indicated (Mazzaferri 2007; Perros et al. 2014; Pitoia and Miyauchi 2015).

Two main difficulties arise from these modern guidelines: (i) a subset of these tumours progress and metastasise (Page, et al. 2009; Roti, et al. 2006); (ii) patients, when presented with a cancer diagnosis, often prefer comprehensive therapy, which leaves them with the best prognosis and the lowest risk of recurrence, often despite the potential cost of any associated treatment morbidity. While current tumour staging systems are unable to guide therapy in papillary microcarcinomas, the potential for use of TSH to assist in assessing prognosis is appealing.

The association between raised serum TSH measurements and papillary thyroid microcarcinoma has been studied (Table 4), and some have suggested this as a means to estimate thyroid cancer risk in those with thyroid nodule of less than 1 cm in size (Moon, et al. 2012). However not all studies are consistent. Sohn, et al. (Sohn, et al. 2014) demonstrated the association

between higher TSH and risk of malignancy in tumours over 1cm, but not in papillary microcarcinomas. Similarly, an Italian study showed that TSH was not significantly different in thyroid papillary microcarinoma patients compared to their controls consisting of patients with negative histology (Negro, et al. 2013; Sohn et al. 2014). A meta-analysis of nine studies encompassing 6,523 subjects demonstrated that some smaller studies were biased due to heterogeneous controls, and overall confirmed a significant association between higher serum TSH and papillary microcarcinoma, supporting the hypothesis that TSH is involved in differentiated thyroid tumorigenesis. The authors stated that there is insufficient evidence to show that TSH is directly involved in thyroid carcinoma initiation but the data support the hypothesis that raised TSH is associated with risk of cancer and progression (Shi et al. 2016). At present, it is unclear how the increased detection of small indolent microcarcinomas influences the utility of using serum TSH in clinical decision algorithms.

Whether TSH is an important factor in disease initiation or progression remains unclear. An argument against its involvement in tumour initiation is the lack of TSH receptor mutations interfering with signal transduction in thyroid carcinomas (Matsuo, et al. 1993). Furthermore, thyroid carcinomas can occur in patients with a range of serum TSH, including in those who take exogenous thyroid hormones and have suppressed serum TSH concentrations for treatment of other thyroid diseases (Satta, et al. 1993).

On the contrary, a mouse-model with a knock-in of oncogenic BRAF generated by Franco et al. developed invasive thyroid carcinomas and concomitantly became profoundly hypothyroid as demonstrated by significantly raised TSH levels. Following knockout of the TSH receptor (to genetically replicate ablation of the TSH signalling pathway) there was a significant lag in the period before tumour formation, and the tumours that developed were much less aggressive (Franco, et al. 2011). These findings contribute to the idea that TSH per se may not be oncogenic independently, but raised concentrations are likely to contribute significantly to tumour development and progression.

Serum TSH and follicular thyroid cancer

Follicular thyroid carcinomas provide a unique diagnostic challenge, in that they cannot be diagnosed by cytological evaluation alone. While there may be factors indicating neoplastic change in fine needle aspirates, follicular carcinoma is defined as a tumour that invades the capsule, a feature that cannot be identified on cytological evaluation rendering these cancers indistinguishable from thyroid adenomas using cytopathology. The standard treatment of choice is therefore diagnostic hemithyroidectomy, which requires no further surgery in adenomatous lesions, but is usually followed up by completion hemithyroidectomy, radioiodine ablation and suppression of TSH in the majority of invasive follicular carcinomas (McHenry and Phitayakorn 2011; Perros et al. 2014; Pitoia and Miyauchi 2015).

Raised serum TSH levels have been demonstrated in patients with follicular carcinoma compared to those with benign follicular disease (Kunt, et al. 2015). While the TSH level is unlikely to be the single factor in follicular thyroid cancer development, some have advocated using its measurement in combination with other determinators of risk stratification, even to the point of defining treatment, i.e. whether to proceed with hemithyroidectomy or not (Kuru, et al. 2009). Despite the potential for the application of TSH measurements in the management of follicular thyroid carcinomas, there is a paucity of studies addressing this specifically (Zheng et al. 2016).

