SHORT COMMUNICATION

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Does thyroid-stimulating hormone influence the prognosis of patients with endometrial cancer? A multicentre trial

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Background: Thyroid function has been suggested to interfere with tumour biology and prognosis in different cancers. The present study was performed to investigate the impact of pre-therapeutic serum thyroid-stimulating hormone (TSH) levels on the prognosis of patients with endometrial cancer.

Methods: Pre-therapeutic serum TSH was investigated in 199 patients with endometrial cancer. After stratification in TSH risk groups, univariate and multivariable survival analyses were performed.

Results: Elevated TSH was independently associated with poor disease-specific survival in univariate/multivariable survival analyses ($P = 0.01$ and $P = 0.03$, respectively).

Conclusion: Thyroid-stimulating hormone may serve as a novel and independent prognostic parameter for disease-specific survival in patients with endometrial cancer.

The thyroid gland's integrity is of decisive importance for the metabolic activity and function of nearly every organ system in adults. Experimental and clinical studies suggest a possible interaction between thyroid function and tumour biology and prognosis in different cancers (Hercbergs *et al*, 2003; Tang *et al*, 2004; Cristofanilli *et al*, 2005; Nelson *et al*, 2006; Schmidinger *et al*, 2011).

Hypothyroidism, either clinically overt or subclinical, is a common disorder, especially in middle-aged and elderly women. Being defined as commonly encountered comorbidities in patients with endometrial cancer, increased body mass index and age are positively associated with elevated serum thyroid-stimulating hormone (TSH) levels (Knudsen *et al*, 2005; Iqbal *et al*, 2006). Moreover, it is in patients with endometrial cancer that higher serum TSH levels have been found when compared with healthy women (Kanat-Pektas *et al*, 2010).

The present multicentre trial aims to evaluate the association between pre-therapeutic serum TSH levels and the prognosis in patients with endometrial cancer.

MATERIALS AND METHODS

Patients. A total of 199 patients with endometrial cancer were included in the present Austrian multicentre trial (Department of Gynaecology and Gynaecological Oncology, Medical University of Vienna, Austria, $n = 92$; Department of Gynaecology and Obstetrics, Medical University Innsbruck, Austria, $n = 107$). Clinical and laboratory data were extracted from the respective electronic gynaecologic oncology registries. Patients who did not receive standardised treatment because of age or significant comorbidities, and patients with additional, coexisting malignant disease were excluded from analysis.

Clinical management. Patients were surgically staged according to the International Federation of Gynecology and Obstetrics (FIGO)/American Joint Committee on Cancer (AJCC) classification system of FIGO 6th annual report 2006, using the 1988 FIGO classification (Creasman *et al*, 2006). Patients were treated and

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followed according to international guidelines, as described previously (Seebacher *et al*, 2010).

Recurrent disease was either diagnosed by biopsy or by imaging methods, following standard clinical guidelines. If patients did not present for scheduled follow-up visits, the administrative personnel or nurses contacted them.

TSH measurement. Blood samples (serum) were obtained routinely by peripheral venous puncture before therapy during pretreatment examination. According to recommendations of the National Academy of Clinical Biochemistry, a TSH serum level of 2.5 $mU l^{-1}$ was considered as upper limit of normal of the euthyroid reference range (Baloch *et al*, 2003).

Statistical analysis. Values are given as number (percentage) or median (minimum–maximum) as appropriate. Kruskal–Wallis one-way analysis of variance was used to assess the association between the medians of pretreatment serum TSH and clinical–pathological parameters.

For survival analysis, patients were assigned to two prognostic groups according to their pre-therapeutic serum TSH levels as follows: TSH $\leqslant$ 2.5 $mU l^{-1}$ (normal low) and TSH $>$2.5 $mU l^{-1}$ (elevated). Survival probabilities were calculated by the product limit method of Kaplan and Meier. Differences between groups were tested using the log-rank test. The results were analysed for the end point of disease-free and disease-specific survival. Events were defined as first diagnosis of recurrent disease or cancer-related death at the time of the last follow-up visit, respectively. Patients who died of other causes than endometrial cancer or patients alive were censored with the date of death or last follow-up, respectively. Univariate and multivariable Cox regression models were performed, comprising the TSH groups (elevated *vs* normal low), FIGO tumour stage (FIGO IV *vs* FIGO III *vs* FIGO II *vs* FIGO I), histological grade (G3 *vs* G2 *vs* G1), and the patients' mean age ($>$66.5 *vs* $\leqslant$66.5 years). Results of univariate and multivariable survival analyses are given as *P*-value (hazard ratio (HR) and 95% confidence interval (95% CI)). The *P*-values of $<$0.05 were considered statistically significant. We used the statistical software SPSS 20.0 for Mac (IBM SPSS Statistics 20.0.0, IBM Germany GmbH, Ehningen, Germany) for statistical analysis.

