Original Study

The Predictive and Prognostic Value of Precystectomy Serum Gamma-Glutamyltransferase Levels in Patients With Invasive Bladder Cancer

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Abstract

This retrospective analysis investigated the predictive and prognostic value of serum gamma-glutamyltransferase (GGT) in 324 patients undergoing RC for invasive bladder cancer (BC). Elevated preoperative serum GGT levels was associated with increased risk of locally advanced BC and mortality after RC. The data suggest that GGT levels may be a useful for improved prognostication in invasive BC.

Introduction: The aim of the study was to elucidate the predictive and prognostic value of serum gamma-glutamyltransferase (GGT) in patients with invasive bladder cancer (BC). **Patients and Methods:** Preoperative serum GGT concentrations were assessed in 324 patients treated with RC for cM0 BC between 2002 and 2013. Laboratory values were obtained 1 to 3 days prior to RC. Uni- and multivariable analyses were carried out to evaluate clinicopathologic risk factors for survival. The median follow-up was 36 months (IQR: 10-55). **Results:** Elevated preoperative GGT levels were diagnosed in 77 patients (23.8%). Elevated GGT was significantly associated with higher ECOG PS and tumor stage (both $P = .001$), lymph-node tumor involvement ($P < .001$), positive surgical margins ($P = .018$), lymphovascular invasion ($P = .024$), muscle-invasive disease at primary diagnosis ($P = .033$), increased tumor size ($P = .035$), hydronephrosis at RC ($P = .049$) and increased preoperative CRP, GPT and GOT levels (both $P < .001$). Patients with elevated GGT had decreased 3-year overall (49.2% vs. 69.6%; $P = .005$) and cancer-specific survival (71.1% vs. 80.9%; $P = .042$) compared with patients with normal levels. On multivariable analysis, advanced tumor stage ($P = .032$), lymph node positive disease ($P = .030$), positive soft tissue surgical margins ($P = .014$), hydronephrosis at RC (both $P = .010$), higher ECOG performance status and elevated GGT ($P = .043$) levels were independent predictors of all-cause mortality. **Conclusion:** Elevated preoperative serum GGT levels are associated with increased risk of locally advanced BC and mortality after RC. These data suggest that GGT levels may be useful for improved prognostication in invasive BC.

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Introduction

Over the past decades, a variety of serological and hematological parameters has been investigated in numerous retrospective series in terms of their predictive and prognostic potential in patients undergoing radical cystectomy (RC) for invasive bladder cancer (BC).[1] These markers are usually routinely determined before RC and thus can be easily evaluated retrospectively. However, due to the lack of postoperative data, none of these markers has yet been established for routine use in clinical decision making.[2-4] These markers include, for example, serum C-reactive protein (CRP),[5] hemoglobin level,[6] plaletet count[7] and the De-Ritis ratio,[8] which reflects the ratio of the 2 liver enzymes GOT/GPT and is usually considered an indicator of severity of liver diseases in clinical practice.

Another hepatologic parameter which is important in clinical practice is serum gamma-glutamyltransferase (GGT). GGT is a membrane-bound enzyme and plays a key role in glutathione metabolism. This metabolism is essential for cellular protection against various oxidants.[9] An increase in glutathione and GGT levels, which is regularly observed in the tumor microenvironment,

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may be related to pathologically increased oxidative stress. Moreover, GGT plays a role in tumor development and progression as well as anticancer drug resistance.[10-12] In addition, GGT has been shown to be an important prognostic biomarker in various carcinomas, including prostate cancer,[13] renal cell carcinoma,[14] breast cancer[15] and ovarian cancer.[16] However, there is a lack of data concerning the prognostic role of GGT in patients treated with RC.[17] Therefore, the present study aimed to investigate whether preoperative serum GGT levels correlate with oncologic outcomes after RC for BC.

