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Prognostic significance of gamma-glutamyltransferase in patients with endometrial cancer: a multi-centre trial

V Seebacher[1], S Polterauer[1], C Grimm[1], J Rahhal[1], G Hofstetter[2], E-M Bauer[2], H Husslein[3], H Leipold[3], C Marth[2], A Reinthaller[1] and N Concin[*,2]

[1]Department of Gynaecology and Gynaecological Oncology, Comprehensive Cancer Centre Vienna, Medical University of Vienna, 1090 Vienna, Austria; [2]Department of Gynaecology and Obstetrics, Medical University Innsbruck, Christoph-Probst-Platz Innrain 52, 6020 Innsbruck, Austria; [3]Department of Obstetrics and Gynaecology, Landeskrankenhaus Klagenfurt, 9020 Klagenfurt am Wörthersee, Austria

BACKGROUND: Gamma-glutamyltransferase (GTT), a known marker for apoptotic balance, seems to promote tumour progression, invasion and drug resistance. Recently, high GGT serum levels were shown to be associated with impaired prognosis in patients with cervical cancer. The aim of this study was to investigate the value of pre-therapeutic serum GGT levels as prognostic parameter in patients with endometrial cancer.

METHODS: Within the present multi-centre trial, clinical–pathological parameters and pre-therapeutic serum GGT levels were evaluated in 874 consecutive patients with endometrial cancer. Patients were stratified in GGT risk groups, and univariate and multivariable survival analyses were performed.

RESULTS: Mean pre-therapeutic serum GGT level was 30.8 (41.5) UI^{-1}. Elevated and highly elevated serum GGT levels ($P = 0.03$ and $P = 0.005$), tumour stage ($P < 0.001$ and $P < 0.001$), grade ($P < 0.001$ and $P = 0.02$) and age ($P < 0.001$ and $P < 0.001$) were independently associated with progression-free survival in univariate and multivariable survival analyses. Pre-therapeutic GGT was not associated with advanced tumour stage ($P = 0.6$), higher histological grade ($P = 0.6$) or unfavourable histological subtype ($P = 0.3$).

CONCLUSION: Pre-therapeutic serum GGT is a novel and independent prognostic parameter for progression-free survival of patients with endometrial cancer. Stratifying patients into prognostic subgroups could be used for patient counselling and individualised treatment planning.

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The enzyme gamma-glutamyltransferase (GGT) has a substantial role in the metabolism of glutathione (γ-glutamyl-cysteinyl-glycine; GSH). For maintaining adequate levels of intracellular GSH, GGT catalyses the degradation of extracellular GSH, thus providing component amino acids that are then available for further intracellular GSH production. Within the cell GSH functions as a major antioxidant, neutralising reactive oxygen compounds and free radicals (Whitfield, 2001). Gamma-glutamyl-transferase expression is found predominantly on the luminal surface of secretory epithelial cells, especially of the hepato-biliary tract, the pancreas and the kidneys. Abnormal GGT expression is found in several human tumours, including breast cancer, ovarian cancer and cervical cancer (Hanigan, 1998). Recently, a possible role of GGT in tumour progression, invasion, drug resistance and prognosis has been suggested (Whitfield, 2001). Underlying mechanisms of GGT on tumour biology are yet still unknown.

In clinical practice, serum GGT is commonly used as a marker for hepato-biliary disease and alcohol intake (Whitfield, 2001). Elevated serum GGT was shown to be associated with all-cause, hepato-biliary, vascular and cancer mortality in both men and women (Kazemi-Shirazi *et al*, 2007; Ruhl and Everhart, 2009). Moreover, two large prospective epidemiological cohort studies in 79 279 and 92 843 individuals ascertained an association between elevated serum GGT and an increased risk of developing cancer (Strasak *et al*, 2008a, b). Recently, these results were confirmed in a large Swedish cohort study comprising 545 460 men and women (Van Hemelrijck *et al*, 2011).