Institutional review board. The present trial was approved by the institutional review boards, that is, the Ethics-Committees of the Medical University of Vienna (Project 248/2009, 21-04-2009), as well as of the Medical University Innsbruck (UN4144).

RESULTS

Clinical characteristics of patients. Clinical characteristics of recruited patients are listed in Supplementary Table 3. The median (minimum–maximum) pre-therapeutic serum TSH level was 1.27 (0.01–14.8) $mU l^{-1}$. In all, 173 patients (86.9%) and 26 patients (13.1%) showed pre-therapeutic serum TSH levels $\leqslant$2.5 and $>$2.5 $mU l^{-1}$, respectively. As far as data were available, 70.2% of patients presented with obesity, 63.6% with hypertension, and 32% with diabetes mellitus. Lymph node status was available in 111 patients. Lymph node involvement was noted in 27 patients (13.6%). Radiotherapy was performed in 103 patients and chemotherapy in 34 patients. Patients' characteristics were distributed equally within the two study centres (data not shown).

Association between TSH and clinical–pathological parameters. No association could be found between elevated pre-therapeutic serum TSH and advanced FIGO tumour stage ($P=0.6$), high histological grade ($P=0.8$), unfavourable histological subtype ($P=0.9$), older patient age ($P=0.5$), or lifestyle factors such as obesity ($P=0.4$), hypertension ($P=0.9$), or diabetes mellitus ($P=0.5$).

Association between TSH and survival. Results on the 5-year disease-free and disease-specific survival stratified for FIGO tumour stage, histological grade, histological subtype, patients' age, and TSH risk groups are shown in Table 1. In univariate analysis, the elevated TSH risk group was associated with poor disease-free and disease-specific survival. In multivariable analysis, the elevated TSH risk group was independently association with poor disease-specific survival. Results of univariate and multivariable analyses are provided in Tables 1 and 2, respectively. Figure 1 shows Kaplan–Meier curves for TSH groups (normal low *vs* elevated) according to disease-specific survival.

Table 1. The 5-year disease-free and disease-specific survival

Parameter	The 5-year disease-free survival, % (s.e.)	*P*-value[a]	The 5-year disease-specific survival, % (s.e.)	*P*-value[a]
Stage[b]		$<$0.001		$<$0.001
FIGO IV	30.0 (14.5)		33.3 (15.7)	
FIGO III	45.0 (10.0)		50.8 (10.8)	
FIGO II	69.8 (14.9)		90.9 (8.7)	
FIGO I	86.7 (3.8)		91.9 (3.3)	
Grade		$<$0.001		$<$0.001
G3	53.7 (8.6)		56.0 (11.1)	
G2	75.7 (6.3)		78.5 (7.1)	
G1	87.7 (4.5)		92.2 (3.8)	
Histological subtype		0.1		0.2
Non-endometrioid	64.1 (10.5)		70.0 (12.4)	
Endometrioid	76.5 (4.0)		80.8 (3.9)	
Age		0.09		0.6
$>$67.5 years	66.3 (6.2)		76.5 (5.8)	
$\leqslant$67.5 years	82.3 (4.4)		82.3 (4.8)	
TSH		0.01		0.01
$>$2.5 $mU l^{-1}$	49.9 (11.5)		57.7 (11.8)	
$\leqslant$2.5 $mU l^{-1}$	79.4 (3.6)		83.7 (3.7)	
Obesity[c]		0.3		0.07
Yes	75.3 (5.2)		80.7 (5.6)	
No	80.6 (6.7)		93.3 (4.6)	
Hypertension[d]		0.5		0.5
Yes	78.8 (6.6)		91.6 (3.7)	
No	76.4 (6.9)		84.2 (6.5)	
Diabetes mellitus		0.4		0.2
Yes	74.0 (9.4)		78.3 (10.1)	
No	82.5 (5.2)		90.1 (4.3)	
Study centre		0.3		0.1
Vienna	78.2 (4.8)		84.8 (4.0)	
Innsbruck	70.7 (5.7)		71.3 (6.9)	