Patients and Methods

Patient Cohort

After obtaining approval of the local ethics committee (protocol number: 417/2010A), we reviewed our cystectomy database to identify 324 consecutive patients with known preoperative GGT levels who underwent RC for stage cM0 BC between 2002 and 2013. We included all patients treated with RC for (1) histologically confirmed muscle-invasive BC, (2) NMIBC at high to highest-risk of progression or (3) persistent NMIBC after failure of intravesical therapy. RC with lymph node dissection and urinary diversion was conducted according to standardized techniques.[18]

Clinical and Histologic Assessment

The following clinical and histopathologic parameters were recorded: age at RC, gender, Eastern Cooperative Oncology Group (ECOG) performance status (PS), alcohol consumption, number of TUR-BT prior to RC, median time between last TUR-BT and RC, tumor grade and multifocality, hydronephrosis at RC, muscle-invasive disease (MIBC) at primary diagnosis (PD), clinical and pathologic tumor stage, histopathologic lymph node tumor involvement, soft-tissue surgical margins (STSM), histological entity of BC (urothelial vs. nonurothelial), preoperative administration of intravesical immuno- and/or chemotherapy and receipt of postoperative systemic chemotherapy. Patients with NMIBC at PD were further divided into those with progression at RC and those without progression.

Laboratory Investigations

Lab values were determined 1 to 3 days before RC. Normal serum GGT levels were defined as 55U/L or less in men and 38U/L or less in women. In addition, serum levels of glutamic pyruvate transaminase (GPT) and glutamate oxaloacetic transaminase (GOT) were recorded. In men, serum GPT and GOT levels were defined as normal below a concentration of 42U/L and 41U/L, respectively. In women, normal values were defined below 32U/L and 34U/L, respectively. In addition to these lab values, serum creatinine, serum C-reactive protein (CRP), hemoglobin and platelet levels were recorded.

Histological Analysis

The histologic assessment was based on the WHO grading system of 1973 and TNM classification as approved by the AJCC.[19] Cystectomy specimens were macro- and microscopically assessed according to standardized protocols based on H&E and immunohistochemical staining to identify the presence of urothelial and nonurothelial histology. Lymphovascular invasion was defined as the presence of malignant cells within an endothelial lining. Surgical margins were considered positive in case of malignant cells at any soft tissue margin of the specimen.[20]

Follow-up

For follow-up, we evaluated data from electronic medical records and tumor registry to determine tumor recurrence and patient vital status. Due to the retrospective approach of the study, a standardized follow-up protocol did not exist for all patients during the treatment period. Nonetheless, in general, patients were examined every 3 to 4 months during the first year, semiannually during the second and third years, and annually thereafter as recommended by guidelines.[4,18] Oncologic evaluation included computed tomography and/or magnetic resonance imaging at regular intervals. Additionally, physical examination with cystoscopy, urine cytology, urethral lavage, laboratory tests, intravenous pyelography, and bone scintigraphy were performed if indicated.[4] Recurrence was defined as any local recurrence of tumor in the surgical bed and distant organs but not in the remaining urothelium given its prognostic difference.[4,21] Patients with urothelial recurrence (N = 18) were separately assessed for OS analysis. Patients who did not experience recurrence, death due to progressive BC disease, or death from any cause were censored at last follow-up. The median follow-up time was 36 months (IQR: 10-55).

Statistics

Correlation between various clinicopathologic parameters and serum GGT levels was determined using Fisher's Exact or Pearson Chi-square test. The effects of serum GGT, GPT and GOT levels on overall survival (OS), cancer-specific survival (CSS), and recurrence-free survival (RFS) were assessed using Kaplan-Meier analysis with log-rank test. Survival endpoints were calculated from the time of RC to the time of documented recurrence or death. Univariable Cox-regression models were used to assess risk factors for recurrence and (cancer-specific) mortality. For mortality risk factors, a multivariable Cox proportional hazards model was constructed that included established clinicopathologic risk factors for mortality and parameters that were found to be significantly associated with elevated serum GGT levels in univariable analysis. Values for continuous variables are expressed as mean, median, and interquartile range (IQR). All tests were 2-sided. A $P < .05$ was considered significant. Analysis was performed using the JMP 12.2 software package (Cary, NC, USA).