TSH and non-differentiated thyroid cancer

Due to the different pathophysiology of medullary thyroid cancer, TSH concentrations are not implicated in the likelihood of diagnosis, nor in the follow up monitoring of these tumours. Responsiveness of thyroid cancer to TSH depends on TSH receptor expression, and de-differentiated cancers demonstrate significant reductions in expression of thyroid specific proteins including TSH receptors, thyroid peroxidase and thyroglobulin (Brabant, et al. 1991; Sheils and Sweeney 1999). Anaplastic thyroid cancers represent extreme forms of dedifferentiated tumours and these tumours are characteristically very difficult to treat due to the lack of expression of proteins involved in the

thyroid machinery. Expression of the sodium iodide symporter is often absent, thereby significantly reducing the functional effectiveness of radioiodine ablation and treatment. Current therapeutic approaches include the re-differentiation of these tumours with various agents to improve treatability (Dong, et al. 2013; Kang, et al. 2011; Schmutzler and Kohrle 2000). In view of the inherent lack of expression of normal TSH receptors in anaplastic thyroid cancers, serum TSH concentrations have not been studied in relation to the diagnosis or progression of these tumours. It seems unlikely that finding of altered TSH levels in this context, would aid the choice of available treatment options nor would it affect the very poor prognosis associated with these rare thyroid cancers.

TSH in follow up of patients with thyroid malignancy

Until recently, the long term management of differentiated thyroid cancers included the suppression of serum TSH concentrations with supraphysiological concentrations of levothyroxine for extended periods of time, regardless of the tumour-specific risk stratification. Current guidelines recommend against TSH suppression into low risk tumours which have not been treated with radioiodine or those who are stratified in the excellent response categories following dynamic risk stratification (Haugen et al. 2015; Perros et al. 2014; Pitoia and Miyauchi 2015). For those tumours that have not undergone further risk stratification at 1-year post-treatment, current practice is to suppress TSH levels with exogenous thyroid hormone to less than 0.1 mU/l for 5-10 years post-treatment. At this point, depending on the clinical response, the TSH suppression can be relaxed (Perros et al. 2014). Some studies have indicated that TSH suppression may inhibit the generation of new thyroid nodules, as well as the growth and tumourigenic potential in existing nodules (Papini et al. 1998), although current guidelines do not recommend of thyroid hormone suppressive therapy in patients with thyroid nodules (Haugen et al. 2015; Perros et al. 2014; Pitoia and Miyauchi 2015).

TSH suppression in differentiated thyroid cancer follow-up

Suppressive serum TSH to very low level reduces the rates of thyroid cancer recurrence and has been shown to improve differentiated thyroid cancer patient outcomes. TSH is a growth factor for thyroid nodules, and it is considered that suppression of TSH can prevent new nodule formation as well as inhibition of current nodules (Papini et al. 1998). In the context of differentiated thyroid carcinoma treatment, after resection of thyroid carcinoma and radioiodine treatment, TSH suppression therapy positively affects cancer outcomes including disease-specific survival (Mazzaferri and Jhiang 1994), and reduces recurrence (Pujol et al. 1996). Therefore it is widely recommended that patients have TSH suppression after successful treatment in the early post-operative period (Haugen et al. 2015).

Risks associated with TSH suppression

Despite the widespread use of TSH suppression in patients who have been treated for differentiated thyroid cancer, this treatment approach is not completely without risk. Subclinical hyperthyroidism has been demonstrated to have significant deleterious health conseqeunces. This includes a spectrum of cardiovascular risks, including atrial fibrillation and coronary heart disease morbidity and mortality (Collet, et al. 2012). There is also a documented association with dementia, decreased cognitive function (Annerbo and Lokk 2013) and osteoporosis (Biondi, et al. 2015; Polovina, et al. 2015).

