



Pre-orchietomy tumor marker levels should not be used for International Germ Cell Consensus Classification (IGCCCG) risk group assignment

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Abstract

Purpose To investigate whether the use of pre-orchietomy instead of pre-chemotherapy tumor marker (TM) levels has an impact on the International Germ Cell Consensus Classification (IGCCCG) risk group assignment in patients with metastatic germ cell tumors (GCT).

Methods Demographic and clinical information of all patients treated for primary metastatic testicular non-seminomatous GCT in our tertiary care academic center were extracted from medical charts. IGCCCG risk group assignment was correctly performed with pre-chemotherapy marker levels and additionally with pre-orchietomy marker levels. Agreement between pre-chemotherapy and pre-orchietomy risk group assignments was assessed using Cohen's kappa.

Results Our cohort consisted of 83 patients. The use of pre-orchietomy TMs resulted in an IGCCCG risk group upstaging in 12 patients (16%, 8 patients from good to intermediate risk and 4 patients from intermediate to poor risk) and a downstaging in 1 patient (1.2%, from intermediate- to good-risk). The agreement between pre-orchietomy and pre-chemotherapy IGCCCG risk groups resulted in a Cohen's kappa of 0.888 ($p < 0.001$).

Conclusions Using pre-orchietomy TMs can result in incorrect IGCCCG risk group assignment, which in turn can impact on the clinical management and follow-up of patients with metastatic GCT. Thus, adherence to the IGCCCG standard using pre-chemotherapy TMs levels is recommended.

Keywords Testicular germ cell tumor · Biomarkers, tumor · Prognosis

Introduction

One-third of all patients presenting with testicular germ cell tumors (GCT) have metastases at initial diagnosis (Beyer et al. 2013; DeSantis et al. 2014). An additional 15–30% of patients with initially localised disease will develop metastatic disease during follow-up (Chung et al. 2015; Daugaard et al. 2014). In 1997, the International Germ Cell Cancer

Cooperative Group (IGCCCG) published a prognostic classification system, which is based on the histological subtype (seminoma vs. non-seminoma), the location of the primary tumor, the extent of metastatic spread as well as the level of the pre-chemotherapy tumor markers (TM) alpha-fetoprotein (AFP), human chorionic gonadotropin (bHCG) and lactate dehydrogenase (LDH) (International-Germ-Cell-Cancer-Collaborative-Group 1997). In clinical practice, the IGCCCG risk group assignment is sometimes incorrectly performed by using pre-orchietomy instead of pre-chemotherapy TM levels. This mistake may impact on the treatment and follow-up intensity and thus, on the oncological outcome.

The aim of our investigation was to assess whether the use of pre-orchietomy instead of pre-chemotherapy TM levels has an impact on the IGCCCG risk group assignment and thus intensity of treatment in patients with metastatic testicular GCT.

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Table 1 Baseline characteristics

	N = 83
Age (years) (\pm SD)	30 (\pm 9)
IGCCCG risk groups	
Good risk, <i>n</i> (%)	50/83 (60%)
Intermediate risk, <i>n</i> (%)	19/83 (23%)
Poor risk, <i>n</i> (%)	14/83 (17%)
Site of metastases	
Retroperitoneal lymph nodes	74/83 (89%)
Lung	47/83 (57%)
Mediastinal	20/83 (24%)
Neck	8/83 (10%)
Liver	5/83 (6%)
Bone	4/83 (5%)
Brain	2/83 (2%)
Other	4/83 (5%)
Pre-chemotherapy tumor markers levels	
AFP (μ g/l)[IQR]	53.7 [3.8–627.0]
bHCG (U/l) [IQR]	51.0 [0.0–2862.0]
LDH (U/l) [IQR]	387 [450–720]

AFP Alpha-fetoprotein, bHCG beta-human chorionic gonadotropin, LDH lactate dehydrogenase, SD standard deviation

Patients and methods

We identified patients who underwent first-line chemotherapy for primary metastatic non-seminomatous GCT of the testis in our institution between 1991 and 2015. Patients with extragonadal GCTs, bilateral testicular GCTs or missing follow-up information were excluded from our analysis. Pre-chemotherapy baseline characteristics (age, histology of the primary tumor, site and extent of metastases) and pre-orchietomy and pre-chemotherapy TM levels were retrieved from electronic medical records as both assessments are clinical routine at our center.

IGCCCG risk group assignment was correctly performed with pre-chemotherapy TM levels and compared to the incorrect one based on pre-orchietomy TM levels. Agreement between pre-chemotherapy and pre-orchietomy IGCCCG risk group assignments was assessed using Cohen's kappa. A kappa of 0.61–0.8 was interpreted as substantial and 0.81–1.00 as an excellent agreement (Landis and Koch 1977).