Abbreviations: FIGO = International Federation of Gynecology and Obstetrics; s.e. = standard error; TSH = thyroid-stimulating hormone.
[a]Kaplan–Meier analysis (log-rank test).
[b]According to the 1988 FIGO stating system.
[c]Body mass index $>$30 $kg m^{-2}$.
[d]Systolic blood pressure $\geqslant$160 or diastolic blood pressure $\geqslant$100 mm Hg.

Table 2. Multivariable survival analyses

	Disease-free survival		Disease-specific survival	
	HR (95% CI)	*P*-value[a]	HR (95% CI)	*P*-value[a]
Stage[b] (FIGO IV *vs* III *vs* II *vs* I)	2.2 (1.6–3.1)	<0.001	2.4 (1.6–3.6)	<0.001
Grade (G3 *vs* G2 *vs* G1)	1.6 (0.9–2.6)	0.06	1.7 (0.9–3.1)	0.05
Age (>67.5 years *vs* ⩽ 67.5 years)	1.8 (0.9–3.6)	0.09	1.4 (0.6–3.3)	0.4
Histologic subtype (non-endometrioid *vs* endometrioid)	0.6 (0.2–1.5)	0.3	0.6 (0.1–1.9)	0.4
Study centre (Vienna *vs* Innsbruck)	1.2 (0.6–2.6)	0.5	1.3 (0.5–3.3)	0.5
TSH (>2.5 *vs* ⩽2.5 mU l^{-1})	2.1 (0.9–4.8)	0.057	2.7 (1.1–6.7)	0.03

Abbreviations: 95% CI = 95% confidence interval; FIGO = International Federation of Gynecology and Obstetrics; HR = hazard ratio; TSH = thyroid-stimulating hormone
[a]Cox regression model.
[b]According to the 1988 FIGO stating system.

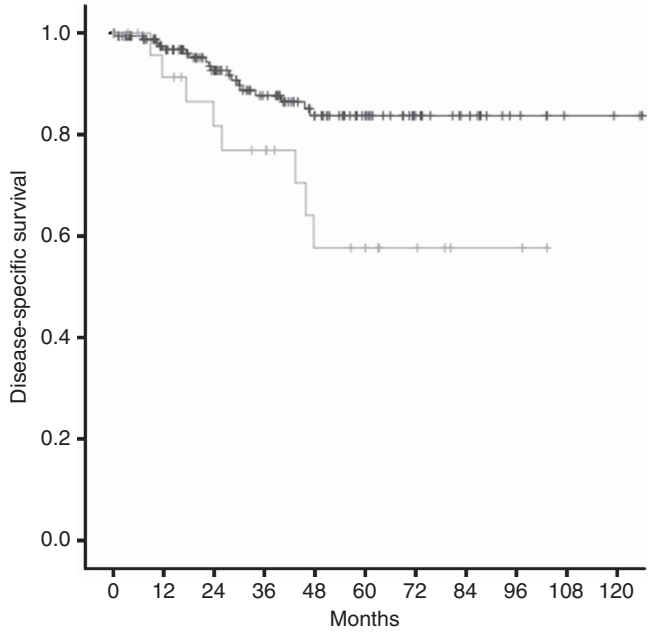

Figure 1. **Kaplan–Meier curves for pre-therapeutic TSH risk groups 'normal low' (upper line) *vs* 'elevated' (lower line) and disease-specific survival (*P* = 0.01).**

DISCUSSION

The present multicentre trial investigates the influence of TSH on the prognosis of patients with endometrial cancer. Present data demonstrate an independent association between elevated pre-therapeutic serum TSH levels and poor disease-specific survival in patients with endometrial cancer. These findings are interesting from the clinical point of view, as hypothyroidism is a common disorder, especially in elderly women.