Within the female reproductive tract GGT expression was found in endometrial and endocervical glands. In patients with cervical cancer, elevated serum GGT level was associated with impaired prognosis (Polterauer *et al*, 2011). We performed the present multi-centre trial to evaluate the association between pre-therapeutic serum GGT and prognosis in a large number of patients with endometrial cancer.

PATIENTS AND METHODS

Patients

A total 874 patients with endometrial cancer were included in the present Austrian multi-centre trial (Department of Gynaecology and Gynaecological Oncology, Comprehensive Cancer Centre, Medical University of Vienna, Vienna, Austria, $n = 430$; Department of Gynaecology and Obstetrics, Medical University

*Correspondence: Professor N Concin; E-mail: nicole.concin@i-med.ac.at
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Innsbruck, Innsbruck, Austria, $n=362$; Department of Gynaecology, LKH Klagenfurt, Klagenfurt, Austria, $n=82$). Clinical and laboratory data were extracted from the respective electronic gynaecologic oncology registries.

Before therapy, a physical examination by a consultant in Internal Medicine and blood tests were performed. The data were documented electronically and in the patients' charts. Patients who presented with pre-existing co-morbidities, which are known to be related to elevated GGT (i.e., alcohol abuse, hepato-biliary tract, pancreatic, and heart disease or alcohol abuse) were excluded from the study. Patients who did not receive standardised treatment because of age or significant co-morbidities were excluded from analysis. Patients with additional, co-existing malignant disease were also excluded from analysis.

Clinical management

Diagnosis of endometrial cancer was established by dilation and curettage. Subsequently, patients were clinically and/or surgically staged according to the International Federation of Gynecology and Obstetrics (FIGO)/American Joint Committee on Cancer classification system of FIGO sixth annual report 2006, using the 1988 FIGO classification (Creasman *et al*, 2006). Patients were treated and followed according to international guidelines, as described previously (Seebacher *et al*, 2010).

Pelvic and para-aortic lymphadenectomy was recommended except for FIGO tumour stage Ia and Ib, with histological grade 1 and 2, and endometrioid histology. In patients with high-intermediate-risk or high-risk disease, adjuvant radiotherapy was provided according to standardised treatment protocols (Nag *et al*, 2000). Adjuvant chemotherapy and/or hormonal therapy were used in selected patients with advanced disease.

If patients did not present for scheduled follow-up visits administrative personnel or nurses contacted them. If any clinically suspicious symptom and/or tumour marker elevation was detected, computed tomography was performed. Recurrent disease was either diagnosed by biopsy or by imaging methods, following standard clinical guidelines.

GGT measurement

Blood samples (serum) were obtained routinely by peripheral venous puncture before therapy during pre-treatment examination. Serum GGT concentrations were analysed with an enzyme kinetic assay (Modular Hitachi 747 and Hitachi 917, Roche Diagnostics, Basel, Switzerland), as described previously (Kazemi-Shirazi *et al*, 2007).

Statistical analysis

Values are given as means (s.d.). Chi-square test was used to assess the association with obesity and tumour stage. One-way ANOVA was used to assess the association between pre-treatment serum GGT levels and clinical–pathological parameters.

For survival analysis, patients were assigned to previously established GGT risk groups (Franzini *et al*, 2006; Polterauer *et al*, 2011), as follows: GGT $<17.9\,U\,l^{-1}$: group A (normal low); GGT 18.0 to $35.9\,U\,l^{-1}$: group B (normal high); GGT 36.0 to $71.9\,U\,l^{-1}$: group C (elevated); and GGT $>72.0\,U\,l^{-1}$: group D (highly 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 endpoint of progression-free survival. Events were defined as cancer-related death or progression at the time of the last follow-up visit. Patients who died of other causes than endometrial cancer or patients alive with no or stable disease were censored with the date of death or last follow-up, respectively. Univariate and multivariable Cox regression models were performed, comprising the GGT risk groups (groups D and C *vs* groups B and A), FIGO tumour stage (FIGO IV *vs* FIGO III *vs* FIGO II *vs* FIGO I), histological grade (G3 *vs* G2 *vs* G1), histological subtype (non-endometrioid carcinoma *vs* endometrioid adenocarcinoma) and the patients' mean age (>66.7 years *vs* $\leqslant 66.7$ years). Effects of life style factors (obesity, hypertension and diabetes mellitus) and the specific study-centre (Vienna *vs* Innsbruck *vs* Klagenfurt) on survival were evaluated by univariate survival analysis. Results of univariate and multivariable survival analyses are given as *P*-value (hazard ratio and 95% confidence interval). *P*-values <0.05 were considered statistically significant. We used the statistical software SPSS 16.0 for Mac (SPSS 16.0.1, SPSS Inc., Chicago, IL, USA) for statistical analysis.

