

## Thyroid stimulating hormone in thyroid cancer: does it matter?

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1 Endocrine related cancer review

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3 **Thyroid stimulating hormone in thyroid cancer: does it matter?**

4

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## 21 **Serum TSH in thyroid cancer: does it matter?**

### 22 **Abstract**

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

39

## 40 **TSH in thyroid cancer: does it matter?**

### 41 **Introduction**

42           Differentiated thyroid malignancy is the most common endocrine malignancy and over the  
43 last few decades, its incidence has increased dramatically worldwide (Kitahara and Sosa 2016; Sipos  
44 and Mazzaferri 2010). It is currently the fifth most common malignancy in women in the US and an  
45 estimated 62,000 new cases were found in North American men and women in 2015 (American  
46 Cancer Society 2015). Thyroid cancer causes more deaths than any other endocrine cancer (Monson  
47 2000) and there will be an estimated 1,980 deaths from thyroid cancer in the US in 2016 (American  
48 Cancer Society 2016). The reasons for the observed increase in incidence have been widely debated  
49 (Wartofsky 2010) and include enhanced detection of subclinical thyroid cancer due to the growing  
50 use of diagnostic imaging as well as exposure to a number of environmental factors (Kitahara and  
51 Sosa 2016). Whilst better access to health care in countries with high socio-economic status may in  
52 part explain the rising incidence, observations of increased thyroid cancer rates in lower socio-  
53 economic countries, an increasing number of larger tumours as well as the changing thyroid cancer  
54 molecular profiles indicate that other factors are likely to be involved (Vigneri, et al. 2015). A  
55 number of disease modifiable factors including obesity have been identified as potential aetiological  
56 factors (Schmid, et al. 2015). Moreover a variety of thyroid-specific environmental carcinogens have  
57 been implicated including ionising radiation, increased dietary iodine intake and environmental  
58 pollutants (Vigneri et al. 2015). Overall, the observed changes in thyroid cancer incidence are likely  
59 due to a combination of detection bias and true increases in incidence.

60           Thyroid cancer often presents as a solitary nodule or as a part of a multinodular goitre. This  
61 creates an important clinical dilemma as thyroid nodules are very common occurring in 50-67% of  
62 the population and more than 90% are benign (Durante, et al. 2015; Hegedus 2004; Mazzaferri 1992;  
63 Popoveniuc and Jonklaas 2012). Detection rates of thyroid nodules are increasing due to widespread  
64 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).

89           The diagnosis and post-therapy monitoring of patients with thyroid nodules and cancer is  
90 important. We were the first to publish that serum TSH is raised in patients with malignant thyroid  
91 nodules compared to those with benign disease (Boelaert et al 2006), and subsequent studies have  
92 shown that pre-operative serum TSH is proportionally higher in those with more aggressive disease  
93 (Boelaert, et al. 2006; Figuera, et al. 2015; Haymart, et al. 2009; Jonklaas, et al. 2008; McLeod, et al.  
94 2014). This review aims to explore the relationship between TSH and thyroid cancer, both before  
95 and after a diagnosis of malignancy is made.

96

## 97 **Thyroid-stimulating hormone**

### 98 ***Hormone structure and biochemical details***

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

### 109 ***TSH function in the normal thyroid***

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

## 118 **Diagnosing thyroid malignancy**

### 119 ***Types of thyroid cancer***

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

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

### 129 ***Current diagnostic approaches and limitations***

130 Guidelines recommend that patients suspected to have thyroid malignancy are assessed by  
131 a physician with a specialist interest in thyroid cancer care, and who is a regular member of the  
132 multi-disciplinary team (Perros et al. 2014). It is paramount to perform a full clinical assessment  
133 which includes taking a personal and family history as well as careful clinical examination (Hegedus  
134 2004; Hegedus et al. 2003; Perros et al. 2014; Pitoia and Miyauchi 2015). In many cases, however,  
135 thyroid glands harboring malignancy are clinically indistinguishable from those that do not and there  
136 is substantial variation among practitioners in evaluating nodules. Features suggestive of malignancy  
137 include the presence of firm, fixed thyroid lumps, vocal cord palsy, a positive family history, rapid  
138 nodule growth and being at the extremities of age (>60 years or <20 years) (Hegedus et al. 2003).  
139 Table 1 displays clinical characteristics associated with an increased risk of malignancy.

