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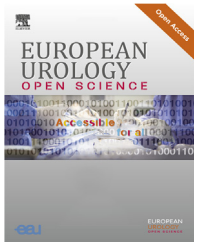

European Association of Urology

Brief Correspondence

The Value of Tumour Markers in the Detection of Relapse—Lessons Learned from the Swiss Austrian German Testicular Cancer Cohort Study

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Abstract

The tumour markers alpha-fetoprotein (AFP), beta human chorionic gonadotropin (βHCG), and lactate dehydrogenase (LDH) have established roles in the management and follow-up of testicular cancer. While a tumour marker rise can serve as an indicator of relapse, the frequency of false-positive marker events has not been studied systematically in larger cohorts. We assessed the validity of serum tumour markers for the detection of relapse in the Swiss Austrian German Testicular Cancer Cohort Study (SAG TCCS). This registry was set up to answer questions on the diagnostic performance and impact of imaging and laboratory tests in the management of testicular cancer, and has included 948 patients between January 2014 and July 2021.A total of 793 patients with a median follow-up of 29.0 mo were included. In total, 71 patients (8.9%) had a proven relapse, which was marker positive in 31 patients (43.6%). Of all patients, 124 (15.6%) had an event of a false-positive marker elevation. The positive predictive value (PPV) of the markers was limited, highest for βHCG (33.8%) and lowest for LDH (9.4%). PPV tended to increase with higher levels of elevation. These findings underline the limited accuracy of the conventional tumour markers to indicate or rule out a relapse. Especially, LDH as part of routine follow-up should be questioned.

Patient summary: With the diagnosis of testicular cancer, the three tumour markers alpha-fetoprotein, beta human chorionic gonadotropin, and lactate dehydrogenase are routinely measured during follow-up to monitor for relapse. We demonstrate that these markers are often falsely elevated, and, by contrast, many patients do not have marker elevations despite a relapse. The results of this study can lead to improved use of these tumour markers during follow-up of testis cancer patients.

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Follow-up of patients with testicular cancer usually consists of regular imaging, clinical examination, and analysis of serum tumour markers. Three serum tumour markers have established roles in the management of men with testicular cancer: alpha-fetoprotein (AFP), beta human chorionic gonadotropin (βHCG), and lactate dehydrogenase (LDH). A rise in serum tumour markers during follow-up can serve as an indicator for relapse. However, single elevations of markers must be interpreted with caution, paying particular attention to conditions that may cause false-positive elevations [1–5]. So far, the frequency of false-positive marker events has not been studied systematically in larger cohorts.

The Swiss Austrian German Testicular Cancer Cohort Study (SAG TCCS) was set up in 2014 to answer questions on performance and clinical impact of imaging and laboratory tests for early detection of relapse of testicular cancer.

SAG TCCS enrols patients with histologically proven stage I or metastatic seminomatous (seminoma) or non-seminomatous (nonseminoma) germ cell tumours who underwent active surveillance or completed treatment within the past 3 mo. Patients undergo predefined follow-up depending on disease stage, histology, and risk group (full protocol and follow-up schedules are provided in the Supplementary material) [6]. The registry collects clinical data on disease characteristics, laboratory values including serum tumour markers during follow-up, as well as imaging modalities.

We here present the first analysis of the registry on the value of serum tumour markers for the detection of relapses in testicular cancer.

Between January 2014 until data cut-off for the current analysis (July 2021), 948 patients were included into the registry. A total of 155 patients were excluded because of missing information or insufficient follow-up time; data of 793 patients with a median follow-up of 29.0 mo (IQR 13.1–50.1) were included in this analysis. All patients had newly diagnosed stage I or metastatic testicular cancer.

Baseline characteristics of patients are provided in Table 1. A majority of 63% had seminoma and 37% of patients had nonseminoma. Nonseminoma patients were significantly younger than patients with seminoma (median 30.8 vs 40.6 yr). Most patients presented with stage I disease (64% of nonseminoma and 82% of seminoma patients, respectively). While 75% of nonseminoma patients had any kind of tumour marker elevation at baseline (preoperatively), this number was significantly lower with only 41% in seminoma. In nonseminoma, 60% were found to have elevated AFP, 57% elevated βHCG, and 25% elevated LDH levels. For seminoma, the corresponding numbers were 2%, 24%, and 27%, respectively. Limited elevations of AFP levels were confirmed despite pure seminoma histology (median 1.4 × upper limit of normal [ULN]).