Institutional review board

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

RESULTS

Patients' characteristics

Patients' baseline characteristics are given in Table 1, clinical–pathological characteristics in Table 2. Mean (s.d.) pre-therapeutic serum GGT level was 30.8 (41.5) $U\,l^{-1}$. We used the previously described GGT risk groups (Franzini *et al*, 2006; Polterauer *et al*, 2011) for stratification, assigning 356 (40.7%) patients to group A (normal low), 338 (38.7%) patients to group B (normal high), 117 (13.4%) patients to group C (elevated) and 63 (7.2%) patients to group D (highly elevated). We observed a high incidence of obesity, diabetes mellitus and hypertension in our patients' collective (Table 1). Advanced FIGO tumour stages III and IV were less common in obese patients than in patients of normal weight ($P=0.009$). Patients' characteristics were distributed equally within the three study centres (data not shown).

Association between GGT and clinical–pathological parameters and life style factors

The association between pre-therapeutic serum GGT levels and clinical–pathological parameters is provided in Table 3. We could

Table 1 Patients' baseline characteristics

Parameter	Number (%) or mean (s.d.)
Total number of patients enrolled	874
GGT ($U\,l^{-1}$)	30.8 (41.5)
Age at diagnosis (years)	66.7 (11.5)
Obesity[a]	
No	349 (39.9)
Yes	353 (40.4)
NA	172 (19.7)
Hypertension[b]	
No	449 (51.4)
Yes	277 (31.7)
NA	148 (16.9)
Diabetes mellitus	
No	589 (67.4)
Yes	138 (15.8)
NA	147 (16.8)

Abbreviations: GGT = gamma-glutamyltransferase; NA = data not available. [a]Body mass index $\geqslant 30\,kg\,m^{-2}$. [b]Systolic blood pressure $\geqslant 160$ mm Hg or diastolic blood pressure $\geqslant 100$ mm Hg.

Table 2 Clinical–pathological parameters ($n = 874$)

Parameter	Number (%) or mean (s.d.)
Stage[a]	
FIGO Ia	146 (16.7)
FIGO Ib	359 (41.1)
FIGO Ic	123 (14.1)
FIGO IIa	36 (4.1)
FIGO IIb	41 (4.7)
FIGO IIIa	54 (6.2)
FIGO IIIb	14 (1.6)
FIGO IIIc	53 (6.1)
FIGO IVa	3 (0.3)
FIGO IVb	31 (3.5)
NA	14 (1.6)
Grade	
G1	353 (40.4)
G2	330 (37.8)
G3	181 (20.7)
NA	10 (1.1)
Histological subtype	
Endometrioid histology	789 (90.3)
Non-endometrioid histology	85 (9.7)
Time of follow-up (months)	45.0 (33.6)
Recurrence status	
Number of patients with recurrent disease	153 (17.5)
Time to recurrent disease (months)	15.5 (15.9)
Status at last observation	
Disease-free	649 (74.2)
Stable disease	26 (3.0)
Progressive disease	25 (2.9)
Cancer-related death	90 (10.3)
Death related to other causes	84 (9.6)

Abbreviations: FIGO = International Federation of Gynecology and Obstetrics; NA = data not available. [a]According to the 1988 FIGO staging system.