140 The serum TSH concentration is routinely measured to exclude the presence of a toxic  
141 nodule causing subclinical or overt hyperthyroidism in all patients (Hegedus et al. 2003; Perros et al.  
142 2014; Pitoia and Miyauchi 2015). If the TSH is below the laboratory reference range, assays for free  
143 triiodothyronine (fT3) and free thyroxine (fT4) are required in order to exclude overt  
144 hyperthyroidism (raised free T4 and free T3) or "T3-toxicosis" (raised serum free T3 alone). Similarly,  
145 if TSH is raised then overt hypothyroidism must be excluded (this being indicated by low fT4 with a  
146 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

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

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

## 185 **Serum TSH in the diagnosis of thyroid cancer**

### 186 ***TSH and promotion of thyroid cancer growth***

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

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

201 Higher pre-operative serum TSH concentrations have also been associated with more  
202 advanced cancer stage at diagnosis. Mean serum TSH levels were higher in those with stage III and  
203 IV disease and in those with larger tumours or in cancers associated with lymph node metastases  
204 (Fiore, et al. 2009; Haymart et al. 2008; Shi, et al. 2016). A meta-analysis of 28 studies, analysing  
205 42,032 control subjects and 5,786 patients with thyroid cancers has confirmed that higher pre-  
206 operative TSH levels are associated with increased risk of thyroid malignancy as well as a correlation  
207 with higher disease grade (McLeod et al. 2012). A more recent meta-analysis of 56 studies  
208 encompassing 20,227 thyroid cancer cases and 50,003 controls with benign thyroid nodules has  
209 confirmed that higher serum TSH level were significantly associated with thyroid cancer size and  
210 with the presence of lymph node metastasis (Zheng et al. 2016). These findings are consistent with  
211 serum TSH having a role in the promotion of thyroid tumour growth and aggressiveness.

212 Indeed TSH is a known growth factor for thyroid nodules and suppression of serum TSH  
213 concentrations by administering exogenous thyroid hormone may inhibit the growth of established  
214 nodules as well as the development of new nodules (Papini, et al. 1998). Benign and malignant  
215 thyroid tumours express functional TSH receptors on the plasma membrane (Ichikawa, et al. 1976)  
216 and TSH increases adenylate cyclase activity leading to cAMP production and cell growth through  
217 stimulation of these receptors in vitro (Carayon, et al. 1980). Importantly the expression of TSH  
218 receptors in DTC has been associated with an improved prognosis (Shi, et al. 1993). Differentiated  
219 thyroid cancers usually retain responsiveness to TSH and suppressive doses of levothyroxine can be  
220 used to inhibit the progression of metastatic thyroid cancer (Simpson, et al. 1988) as well as  
221 decrease rates of recurrence in patients treated with surgery or radioactive iodine (Biondi, et al.  
222 2005; McGriff, et al. 2002), in keeping with TSH's tropic effect on thyroid tissue promoting neoplasia  
223 and carcinogenesis.

224 ***TSH and the initiation of thyroid cancer***

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

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

241 ***Serum TSH and thyroid autoimmunity***

242 Several studies have indicated an association between thyroid autoimmunity and thyroid  
243 malignancy (Boelaert 2009; Haymart et al. 2008; McLeod et al. 2012). There is an increased  
244 incidence of thyroid cancer in patients with Hashimoto's disease. Our previous study (Boelaert et al.  
245 2006) demonstrated that although raised thyroid peroxidase (TPO) levels did not independently  
246 predict malignancy, patients with cancer had significantly higher levels of TPO antibody than  
247 patients with benign disease. Fiore et al. (Fiore et al. 2009) demonstrated that TSH was higher in  
248 patients independent of whether they had raised TPO antibodies or not, and that there was no  
249 difference in rates of thyroid carcinoma between the autoimmune thyroid disease population and

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

#### 262 ***Aetiology of raised serum TSH concentrations in thyroid cancer***

263         There is no consensus on why serum TSH is raised in differentiated thyroid cancer nor do we  
264 fully understand the cause and effect relationship (Boelaert 2009). Iodine deficiency causes a  
265 consequent rise in serum TSH concentrations and chronic iodine deficiency is a well-established risk  
266 factor for the development of goitre and follicular thyroid cancer (Feldt-Rasmussen 2001; Lind, et al.  
267 1998; Nagataki and Nystrom 2002). However, a causal role for TSH in the initiation of thyroid cancer  
268 has not been exclusively demonstrated and it remains unclear if serum TSH concentrations are  
269 higher as a consequence of the presence of thyroid malignancy.