In total, 158 patients (19.9%) of the whole cohort experienced an event of tumour marker elevation at any time during follow-up. Elevated markers were seen as "false positive" if patients remained free from a proven relapse documented by imaging for a minimum of 6 mo after the incident. Considering this definition, 124 patients (15.6%) experienced a false-positive marker event at any time during follow-up: 31 for AFP, 13 for βHCG, and 82 for LDH (multiple elevations in the same individual could be found; therefore, the isolated values for AFP, βHCG, and LDH do not sum up to 124). Seventy-six patients had only a single event of false-positive marker elevation, and the remaining patients showed multiple events; 16 patients had six or more incidents of marker elevation without a proven

Table 1 – Baseline, marker, and relapse characteristics of patients included in the registry

	Nonseminoma	Seminoma
Total number, *n* (%)	292 (37)	501 (63)
Age at entry, median (IQR), $p < 0.001$	30.8 (25.5–37.4)	40.6 (33.0–50.7)
Stage at diagnosis [a], *n* (%)		
I	186 (64)	412 (82)
IIA	26 (9)	20 (4)
IIB	17 (6)	24 (5)
IIC	7 (2)	20 (4)
III	55 (19)	25 (5)
Primary extragonadal, *n* (%)	8 (3)	6 (1)
IGCCCG Prognosis Group, *n* (%)		
Good	73 (70)	80 (90)
Intermediate	18 (17)	9 (10)
Poor	14 (13)	0
Baseline tumour markers, *n* (%)		
No marker elevation [b]	63 (22)	284 (57)
Any elevation of markers, $p < 0.001$	218 (75)	203 (41)
AFP abnormal[1]	175 (60)	10 (2) [c]
AFP normal	106 (36)	474 (95)
AFP value per ULN (IQR), $p < 0.001$	8.4 (2.6–39.3)	1.4 (1.2–1.9)
βHCG abnormal[2]	166 (57)	121 (24)
βHCG normal	114 (39)	363 (72)
βHCG value per ULN (IQR), $p < 0.001$	17.3 (4.4–155.1)	4.3 (2.0–28.8)
LDH abnormal[3]	73 (25)	137 (27)
LDH normal	194 (66)	337 (67)
LDH value per ULN (IQR), $p = 0.520$	1.5 (1.2–2.5)	1.5 (1.2–2.4)
Proven relapses, *n* (%)	20 (7)	51 (10)
Time of relapse (years from semicastration), median (IQR)	0.4 (0.3–1.0)	1.0 (0.6–1.5)
Initial disease stage, *n* (%)		
I	18 (90)	46 (90)
IIA	0	0
IIB	0	2 (4)
IIC	0	0
III	2 (10)	3 (6)
Elevated markers at relapse [d], *n* (%)		
No elevation	5 (25)	35 (69)
Elevated AFP	5 (25)	2 (4)
AFP per ULN (IQR)	4.5 (2.0–10.4)	1.3 (1.0–1.5)
Elevated βHCG	10 (50)	11 (22)
βHCG per ULN (IQR)	2.2 (1.2–20.9)	3.6. (1.6–29.3)
Elevated LDH	3 (15)	5 (10)
LDH per ULN (IQR)	1.4 (1.2–1.4)	1.3 (1.1.–1.9)
False positive marker event (total 124 patients)	46	78
Status of patients at last follow-up		
Alive	292	500
Death	0	1 [e]

AFP = alpha-fetoprotein; βHCG = beta human chorionic gonadotropin; IGCCCG = International Germ-cell Cancer Collaborative Group; IQR = interquartile range; LDH = lactate dehydrogenase; ULN = upper limit of normal.

[a] Information missing for one patient in the nonseminoma group.

[b] Baseline marker information missing for 11 nonseminoma and 14 seminoma patients; missing information for AFP[1] = 28 patients, βHCG[2] = 19 patients, LDH[3] = 52 patients.

[c] Elevated AFP levels were confirmed despite pure seminoma histology (elevation was minimal and judged as clinically not meaningful).

[d] Missing marker measurement at relapse: AFP = one patient, βHCG = one patient, and LDH = two patients.

[e] Death from gastric lymphoma; patient did not experience relapse of his testicular cancer (initially stage I seminoma on active surveillance).