Results

Of the 324 patients, preoperatively elevated serum GGT, GPT and GOT levels were diagnosed in 77 (23.8%), 20 (6.2%), and 18 (5.5%), respectively. In univariable analysis, elevated serum GGT levels were significantly associated with the following parameters (Table 1): advanced histopathologic tumor stage (pT3a; $P = .001$), lymph node metastasis ($P < .001$), positive STSMs ($P = .018$), lymphovascular invasion ($P = .024$), increased tumor size (continuously coded; $P = .035$), muscle-invasive BC at primary diagnosis ($P = .033$), preoperative hydronephrosis ($P = .049$), higher ECOG performance status ($P < .001$) and preoperatively elevated serum CRP, GPT and GOT concentration (all $P < .001$). Of the patients with NMIBC at PD, those who had progressed to MIBC at RC did

Table 1 Clinical and Histopathological Characteristics of Patients Treated With Radical Cystectomy for Bladder Cancer Subanalyzed for Elevated Versus Normal GGT Levels

Parameter	Elevated GGT levels	Normal GGTLevels	*P*
Number of patients (%)	77 (23.8)	247 (76.2)	
Gender Male Female	 61 (79.2) 16 (20.8)	 181 (73.3) 66 (26.7)	 .36
Mean age at RC [a] Median IQR	67 66 60-74	67 69 61-75	 .56
Mean time between last TUR-BT and RC [d] Median IQR	 62 34 20-60	 50 32 20-50	 .31
Mean number of TUR-BTs before RC Median IQR	 1.8 1 1-2	 2.1 1 1-3	 .19
ECOG PS at RC 0 1 2 3	 54 (70.1) 21 (27.3) 1 (1.3) 1 (1.3)	 219 (88.7) 22 (8.9) 5 (2.0) 1 (0.4)	 **.001**
Alcohol consumption Yes No Unknown	 46 (59.7) 25 (32.5) 6 (7.8)	 152 (61.5) 93 (37.7) 2 (0.8)	 .78
Clinical tumor stage ≥cT3 ≤ cT2 Data not available	 27 (35.1) 47 (61.0) 3 (3.9)	 61 (24.7) 184 (74.5) 2 (0.8)	 .055
pT-stage ≥ pT3a ≤ pT2b	 50 (64.9) 27 (35.1)	 107 (43.3) 140 (56.7)	 **.001**
Histopathological nodal stage pN+ pN0 pNX	 26 (33.8) 40 (52.0) 11 (14.3)	 58 (23.5) 182 (73.7) 7 (2.8)	 **< .001**
STSMs Positive Negative Not assessed	 18 (23.4) 59 (76.6) 0 (0)	 26 (9.4) 214 (77.3) 7 (2.5)	 **.018**
Lymphovascular invasion LVI LV0 LVX	 35 (45.5) 37 (48.1) 5 (6.5)	 77 (31.2) 155 (62.8) 15 (6.1)	 **.024**
Tumor multifocality Present Absent	 26 (33.8) 51 (66.2)	 83 (33.6) 164 (66.4)	 1.0
Estimated tumor size at RC [cm] Mean Median IQR	 3.4 3.1 2.0-4.3	 2.9 2.8 1.7-3.9	 **.035**
Tumor grade G1 G2 G3 GX Not available	 0 (0) 20 (26.0) 54 (70.1) 0 (0) 3 (3.9)	 2 (0.8) 69 (27.9) 156 (63.2) 3 (1.2) 17 (6.9)	 .57

(*continued on next page*)

Table 1 (*continued*)