Table 3 Mean plasma GGT levels in patients with endometrial cancer broken down by clinical–pathological parameters ($n = 874$)

	Mean (s.d.) plasma GGT levels (mg dl^{-1})	*P*-value
Stage[a]		0.6
I	29.9 (43.8)	
II	31.0 (34.6)	
III	33.7 (36.9)	
IV	38.2 (33.5)	
Grade[a]		0.6
G1	33.1 (52.9)	
G2	29.3 (31.9)	
G3	29.5 (31.4)	
Histological subtype[a]		0.3
Endometrioid	30.9 (42.2)	
Non-endometrioid	25.8 (25.8)	
Age[a]		0.09
⩽66.7 Years	33.2 (50.9)	
>66.7 Years	28.4 (28.8)	
Obesity[a,b]		0.4
No	33.4 (33.0)	
Yes	31.1 (53.9)	
Diabetes mellitus[a]		0.3
No	31.5 (32.9)	
Yes	35.5 (32.9)	
Hypertension[a,c]		0.3
No	30.7 (37.9)	
Yes	34.4 (53.3)	

Abbreviations: ANOVA = analysis of variance; GGT = gamma-glutamyl transferase. [a]One-way ANOVA. [b]Body mass index > 30 kg m^{-2}. [c]Systolic blood pressure ⩾160 or diastolic blood pressure ⩾100 mm Hg.

not show an association between high pre-therapeutic serum GGT and advanced FIGO tumour stage, high histological grade or unfavourable histological subtype. Gamma-glutamyltransferase was not associated with obesity, hypertension, age or diabetes mellitus.

Association between GGT and survival

In univariate analysis, advanced FIGO tumour stage, high histological grade, unfavourable histological subtype, older age and elevated or highly elevated GGT risk groups were associated with poor progression-free survival. In univariate analysis, we did not observe a difference in survival between the three study centres. Obesity, hypertension and diabetes mellitus were not associated with progression-free survival in univariate analysis. Therefore, we did not include these parameters in the multivariable analysis. Elevated or highly elevated GGT risk groups remained independently associated with progression-free survival in multivariable analysis. Results of univariate and multivariable analyses are provided in Tables 4 and 5, respectively.

Figure 1 shows Kaplan–Meier curves for pooled GGT risk groups (C + D *vs* A + B) according to progression-free survival. Patients assigned to the groups of normal low and normal high GGT (A and B) and patients assigned to the groups of elevated and highly elevated GGT (C and D) had 5-year progression-free survival rates of 85.1% and 76.7%, respectively ($P = 0.03$).

DISCUSSION

The present multi-centre trial evaluates the role of pre-therapeutic serum GGT in patients with endometrial cancer. Our data demonstrate an independent association between high pre-therapeutic serum GGT levels and a poor prognosis in patients with endometrial cancer.

We stratified patients into previously described and established prognostic subgroups (Polterauer *et al*, 2011). Patients of groups A and B (lower GGT serum level) had significantly longer 5-year progression-free survival rates (89.4%) than patients of groups C and D (higher GGT serum level) (76.7%). Our findings seem plausible, as GGT is a known marker of apoptosis and has previously been described to be associated with disease stage and survival in cervical cancer (Polterauer *et al*, 2011). Our findings are interesting from clinical point of view. Gamma-glutamyltransferase could preoperatively be used for assigning patients to distinctive prognostic subgroups and, if validated in a large independent trial, be incorporated into a nomogram predicting endometrial cancer prognosis.