Similar to results by previous authors, serum TSH levels were not associated with clinical–pathological parameters (Kanat-Pektas *et al*, 2010). This finding could suggest that TSH might be associated with systemic processes interacting with carcinogenesis, for example, hormonal imbalance or inflammation, rather than with the local neoplastic transformation. Previously published studies reported on an association between lifestyle factors, such as obesity, hypertension, and diabetes mellitus, and thyroid function. These factors were found to be unrelated with TSH in this study (Knudsen *et al*, 2005; Iqbal *et al*, 2006).

Thyroid disorders have previously been associated with the prognosis in cancer. Yet, hypothyroidism seems to have various effects on different types of cancer. While improving treatment outcome of head and neck cancer, glioma, and breast cancer, high serum TSH levels were associated with poor survival in patients with renal cell carcinoma (Hercbergs *et al*, 2003; Cristofanilli *et al*, 2005; Nelson *et al*, 2006; Schmidinger *et al*, 2011). This inconsistency might reflect differences in tumour genesis between endometrial and other types of cancer as well as a multifunctional nature of TSH.

A strong interaction between the hypothalamus–pituitary–thyroid axis and the balanced secretion of estradiol and progesterone by granulosa cells is well known. Hypothyroidism interferes with ovarian function, causing the formation of ovarian cysts and infertility (Stavreus-Evers, 2012). In patients with polycystic ovarian syndrome (PCOS), a higher prevalence of hypothyroidism has been demonstrated. Hypothyroidism thereby seems to worsen PCOS by decreasing the levels of sex hormone-binding globulin and by increasing the conversion of androstenedione to testosterone and its aromatisation to estradiol (Janssen *et al*, 2004). Without adequate opposition by a progestin, the incurred chronic excess exposure to endogenous estradiol constitutes one of the main risk factors for endometrial cancer.

Another effect of TSH on adipose tissue is the release of leptin. Besides regulating energy homeostasis and neuroendocrine processes, leptin acts as a potential growth stimulator in normal and neoplastic cancer cells (Menendez *et al*, 2003). Recent studies suggest a role of leptin in promoting endometrial cancer growth and invasion by regulating proangiogenic and proinflammatory factors (Liu *et al*, 2011). In human breast cancer cells, overlapping actions of estrogen and thyroid hormones on estrogen receptor-α and thereby stimulation of breast cancer cell growth could be demonstrated (Tang *et al*, 2004). As it has been shown that human endometrium expresses TSH receptors, it has been hypothesised that TSH can even directly act on uterus (Poppe and Velkeniers, 2004). Whether TSH possesses a direct biological role in tumour genesis of endometrial cancer or is indirectly promoting cancer development and progression is yet unclear.

This analysis uses data from two large gynaecological cancer centres. Although multicentre data repositories offer the opportunity to narrow study bias, there are several limitations inherent to retrospective study design. Hence, the results of our study are shortened by a lack of random assignment, patient selection, and incomplete data acquisition even though prospectively maintained data bases were extracted.

To our knowledge, this study is the first to investigate the association between pre-therapeutic serum TSH levels and the prognosis in patients with endometrial cancer. These findings, if proven by larger prospective studies, could have major clinical implications. For instance, serum TSH measurements may be used to screen women who are at high risk for endometrial cancer. Another implication may be the utilisation of serum TSH measurements for determination of recurrences during the clinical follow-up. By elucidating the value of TSH as independent prognostic parameter for survival in patients with endometrial cancer, our results provide new insight in possible functional properties of TSH and reflect the yet insufficiently explored impact

of hormonal imbalance on the nature and cause of cancer. Further research should be focussed on clinical utilisation of TSH for prognostic evaluation and the participation of TSH in the pathogenesis of endometrial cancer.

REFERENCES

Baloch Z, Carayon P, Conte-Devoix B, Demers LM, Feldt-Rasmussen U, Henry JF, LiVosli VA, Niccoli-Sire P, John R, Ruf J, Smyth PP, Spencer CA, Stockigt JR. Guidelines Committee, National Academy of Clinical Biochemistry (2003) Laboratory medicine practice guidelines. Laboratory support for the diagnosis and monitoring of thyroid disease. *Thyroid* **13**: 3–126.