Parameter	Elevated GGT levels	Normal GGTLevels	*P*
Hydronephrosis at RC Present Absent Not available	 22 (28.6) 55 (71.4) 0 (0)	 43 (17.0) 203 (82.2) 1 (0.4)	**.049**
MIBC at PD Present Absent Not available	 44 (57.1) 21 (27.3) 12 (15.6)	 119 (48.2) 109 (44.1) 19 (7.7)	**.033**
Nonpure UC pathology at RC Present Absent	 18 (23.4) 59 (76.6)	 40 (16.2) 207 (83.8)	.17
Preop. serum creatinine [mg/dl] Mean Median IQR	 1.1 1 0.8-1.3	 1.0 1 0.8-1.3	.10
Preop. serum C-reactive protein [mg/dl] Mean Median IQR	 2.6 0.8 0.3-2.7	 1.0 0.3 0.1-1.0	**< .001**
Preop. hemoglobin [mg/dl] Mean Median IQR	 13.1 13.5 12.1-14.4	 13.1 13.4 11.2-14.8	.82
Preop. thrombocytes (x$10^3/\mu$l) Mean Median IQR	 322 311 224-376	 300 281 229-357	.15
Serum GPT concentration Elevated Normal Not available	 12 (14.3) 44 (57.1) 21 (27.3)	 8 (3.2) 162 (65.6) 77 (31.2)	**< .001**
Serum GOT concentration Elevated Normal Not available	 13 (16.9) 63 (81.8) 1 (1.3)	 5 (2.0) 240 (86.6) 2 (0.8)	**< .001**
Intravesical BCG and/or chemotherapy Performed Not performed	 19 (24.7) 58 (75.3)	 71 (28.7) 176 (71.3)	.56
Postoperative systemic chemotherapy Adjuvant Palliative	 3 (3.9) 17 (22.1)	 9 (3.6) 38 (15.4)	 1.0 .22

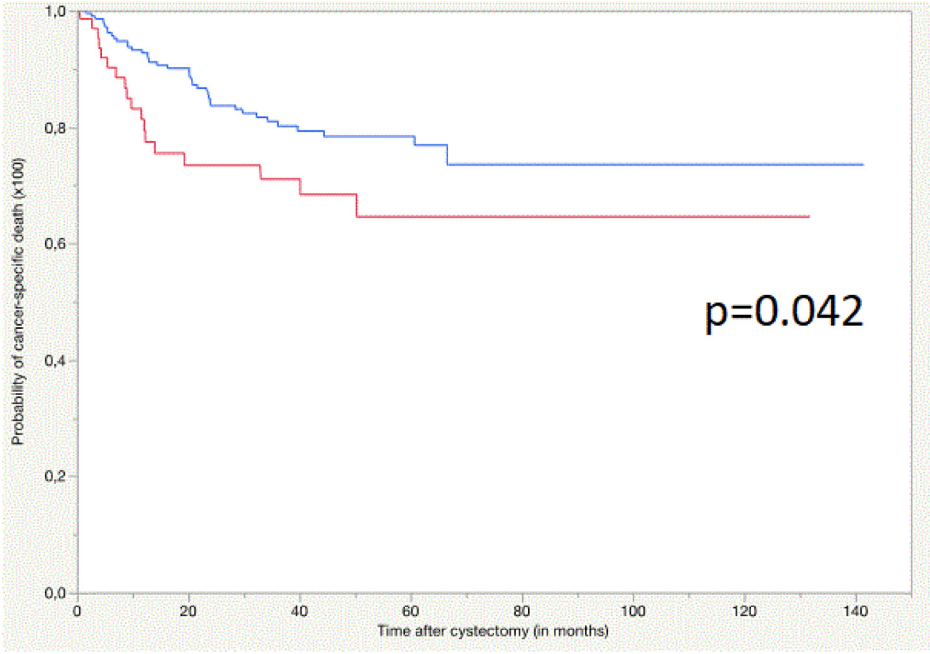
Bold values indicate a statistically significant difference.
Abbreviations: a = year; BCG = Bacille-Calmette-Guerin; d = days; ECOG PS = Eastern Cooperative Oncology Group performance status; GGT = gamma-glutamyltransferase; IQR = interquartile range; MIBC = muscle-invasive bladder cancer; mo = months, *P* = *P* value; PD = primary diagnosis; RC = radical cystectomy; TUR-BT = transurethral bladder tumor resection; UC = urothelial carcinoma.

not have significantly higher serum GGT levels compared to those who still had NMIBC at RC ($P = .47$).