We assessed the association between GGT, clinical–pathological parameters and life style factors. Interestingly, none of the investigated parameters was associated with GGT. As opposed to previous results on the association between GGT and tumour stage in cervical cancer (Polterauer *et al*, 2011), we did not observe an association between GGT and disease stage in endometrial cancer. This might reflect differences in tumour genesis and tumour progression between endometrial and cervical cancer. In endometrial cancer, the apparent dissociation between GGT and tumour stage could suggest that GGT might be associated with

Table 4 Five-year progression-free survival

	5-Year progression-free survival[a] % (s.e.)	*P*-value[a]
Stage		
FIGO IV	23.3 (14.3)	<0.001
FIGO III	67.1 (7.3)	
FIGO II	87.1 (7.0)	
FIGO I	96.0 (1.5)	
Grade		
G3	64.8 (5.0)	<0.001
G2	84.6 (2.7)	
G1	94.4 (1.5)	
Histological subtype		
Non-endometrioid histology	68.3 (6.2)	<0.001
Endometrioid histology	85.5 (1.5)	
Age		
>66.7 Years	76.7 (2.5)	<0.001
⩽66.7 Years	89.4 (1.7)	
GGT		
Elevated and highly elevated GGT[b]	76.7 (3.9)	0.03
Normal low and normal high GGT[c]	85.1 (1.6)	
Obesity[d]		0.7
Yes	88.4 (3.0)	
No	88.3 (2.7)	
Hypertension[e]		0.9
Yes	84.1 (2.6)	
No	84.5 (2.0)	
Diabetes mellitus		0.6
Yes	80.5 (4.3)	
No	84.9 (1.7)	
Study centre		0.3
Vienna	84.4 (2.0)	
Innsbruck	80.9 (2.5)	
Klagefurt	89.7 (5.3)	

Abbreviations: FIGO = International Federation of Gynecology and Obstetrics; GGT = gamma-glutamyltransferase. [a]Kaplan–Meier analysis (log-rank test). [b]Groups C and D. [c]Groups A and B. [d]Body mass index > 30 kg m^{-2}. [e]Systolic blood pressure ⩾160 or diastolic blood pressure ⩾100 mm Hg.

Table 5 Multivariable survival-analysis

	Progression-free survival	
Multivariable analysis[a]	**HR (95% CI)**	***P*-value**
Stage (FIGO IV *vs* III *vs* II *vs* I)	2.6 (2.1–3.3)	<0.001
Grade (G3 *vs* G2 *vs* G1)	1.4 (1.1–2.1)	0.02
Histological subtype (non-endometrioid *vs* endometrioid)	1.4 (0.8–2.6)	0.2
Age (>66.7 years *vs* ⩽66.7 years)	2.3 (1.4–3.7)	<0.001
GGT (groups C and D *vs* groups A and B)	2.1 (1.2–3.4)	0.005

Abbreviations: FIGO = International Federation of Gynecology and Obstetrics; GGT = gamma-glutamyltransferase; HR (95% CI) = hazard ratio (95% confidence interval). [a]Cox regression model. GGT group C = elevated GGT levels, GGT group D = highly elevated GGT levels. GGT group A = normal low GGT levels, GGT group B = normal high GGT level.

systemic changes of the disease, for example, inflammation, rather than with the local neoplastic transformation. Additionally, in this study, the number of patients within the respective groups of tumour stage was imbalanced. This is due to the fact that the majority of cases of endometrial cancer present with irregular uterine bleeding as early symptom and are therefore diagnosed in early tumour stage.

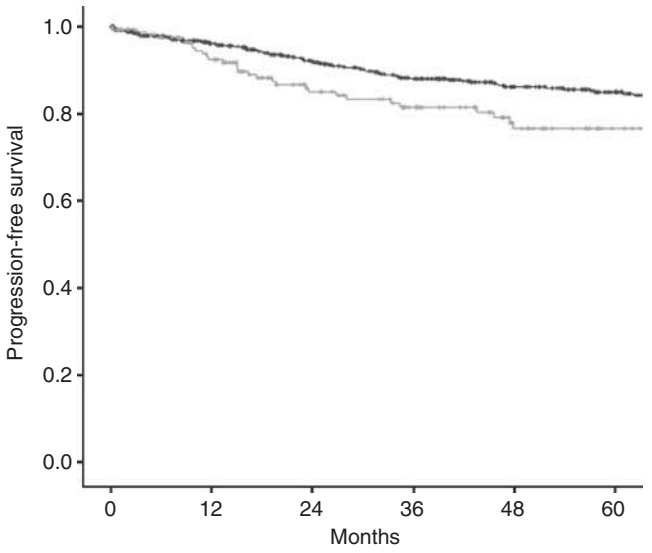

Figure 1 Kaplan–Meier curves for pre-therapeutic GGT level groups A and B (upper line) *vs* C and D (lower line) and progression-free survival ($P = 0.03$).