Table 2 – Calculated details on elevated markers[a]

	AFP	βHCG	LDH
All false positive events (no relapse within 6 mo)	151	53	125
Median elevation per ULN (IQR) [min; max] of false positives	1.3 (1.1–1.6) [1.0; 18.1]	2.0 (1.4–3.0) [1.0; 392]	1.2 (1.0–1.4) [1.0; 7.2]
95% percentile (elevation level per ULN)	1.76	6.52	1.92
All true positive events	18	27	13
Median elevation per ULN (IQR) [min; max] of true positives	1.1 (1.1–1.6) [1.0; 12.3]	2.5 (1.3–19.3) [1.0; 30.4]	1.3 (1.1–1.4) [1.0; 2.1]
95% percentile (elevation level per ULN)	12.27	65.5	2.11
Calculated positive predictive value (%, 95% CI)	10.7 (6.8–16.2)	33.8 (24.3–44.6)	9.4 (5.6–15.5)

AFP = alpha-fetoprotein; CI = confidence interval; βHCG = beta human chorionic gonadotropin; IQR = interquartile range; LDH = lactate dehydrogenase; ULN = upper limit of normal.
AFP values were missing for four events (three for false positive events and one with true positive event).
[a] All events of elevated values were considered (multiple events per patient can occur).

relapse. The majority of these patients showed a pattern of stable and moderate elevation of AFP or βHCG levels over the time of follow-up (Supplementary material). Out of 13 patients with false-positive βHCG events, nine had available follow-up data including measurements of gonadotropins and testosterone to assess factors known to interfere with βHCG levels. Eight of these patients showed any combination of abnormal gonadotropin or testosterone levels or substance abuse (Supplementary material).

Of the 124 patients with a false-positive event, 27 (22%) had additional imaging performed, mostly magnetic resonance imaging scans of the abdomen (78% of the cases). In all other patients, physicians did not consider the marker event suspicious or relevant, and therefore refrained from further investigations.

In total, 71 (8.9%) patients (20 nonseminoma and 51 seminoma) of our cohort suffered from a proven relapse of testicular cancer (clinical details on relapses are provided in the Supplementary material). Diagnosis of relapse was generally based on unequivocal signs on imaging; additional biopsies were left at the discretion of the treating physician. Of these relapsing patients, 40 (56%) had no elevated marker at the time of relapse and 31 patients (44%) had a marker-positive relapse (Table 1); 69% of seminoma and 25% of nonseminoma relapses were marker negative.

Only in 13 out of the 71 relapsing patients (18%), tumour markers were seen as the single, first, most relevant indicator of relapse when treating physicians were asked to choose between patient history, clinical examination, imaging, and tumour markers providing the first indication of a relapse.

Calculating all false- and true-positive marker elevation events, we found a positive predictive value (PPV) of 10.7% for AFP, 33.8% for βHCG, and 9.4% for LDH (Table 2). Even though there were some isolated high false positives, true positives of AFP and βHCG showed a trend towards a higher elevation. However, we did not observe this for LDH. Higher elevations (>2–3 × ULN) also tended towards a higher PPV (Supplementary material).

With our SAG TCCS data, we provide the first systematic analysis on the value of the routinely used serum tumour markers in a larger cohort of testicular cancer patients during their follow-up. We found a very high rate of false-positive events. On the contrary, more than half of the proven relapses were marker negative, and tumour markers only served as the first most relevant indicator of relapse in a minority of cases. Beta HCG had the highest PPV, and higher marker elevations of AFP and βHCG were more likely to be true positives. LDH elevations had a very low PPV. Slight elevations of AFP were often unspecific and occurred even among seminoma patients.

As a conclusion of this analysis, we recommend serial tumour marker determinations in follow-up of testicular cancer before consideration of a relapse diagnosis. While LDH elevation is prognostic at diagnosis, its value in follow-up seems questionable. Centralised care in experienced centres is important, and clinicians should be aware that single elevations of AFP and βHCG can be unspecific false positives and should prompt repeated measurements/-confirmation of dynamics first rather than proceeding immediately to additional examinations and imaging. Treatment should only be initiated upon unequivocal signs of relapse on imaging and ideally histologic verification if possible.

The results of our study underline the limited accuracy of single tumour marker determinations, and stress the importance of systematic and prospective evaluation of new biomarkers for relapse detection such as microRNA [7–10].

***Author contributions*:** Stefanie Fischer had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Gillessen, Cathomas, Rothermundt, Fischer.
Acquisition of data: All authors.
Analysis and interpretation of data: Gillessen, Cathomas, Rothermundt, Fischer, Stalder.
Drafting of the manuscript: Rothermundt, Fischer.
Critical revision of the manuscript for important intellectual content: All authors.
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Appendix A. Supplementary data

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