Of the 324 patients, 109 (33.6%) experienced recurrence, 59 (18.9%) experienced cancer-specific death, and 122 (37.7%) experienced death after RC. Patients with elevated GGT levels had decreased 3-year OS (49.2% vs. 69.6%; $P = .005$), CSS (71.1% vs. 80.9%; $P = .042$; Figure 1) and RFS (52.5% vs. 63.2%; $P = .19$), compared to patients with normal GGT levels. Similarly, increased serum GOT concentration was found to be significantly associated with decreased 3-year OS (43.5% vs. 65.5%; $P = .034$), while no significant association was found for CSS (68.8% vs. 78.6%; $P = .35$) and RFS (47.6% vs. 61.7%; $P = .55$). Elevated serum GPT levels were not significantly associated with 3-year OS (42.3% vs. 67.0%; $P = .14$), CSS (71.6% vs. 78.1%; $P = .97$) and RFS (67.5% vs. 63.8%; $P = .57$). For patients with solitary urothelial recurrence (N = 18), no differences in OS ($P = .39$) was observed between those with preoperatively elevated versus normal serum GGT levels.

In multivariable Cox regression analysis, adjusted for all significant parameters of univariable analysis, higher ECOG performance status, hydronephrosis at RC (both $P = .010$), positive STSMs ($P = 0.014$), lymph node positive disease ($P = .030$), advanced histopathologic tumor stage ($P = .032$), and elevated GGT concen-

Figure 1 . Cancer-specific survival in patients with normal (blue line) versus elevated (red line) preoperative serum GGT concentration treated with radical cystectomy for cM0 bladder cancer ($P = .042$).



Number of patients at risk of cancer-specific death at given time intervals						
Variable/Time	0	12	24	36	48	60
Elevated GGT levels	75	42	33	28	19	12
Normal GGT levels	238	179	140	103	75	53

tration ($P = .043$) were independent prognosticators of all-cause mortality after RC (Table 2).

Discussion

In the present study, preoperatively elevated serum GGT levels were associated with advanced histopathologic features of BC disease and inferior survival after RC. These findings are consistent with a recent study on this topic.[17] Specifically, we found that elevated serum GGT levels were significantly associated with higher ECOG PS, advanced histopathological tumor and nodal stage, STSMs, lymphovascular invasion, increasing tumor size, preoperative hydronephrosis, MIBC at primary diagnosis, and preoperatively increased serum CRP levels. All of these risk factors have been frequently associated with inferior survival after RC.[5,22-24] In addition, they underscore the reproducibility and validity of our results compared with the study by Su et al.[17] In our series, serum GGT was found to be an independent prognostic marker for OS. We refrained from performing multivariable analysis for RFS and CSS (for statistical reasons) as elevated GGT was not found to be significantly associated with RFS and CSS in univariable Cox-regression analysis. Furthermore, serum GGT showed a strong correlation with both primary tumor characteristics and patient-dependent parameters (such as ECOG). This may suggest that serum GGT may also be reflective of tumor-independent parameters and may therefore be relevant for treatment decision making. In addition, we also investigated a possible association between elevated serum GGT and serum GPT/GOT levels and confirmed a significant association, with GOT levels being associated with OS in Kaplan-Meier analysis.

There is evidence in the literature that serum GGT is also of predictive and prognostic significance in other solid urologic tumor types. In patients treated with enzalutamide for mCRPC disease, an

Table 2 Uni- and Multivariable Cox-Regression Analysis for Risk Factors of Survival After Radical Cystectomy in Patients With Bladder Cancer