Outcomes for high grade thyroid cancers have been improved with TSH suppression and some advocate the need for more aggressive suppression in higher stage disease (Jonklaas, et al. 2006). In view of the aforementioned risk factors associated with this approach, current guidelines (Perros et al. 2014) now recommend the use of tools including the FRAX score to determine bone health and fracture risk (Kanis, et al. 2008) in patients who are on suppressive therapy with levothyroxine for 5 years or longer during thyroid cancer follow-up. Overall an individualised approach combining assessment of the patient's response to treatment and risk of disease progression with an evaluation of the potential health risks associated with long term TSH

suppression is advised in establishing the required dose and length of course of levothyroxine therapy.

Conclusion

Patients presenting with a thyroid nodule or thyroid enlargement should have their serum TSH measured as part of the initial assessment. Following our paper in 2006 (Boelaert et al. 2006), a significant body of evidence has accumulated confirming the association between higher serum TSH concentrations and likelihood of thyroid cancer diagnosis. A recent meta-analysis demonstrated this relationship in thyroid tumours of all sizes, including papillary microcarcinomas in adult as well as in paediatric thyroid cancers (Zheng et al. 2016). Several studies and meta-analyses have also established a relationship between raised TSH levels and cancer progression, and increased concentrations were associated with advanced disease and lymph node metastasis (Fiore et al. 2009; McLeod et al. 2012; Zheng et al. 2016).

The diagnostic accuracy of serum TSH as a biochemical predictor of malignancy however has not yet been established and meta-analyses have failed to provide conclusive data to provide a single useful cut-off value to pass TSH as an independent and validated test (McLeod et al. 2012; Zheng et al. 2016) and measurement of this biochemical marker has not yet been incorporated into clinical decision algorithms. There have been suggestions that its measurement may be useful in combination with other tests including ultrasonography and fine needle aspiration cytology. At a time when thyroid nodules are increasingly being diagnosed, and whilst the differentiation between benign and malignant lesions remains difficult in a significant proportion of subjects, it is important to consider incorporating TSH levels into the stratification of patients' thyroid cancer risk.

Furthermore, treatment with TSH suppression in the follow-up of patients with thyroid cancer has been re-evaluated. There are significant long term health risks associated with TSH suppression and further refinement of the stratification approaches regarding the risk of disease progression or recurrence will help identify those patients in whom the risks of long-term

suppressive therapy outweigh the risks. Large prospective studies to evaluate this further will be of utmost importance. Whilst there is little doubt that serum TSH is raised in differentiated thyroid cancer, the full integration of this finding into clinical pathways relating to the diagnosis and management of patients is yet to be undertaken.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Figure Legend

Figure illustrating TSH binding to its receptor in normal thyroid physiology. Potential roles of high serum TSH concentrations in the initiation and progression of thyroid carcinogenesis as well as putative links with thyroid autoimmunity in the context of contributing environmental and genetic factors are indicated.

706 **Table 1: Clinical features suggestive of thyroid malignancy (Hegedus 2004; Popoveniuc and**

707 **Jonklaas 2012)**

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History	Physical examination
Family Hx of MEN, MTC, PTC	Firm nodule
History of head and neck irradiation as child or adolescent	Nodule fixed to adjacent structures
History of Hodgkin and non-Hodgkin lymphoma and irradiation	Growth of nodules, especially during therapy to suppress TSH
Age < 20	Abnormal cervical lymph nodes
Age > 70	Vocal cord paralysis
Male gender	
Symptoms of compression: hoarseness, dysphagia, dyspnoea, cough, dysphonia	

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716 **Table 2: US features associated with thyroid malignancy. (Perros et al. 2014)**

Benign nodule	Malignant nodule: Papillary/medullary	Follicular lesion
Spongiform/honeycomb	Solid and hypoechoic	Hyperechoic/ homogeneous/halo benign
Purely cystic	Irregular margin	Hypoechogencity/loss of halo suspicious
Egg shell calcification	Intranodular vasularity	
Iso/hyper echoic (hypoechoic halo)	Absence of halo	
Peripheral vascularity	Taller than wide	
	Microcalcifications	