Statistical analyses were performed using SPSS Statistics version 21.0 (IBM Corp., Armonk, New York, USA). The results for continuous normally distributed variables are expressed as mean \pm standard deviation (SD). Continuous non-normally distributed variables are presented as median and interquartile ranges (IQR) and categorical variables are presented as number and percent. All *p*

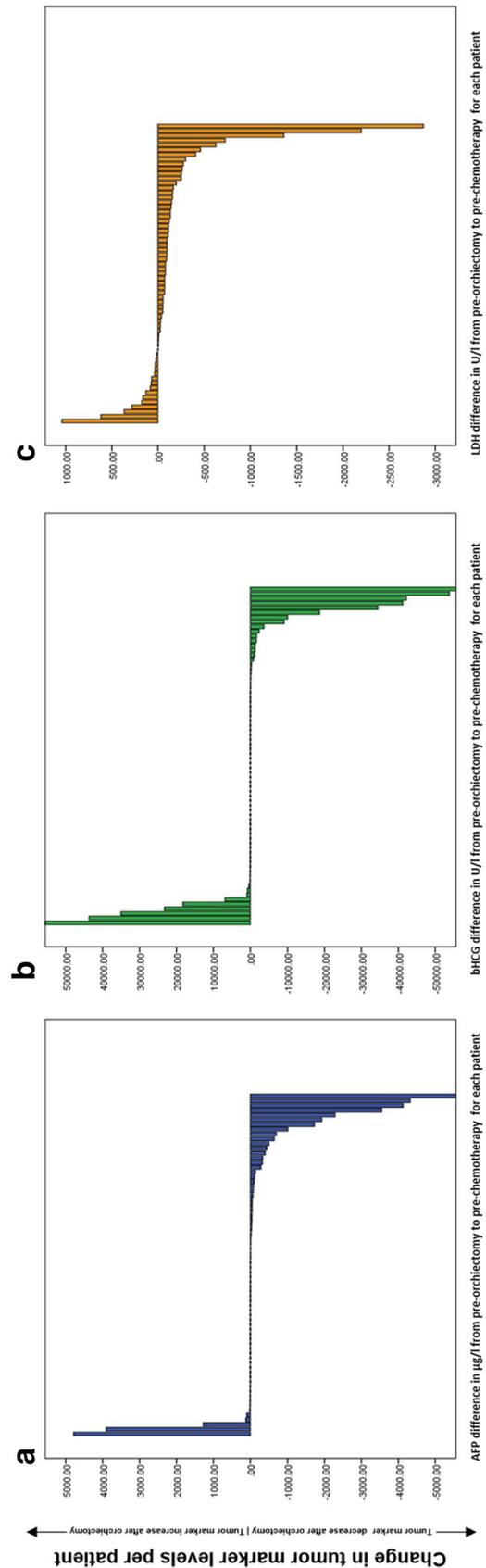


Fig. 1 Waterfall plots of tumor marker changes after orchietomy for AFP (a), HCG (b) and LDH (c)

Table 2 Tumor marker change scores and reasons of patients with upstaging or downstaging of IGCCCG assignments

Correct IGC-CCG	Incorrect pre-orchectomy IGCCCG	Change in IGCCCG assignment	Reasons for stage change	AFP		bHCG		LDH			
				Pre orchectomy (µg/l)	Change (µg/l)	Pre orchectomy (U/l)	Change (U/l)	Pre orchectomy (U/l)	Change (U/l)		
Good	Intermediate	Upstaging	AFP, HCG	1009.4	1006.3	1249.9	0	524	1249.9	518	6
Good	Intermediate	Upstaging	AFP	2294.9	1727.4	9.5	7.2	411	2.3	386	25
Good	Intermediate	Upstaging	AFP	4905	4130.4	13.5	0	700	13.5	445	255
Good	Intermediate	Upstaging	HCG	1.8	0.1	12,528	3456	442	9072	329	113
Good	Intermediate	Upstaging	HCG	499	438.6	37,401	2927	432	34,474	377	55
Intermediate	Poor	Upstaging	AFP	31,800	29,040	6995	3367	553	3628	438	115
Intermediate	Poor	Upstaging	HCG	5	2	65,523	24,313	364	41,210	291	73
Intermediate	Poor	Upstaging	HCG	1.9	-0.8	71,885	29,696	610	42,189	336	274
Intermediate	Poor	Upstaging	HCG	7	2.5	81,326	9917.5	314	71408.5	179	135
Good	Intermediate	Upstaging	LDH	9.3	4.31	13.7	NA	3258	NA	387	2871
Good	Intermediate	Upstaging	LDH	53.7	22.9	24	7.8	1094	16.2	466	628
Good	Intermediate	Upstaging	LDH	4.8	1	4	0	795	4	685	110
Intermediate	Good	Downstaging	AFP	529	-1275	94	207	172	-113	303	-131