Parameter	Univariable						Multivariable	
	RFS		CSS		OS		OS	
	HR (95%-CI)	*P*	HR (95%-CI)	*P*	HR (95%-CI)	*P*	HR	*P*
Elevated versus normal GGT concentration ([IU/ml]	1.34 (0.85-2.04)	.19	0.99-3.02	.054	1.93 (1.31-2.80)	**.001**	5.66 (1.05-30.42)	**.043**
≥ pT3a versus ≤ pT2b	3.36 (2.27-5.06)	**< .001**	4.51 (2.58-8.27)	**< .001**	2.98 (2.06-4.37)	**< .001**	1.32 (0.76-2.29)	.32
pN+ versus pN0	3.67 (2.50-5.38)	**< .001**	6.77 (3.99-11.73	**< .001**	3.32 (2.29-4.80)	**< .001**	2.14 (1.22-3.77)	**.030**
Pos. versus neg. STSMs	3.35 (2.03-5.29)	**< .001**	5.28 (2.93-9.16)	**< .001**	3.98 (2.55-6.04)	**< .001**	2.46 (1.32-4.46)	**.014**
Hydronephrosis at RC Present versus absent	1.77 (1.13-2.68)	**.013**	2.24 (1.26-3.84)	**.007**	2.01 (1.35-2.95)	**< .001**	1.88 (1.14-3.00)	**.010**
LVI versus LV0	2.88 (1.97-4.21)	**< .001**	5.23 (3.05-9.34)	**< .001**	2.41 (1.68-3.47)	**< .001**	1.24 (0.71-2.16)	.45
Tumor grade G3 versus G1/G2	1.92 (1.24-3.09)	**.003**	3.54 (1.78-8.08)	**< .001**	2.02 (1.32-3.20)	**< .001**	1.37 (0.80-2.43)	.74
Nonpure versus pure versus UC	2.19 (1.40-3.33)	**< .001**	2.76 (1.56-4.71)	**< .001**	1.84 (1.19-2.77)	**.006**	0.98 (0.53-1.70)	.93
Tumor size (cont., per [cm]	1.31 (1.17-1.45)	**< .001**	1.32 (1.14-1.52)	**< .001**	1.27 (1.15-1.41)	**< .001**	2.23 (0.62-8.00)	.21
ECOG ≥1 versus 0	0.84 (0.46-1.43)	.53	1.63 (0.82-2.97)	.15	2.22 (1.47-3.27)	**< .001**	2.07 (1.17-3.58)	**.010**
Age at RC (cont. per unit [a])	1.00 (0.98-1.02)	.91	1.01 (0.98-1.04)	.50	1.03 (1.01-1.05)	**.002**	1.02 (0.99-1.04)	.23
Postoperative systemic chemotherapy Received versus not received	7.44 (5.06-11.00)	**< .001**	4.18 (2.50-7.03)	**< .001**	1.73 (1.15-2.53)	**.009**	1.24 (0.74-2.04)	.41
Alcohol intake Yes versus No.	1.20 (0.81-1.79)	.58	0.95 (0.56-1.64)	.44	0.93 (0.65-1.35)	.66	1.16 (0.74-1.86)	.44
MIBC at PD	1.38 (0.92-2.09)	.11	2.23 (1.25-4.20)	**.006**	1.68 (1.14-2.52)	**.008**	1.06 (0.67-1.67)	.81

Bold values indicate a statistically significant difference.
Abbreviations: a = year; CI = confidence interval; CRP = C-reactive protein; CSS = cancer-specific survival; ECOG = Eastern Cooperative Oncology Group performance status; GGT = gamma-glutamyltransferase; HR = hazard ratio; LV0 = lymphovascular invasion absent; LVI = lymphovascular invasion present; MIBC = muscle-invasive bladder cancer; OS = overall survival; PD = primary diagnosis; RFS = recurrence-free survival; STSMs = soft tissue surgical margins; UC = urothelial carcinoma.

increase in serum GGT levels was found to be independently associated with shorter OS.[13] Elevated GGT also correlated with poorer PSA response, higher PSA dynamics and shorter progression-free survival.[13] Similarly, in patients with advanced renal cell carcinoma and tumor thrombus, preoperative serum GGT was found to be associated with poor CSS and decreased RFS.[14]