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718 **Table 3: Summary of studies investigating serum TSH and thyroid cancer diagnosis**

Reference	Journal	Number of patients	Country of study	Significant findings	Serum TSH 'cut off' value
(Boelaert et al. 2006)	J Clin Endocrinol Metab	1,500	UK	Serum TSH is an independent predictor of malignancy in thyroid nodules. Risk of thyroid cancer rises in parallel with serum TSH in the normal range.	0.9 – 5.5 mU/litre
(Polyzos, et al. 2008)	J Cancer Res Clin Oncol	565	Greece	Higher rates of thyroid malignancy in patients with TSH in upper tertile of normal range.	1.5 – 4 mIU/l
(Haymart et al. 2008)	JCEM	843	US	Higher serum TSH is associated with advanced stage-differentiated thyroid cancer.	1.4 – 4.9 mIU/litre
(Jonklaas et al. 2008)	Thyroid	50	US	Higher TSH is associated with increased likelihood of diagnosis of thyroid cancer. Patients with thyroid cancer have lower serum total T3 concentrations.	1.8 – 5.5 mIU/L
(Haymart et al. 2009)	Clinical Endocrinology	1361	US	Risk of thyroid cancer increases with increased TSH independent of age.	No cut off value
(Fiore et al. 2009)	Endocrine Related Cancer	10,178	Italy	Higher TSH in patients with T3-T4 disease and in those with lymph node metastases. Autonomously functioning thyroid nodules are less likely to be malignant.	1.6 – 3.4 mU/ml
(Gerschpacher, et al. 2010)	Thyroid	87	Austria	TSH may play a role in thyroid cancer progression rather than oncogenesis.	
(Zafon, et al. 2012)	Journal of Thyroid Research	386	Spain	TSH levels are higher in patients with DTC. Increment in tumour size rises in parallel with incremental rise in TSH.	No cut off value
(Kim et al. 2013)	Clinical Endocrinology	1759	South Korea	High TSH level within the normal range is an independent risk factor for DTC and can be used as a diagnostic adjunct.	2.31 - 4.80 mIU/l
(Sohn et al. 2014)	Head and Neck	3791	South Korea	Serum TSH may not be useful for clinical risk assessment of small thyroid nodules.	2.13 – 4.2 mU/L
(Fighera et al. 2015)	Endokrynol Pol	622	Brazil	Risk of carcinoma in nodular disease rises in parallel with serum TSH.	above 1.64 mU/L
(Khan, et al. 2016)	Asian Pac J Cancer Prev	73	Pakistan	Higher pre-surgical TSH correlates with thyroid cancer.	
(Shi et al. 2016)	Endocrine Journal	1870	China	Raised TSH is related to cancer stage but not likely to be related to initiation.	Meta-analysis

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723 **Table 4: Table summarising studies investigating TSH and papillary microcarcinoma**

Reference	Journal	Number of patients	Country of study	Significant findings
(Haymart et al. 2008)	JCEM	843	US	Escalating cancer risk with higher TSH level in microcarcinomas. More research warranted.
(Moon et al. 2012)	Head and Neck	483	South Korea	TSH measurement in the context of thyroid micronodule can exclude cancer
(Shi, et al. 2012)	Endocr J	1870	China	TSH does not correlate with microcarcinoma presence and therefore TSH can only be linked with progression of carcinoma
(Negro et al. 2013)	Endocrine Practice	205	Italy	No difference in serum TSH between papillary microcarcinoma group compared to controls
(Sohn et al. 2014)	Head and Neck	3791	South Korea	Serum TSH may not be useful for clinical risk assessment of small thyroid nodules
(Jiao and Zhou 2015)	Zhonghua Yi Xue Za Zhi	365	China	TSH is probably associated with oncogenesis in papillary microcarcinoma (PTMC) although it may only be involved in growth of pre-existing PTMC

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