Creasman WT, Odicino F, Maisonneuve P, Quinn MA, Beller U, Benedet JL, Heintz AP, Ngan HY, Pecorelli S (2006) Carcinoma of the corpus uteri. FIGO 26th annual report on the results of treatment in gynecologic cancer. *Int J Gynaecol Obstet* **95**(Suppl 1): 105–143.

Cristofanilli M, Yamamura Y, Kau SW, Bevers T, Strom S, Patangan M, Hsu L, Krishnamurthy S, Theriault RL, Hortobagyi GN (2005) Thyroid hormone and breast carcinoma. Primary hypothyroidism is associated with a reduced incidence of primary breast cancer. *Cancer* **103**: 1122–1128.

Hercbergs AA, Goyal LK, Suh JH, Lee S, Reddy CA, Cohen BH, Stevens GH, Reddy SK, Peereboom DM, Elson PJ, Gupta MK, Barnett GH (2003) Propylthiouracil-induced chemical hypothyroidism with high-dose tamoxifen prolongs survival in recurrent high grade glioma: a phase I/II study. *Anticancer Res* **23**: 617–626.

Iqbal A, Figenschau Y, Jorde R (2006) Blood pressure in relation to serum thyrotropin: the Tromsø study. *J Human Hypertension* **20**: 932–936.

Janssen OE, Mehlmauer N, Hahn S, Öffner AH, Gärtner R (2004) High prevalence of autoimmune thyroiditis in patients with polycystic ovarian syndrome. *Eur J Endocrinol* **150**: 363–369.

Kanat-Pektas M, Yenicesu O, Gungor T, Bilge U (2010) Predictive power of sexual hormones and tumor markers in endometrial cancer. *Arch Gynecol Obstet* **281**: 709–715.

Knudsen N, Laurberg P, Rasmussen LB, Bulow I, Perrild H, Ovesen L, Jørgensen T (2005) Small difference in thyroid function may be important for body mass index and the occurrence of obesity in the population. *J Clin Endocrinol Metab* **90**: 4019–4024.

Liu Y, Lv L, Xiao W, Gong C, Yin J, Wang D, Sheng H (2011) Leptin activates STAT3 and ERK1/2 pathways and induces endometrial cancer cell proliferation. *J Huazhong Univ Sci Technolog Med Sci* **31**: 365–370.

Menendez C, Baldelli R, Camina JP, Escudero B, Peino R, Dieguez C, Casanueva FF (2003) TSH stimulates leptin secretion by a direct effect on adipocytes. *J Endocrinol* **176**: 7–12.

Nelson M, Hercbergs A, Rybicki L, Strome M (2006) Association between development of hypothyroidism and improved survival in patients with head and neck cancer. *Arch Otolaryngol Head Neck Surg* **132**: 1041–1046.

Poppe K, Velkeniers B (2004) Female infertility and the thyroid. *Best Pract Res Clin Endocrinol Metab* **18**: 153–165.

Schmidinger M, Vogl UM, Bojic M, Lamm W, Heinzl H, Haitel A, Clodi M, Kramer G, Zielinski CC (2011) Hypothyroidism in patients with renal cell carcinoma: blessing or curse? *Cancer* **117**: 534–544.

Seebacher V, Polterauer S, Grimm C, Husslein H, Leipold H, Hefler-Frischmuth K, Tempfer C, Reinthaller A, Hefler L (2010) The prognostic value of plasma fibrinogen levels in patients with endometrial cancer: a multi-centre trial. *Br J Cancer* **16**: 952–956.

Stavreus-Evers A (2012) Paracrine interactions of thyroid hormones and thyroid stimulation hormone in the female reproductive tract have an impact on female fertility. *Front Endocrinol (Lausanne)* **3**: 1–8.

Tang HY, Lin HY, Zhang S, Davis FB, Davis PJ (2004) Thyroid hormone causes mitogen activated protein kinase-dependent phosphorylation of the nuclear estrogen receptor. *Endocrinology* **145**: 3265–3272.

Supplementary Information accompanies this paper on British Journal of Cancer website (http://www.nature.com/bjc)