Therefore, the question arises whether there is a causal relationship on a molecular basis between an elevated serum GGT concentration and unfavorable oncologic outcome. GGT is a membrane-bound enzyme and plays an important role in maintaining the production of intracellular glutathione.[9-12] This represents an important antioxidant that protects cells from reactive oxygen compounds and free radicals. GGT also plays an important role in supplying cells with amino acids and promoting cell proliferation. There is increasing evidence that GGT deregulates tumor cells which leads to tumor progression and higher tumor aggressiveness.[25] It has been suggested that an increase in GGT concentration contributes to the formation of a tumor microenvironment that protects cancer cells from oxidative stress or cytotoxic drugs.[26] Nevertheless, GGT can also promote oxidative effects in certain situations. Persistent oxidative stress leads to genomic instability and imbalance between cell proliferation and apoptosis, which is essential for cancer development and progression.[11] Therefore, elevated GGT might be indicative of a higher tumor aggressiveness by representing the degree of oxidative stress in tumor tissues. In addition, it has been reported that GGT can be induced by inflammatory molecules, such as tumor necrosis factor and interferon.[27,28] Therefore, it can be hypothesized that GGT is associated with tumor-associated inflammatory responses and may also serve as an inflammatory biomarker. Altogether, it is possible that preoperatively elevated serum GGT might be indicative for the presence of micrometastatic disease and should be evaluated in further studies. However, the exact mechanisms by which elevated GGT levels may promote tumor development and progression are not yet understood.

This study has several limitations due to its retrospective nature. It is a study conducted at a single institution where patients were treated within a relatively long period, so potential selection bias cannot be excluded. In general, a median follow-up period of 36 months can be considered sufficient to adequately capture the vast majority of local and distant metastatic recurrences after RC. However, for the few patients with very late recurrences after RC, this follow-up period might be insufficient.[22] We relied on a sex-specific definition of normal GGT levels based on our laboratory standards, so no optimized cut-off value for serum GGT based on ROC analysis was used in this study. It should be noted here that in the study by Su et al, a cutoff value of 40U/L based on ROC-analysis was calculated, which is very close to the standard cut-off values used in our study.[17] Nevertheless, an optimal cut-off value for serum GGT remains to be established in terms of improved prognostication. Considering the correlation of elevated serum GGT levels with parameters of predictive significance, ie, preoperative hydronephro-

sis, clinical tumor stage, we think that preoperative serum GGT levels may have predictive potential, although we must admit that this potential is uncertain at present given the lack of data in the literature. In addition, among the group of patients with NMIBC at PD, we did not find elevated GGT levels to be associated with disease progression to MIBC at RC. This suggests that serum GGT levels may rather be a useful prognostic tool for patients with primary MIBC. In addition, among patients with solitary urothelial recurrence, we did not find significant associations between serum GGT levels and survival which may also be related to the low number of patients. A major advantage is that serum GGT is easily determinable in daily clinical routine and could be used as a new prognostic marker for invasive BC. To the best of our knowledge, this is only the second publication in the literature that systematically addresses the predictive and prognostic potential of serum GGT levels in patients undergoing RC for BC.[17] Therefore, prospective external validation by well-designed independent cohorts from multiple institutions with sufficient follow-up time is needed to confirm these results.

Clinical Practice Points

- There is a lack of data concerning the predictive and prognostic role of serum gamma-glutamyltransferase (GGT) in patients with invasive bladder cancer.
- We found that preoperatively elevated serum GGT was associated with adverse clinical and histopathologic parameters at radical cystectomy.
- In addition, elevated serum GGT concentration was independently associated with decreased overall survival.
- These data suggest that GGT levels may be a useful tool for improved prognostication in invasive BC.

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Disclosure

All authors have nothing to disclose in relation to the contents of the manuscript.

CRediT authorship contribution statement

Georgios Gakis: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Manuel Alexander Schmid:** Formal analysis, Software. **Fahmy Hassan:** Conceptualization, Project administration, Resources. **Arnulf Stenzl:** Conceptualization, Visualization. **Markus Renninger:** Conceptualization, Resources, Supervision.

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