Previous studies described that patients with elevated GGT were found to have elevated risk of diabetes (Perry *et al*, 1998). In addition, GGT was previously shown to be elevated in older patients without cancer (Kazemi-Shirazi *et al*, 2007). The investigators hypothesise that these findings might be caused by selection bias as only patients with endometrial cancer and no healthy controls were included into our analysis. Nevertheless, we observed a high incidence of symptoms related to metabolic disorders. This is in accordance with previous studies, which showed an increase in endometrial cancer incidence in women with metabolic syndrome compared with healthy women (Friedenrich *et al*, 2011, Reeves *et al*, 2011). Interestingly, in our patients collective obese patients showed less cases of advanced tumour stages, which is not supported by previous findings (Reeves *et al*, 2011).

Experimental studies have explored possible effects of GGT and GSH on tumour cell biology. Traditionally, GGT and GSH have been regarded as essential components of the cell's defence apparatus against oxidative stress. Yet, the distribution and concentration of GGT in several tumours raised the question whether increased GGT expression itself has any active role in neoplastic transformation (Corti *et al*, 2010). Apparently, under certain conditions, GGT can exert pro-oxidant effects, impairing cellular proliferative/apoptotic balance, thus modulating tumour formation and progression (Corti *et al*, 2010).

Recently, GSH has been shown to reduce and thereby activate oxidised phosphatase and tensin homolog (PTEN), which acts as a tumour suppressor by inhibiting phosphoinositide 3-kinase-dependent activation of AKT (Kim *et al*, 2010). Phosphatase and tensin homolog gene mutations are the most frequent genetic lesions in endometrial cancer (83%), causing loss of functional PTEN (Mutter *et al*, 2000). Most interestingly, Corti *et al* (2005) showed that GGT promotes *S*-thiolation of cellular proteins and of proteins of the extracellular environment. The dipeptide cysteinyl-glycin originates from cellular GGT-mediated GSH metabolism and efficiently thiolates proteins. This leads to the formation of cysteinyl-glycine mixed disulphides. Of note, PTEN has been found to undergo glutathionylation (Kim *et al*, 2010). Thus, we hypothesise that PTEN might as well undergo 'cysteylglycylation'

mediated by GGT activity. This could possibly lead to a modification or inactivation of PTEN function.

Whether higher GGT possesses a direct biological role in tumour genesis or indirectly reflects increased cellular GGT activity to metabolise extracellular GSH conjugates in accordance to increased demand is yet unclear.

As typical of retrospective studies, our study is limited by biases such as lack of random assignment, patient selection and incomplete data acquisition, although prospectively maintained data bases were extracted. The use of patients from three large cancer centres may reflect a cohort with more aggressive disease, which is the referral pattern for such centres. At the same time, part of our study group performed a prospective cohort study elucidating similar results on the value of GGT as prognostic parameter in patients with endometrial cancer (data not yet published). Our study comprises an even larger number of patients and displays completeness of clinical data. Therefore, despite its retrospective design, our study is of great value.

In endometrial cancer, several biomarkers such as cancer antigen (CA) 125 (Kurihara *et al*, 1998), CA 15.3 (Lo *et al*, 1997), C-reactive protein (Schmid *et al*, 2007) and fibrinogen (Seebacher *et al*, 2010) have been investigated regarding their impact on prognosis. By elucidating the value of serum GGT as independent prognostic parameter for the survival in patients with endometrial cancer, we provide an additional serum marker, which can be routinely assessed within pre-treatment medical examination.

Conflict of interest

The authors declare no conflict of interest.

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