AFP alpha-fetoprotein, bHCG beta-human chorionic gonadotropin, LDH lactate dehydrogenase (upper level of normal is 480 U/l)

Table 3 International Germ Cell Cancer Collaborative Group (IGCCG) risk group assignment using either preorchietomy (columns) or prechemotherapy (rows) tumor marker levels

		Preorchietomy			
		Good risk	Intermediate risk	Poor risk	
Prechemotherapy	Good risk	42	8	0	50
	Intermediate risk	1	14	4	19
	Poor risk	0	0	14	14
		43	22	18	83

Color legend

No change
Upstaging
Downstaging

Highlighted cells in green indicate no change, in red overstaging and in magenta understaging in IGCCCG assignments

values < 0.05 were considered statistically significant. All statistical tests were two-sided. The local ethics committee approved the study protocol (STV KEK-ZH 25-2008).

Results

A total of 83 patients with primary metastatic testicular non-seminomatous GCTs were identified. Their baseline characteristics are summarized in Table 1. TM levels changed after orchietomy as follows: AFP by a median of 5 $\mu\text{g/l}$ (IQR 0–108 $\mu\text{g/l}$), HCG by a median change of 0 U/l (IQR – 5 to 235 U/l), and LDH by a median of 82 U/l (IQR 0–158 U/l). After orchietomy AFP changed over 1000 $\mu\text{g/l}$ in 11 patients, but only 5 patients had to be reclassified (Fig. 1; Table 2). Similarly 14 patients had HCG changes over 5000 U/l after orchietomy, but IGCCCG reclassification, but only 6 patients needed to be reclassified. Significant changes of LDH levels > 720 U/l were observed in 6 patients, but resulted in reclassification of only 3 patients (Fig. 1).

Fifty men (60%) were assigned to the IGCCCG good-risk group, 19 (23%) to the intermediate-risk group, and 14 (17%) to the poor-risk group, if correctly classified according to pre-chemotherapy TM (Table 3). When pre-orchietomy instead pre-chemotherapy TM levels were used for IGCCCG risk group assignment, 43 patients (52%) were assigned to the good-risk group, 22 (27%) to the intermediate-risk group and 18 (21%) to the poor-risk group. Pre-orchietomy TMs resulted in an IGCCCG risk group change in 13 patients (16%). Eight (10%) patients

changed from good- to intermediate-risk and four (5%) patients from intermediate to poor risk. One patient (1%) showed quickly rising AFP levels after orchietomy. Using pre-orchietomy TM levels would have led to an assignment to the good- instead of intermediate-risk group. The overall agreement between pre-chemotherapy and pre-orchietomy IGCCCG risk groups assignment was excellent with a Cohen's kappa of 0.888 ($p < 0.001$).

Discussion

Our analysis revealed that the incorrect use of pre-orchietomy TM levels for prognostic classification frequently results in an upstaging and less frequently in a downstaging of the IGCCCG risk group assignment and thus can lead to incorrect treatments and unnecessary follow-up investigations.

Given that cancer cells in the affected testis represent a relevant source of TM production, the burden of metastatic disease is better represented by the pre-chemotherapy TMs after removal of the primary tumor. In our cohort pre-orchietomy TM levels led to an upstaging from good- to intermediate-risk in 10% and from intermediate- to poor-risk in 5% of all patients. Given the fact that the IGCCCG classification is also used to determine the intensity of subsequent chemotherapy (i.e. 3 cycles for good risk and 4 cycles for intermediate and poor risk) incorrect classification may lead to overtreatment, which would result in unnecessary toxicity (Chovanec et al. 2017; Kerns et al. 2018) without an oncological benefit. Furthermore, incorrect upstaging may also trigger more intense follow-up investigations (e.g. more office visits, TM analyses and potentially harmful CT scans). On the other hand, one patient with rapidly rising AFP levels post-orchietomy would have been incorrectly understaged by pre-orchietomy TM levels. Although our results indicate that only a minority of patients might be affected, incorrect IGCCCG risk group assignment may also have devastating consequences from undertreatment in individual patients.

In conclusion, IGCCCG risk group assignment should be performed carefully to avoid misclassification that can result in over- and undertreatment. Based on our results we suggest to exclusively assign IGCCCG risk groups based on pre-chemotherapy TM levels.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki

Declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was waived by the local ethic committee (STV KEK-ZH 25-2008).

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