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

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

### 279 ***Serum TSH and papillary microcarcinoma***

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

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

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

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

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

320           On the contrary, a mouse-model with a knock-in of oncogenic BRAF generated by Franco et  
321 al. developed invasive thyroid carcinomas and concomitantly became profoundly hypothyroid as  
322 demonstrated by significantly raised TSH levels. Following knockout of the TSH receptor (to  
323 genetically replicate ablation of the TSH signalling pathway) there was a significant lag in the period  
324 before tumour formation, and the tumours that developed were much less aggressive (Franco, et al.  
325 2011). These findings contribute to the idea that TSH per se may not be oncogenic independently,  
326 but raised concentrations are likely to contribute significantly to tumour development and  
327 progression.

328

329 ***Serum TSH and follicular thyroid cancer***

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

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

346 ***TSH and non-differentiated thyroid cancer***

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



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

### 363 **TSH in follow up of patients with thyroid malignancy**

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

### 377 ***TSH suppression in differentiated thyroid cancer follow-up***

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

### 387 ***Risks associated with TSH suppression***

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

395           Outcomes for high grade thyroid cancers have been improved with TSH suppression and  
396 some advocate the need for more aggressive suppression in higher stage disease (Jonklaas, et al.  
397 2006). In view of the aforementioned risk factors associated with this approach, current guidelines  
398 (Perros et al. 2014) now recommend the use of tools including the FRAX score to determine bone  
399 health and fracture risk (Kanis, et al. 2008) in patients who are on suppressive therapy with  
400 levothyroxine for 5 years or longer during thyroid cancer follow-up. Overall an individualised  
401 approach combining assessment of the patient's response to treatment and risk of disease  
402 progression with an evaluation of the potential health risks associated with long term TSH

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

#### 405 **Conclusion**

406 Patients presenting with a thyroid nodule or thyroid enlargement should have their serum  
407 TSH measured as part of the initial assessment. Following our paper in 2006 (Boelaert et al. 2006), a  
408 significant body of evidence has accumulated confirming the association between higher serum TSH  
409 concentrations and likelihood of thyroid cancer diagnosis. A recent meta-analysis demonstrated this  
410 relationship in thyroid tumours of all sizes, including papillary microcarcinomas in adult as well as in  
411 paediatric thyroid cancers (Zheng et al. 2016). Several studies and meta-analyses have also  
412 established a relationship between raised TSH levels and cancer progression, and increased  
413 concentrations were associated with advanced disease and lymph node metastasis (Fiore et al.  
414 2009; McLeod et al. 2012; Zheng et al. 2016).

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

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

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

432

433

434

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446

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685

686 **Figure Legend**

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

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706 **Table 1: Clinical features suggestive of thyroid malignancy (Hegedus 2004; Popoveniuc and**  
 707 **Jonklaas 2012)**

708	
History	Physical examination
Family Hx of MEN, MTC, PTC	Firm nodule 709
History of head and neck irradiation as child or adolescent	Nodule fixed to adjacent structures 710
History of Hodgkin and non-Hodgkin lymphoma and irradiation	Growth of nodules, especially during therapy to suppress TSH 711
Age < 20	Abnormal cervical lymph nodes 712
Age > 70	Vocal cord paralysis
Male gender	713
Symptoms of compression: hoarseness, dysphagia, dyspnoea, cough, dysphonia	714

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

<b>Benign nodule</b>	<b>Malignant nodule: Papillary/medullary</b>	<b>Follicular lesion</b>
Spongiform/honeycomb	Solid and hypoechoic	Hyperechoic/ homogeneous/halo benign
Purely cystic	Irregular margin	Hypoechoic/loss of halo suspicious
Egg shell calcification	Intranodular vascularity	
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 mIU/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
(Figuera 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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