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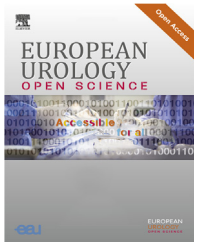

European Association of Urology

Brief Correspondence

Prechemotherapy Not Preorchiectomy Serum Tumor Markers Accurately Identify International Germ Cell Cancer Collaborative Group Prognostic Groups in Nonseminoma

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Abstract

Levels of the serum tumor markers (STMs) α-fetoprotein, human chorionic gonadotropin, and lactate dehydrogenase are used in staging classification for metastatic germ-cell cancers and support decisions on the intensity of first-line treatment for patients with nonseminoma. Use of preorchiectomy instead of prechemotherapy STM levels can lead to inadequate classification. We identified 744 men with metastatic gonadal nonseminoma in the International Germ-Cell Cancer Collaborative Group (IGCCCG) Update Consortium database who had preorchiectomy and prechemotherapy STM levels available. Of these, 22% would have had inadequate IGCCCG prognostic group classification if preorchiectomy levels had been used, which would have resulted in overtreatment of 16% and undertreatment of 6% of men. These findings suggest that use of preorchiectomy instead of prechemotherapy STM results may lead to incorrect IGCCCG classification, which could compromise treatment success or expose patients to unnecessary toxicity.

Patient summary: For men with testicular cancer, levels of tumor markers in their blood are used when making decisions on chemotherapy intensity. Use of test results for samples taken before removal of the cancer-bearing testicle instead of immediately before chemotherapy can lead to inadequate treatment recommendations.

Approximately half of patients with testicular germ-cell cancer (GCC) have metastatic disease at initial diagnosis or during follow-up. In 1997, the International Germ-Cell Cancer Collaborative Group (IGCCCG) published a prognostic classification system based on histology, primary tumor location, extent of metastatic spread, and levels of the serum tumor markers (STMs) α-fetoprotein (AFP), human chorionic gonadotropin (HCG), and lactate dehydrogenase (LDH) [1]. In 2021, the IGCCCG Update Consortium validated the original IGCCCG criteria and identified older age,

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the presence of lung metastases in nonseminoma, and LDH more than 2.5 times the upper limit of normal in seminoma as additional unfavorable prognostic variables [2,3].

The IGCCCG classification is important not only for informing patients and physicians about prognosis but also for deciding on the type and number of chemotherapy cycles. Men in the IGCCCG good prognostic group are treated with three cycles of bleomycin, etoposide, and cisplatin (BEP) or four cycles of etoposide and cisplatin (EP). Patients in the more adverse IGCCCG intermediate or poor prognostic groups require at least four cycles of BEP or have bleomycin replaced by ifosfamide. Allocation of the correct IGCCCG prognostic group is therefore critical to avoid both overtreatment and undertreatment. Any overtreatment would lead to unnecessary side effects. Undertreatment may impair a patient's oncological outcome.

There is wide consensus that use of preorchiectomy instead of prechemotherapy STM levels can lead to such incorrect assignment of a patient's IGCCCG prognostic group. However, there are few data so far to support this consensus and to quantify the potential risk of misclassification. The aim of this retrospective analysis using data from the IGCCCG Update Consortium was to quantify the proportion of IGCCCG group reclassifications that would have occurred if preorchiectomy STM results had been used instead of prechemotherapy STMs as recommended by international guidelines [2,3].

We selected patients with metastatic GCC with testicular primary tumors from the IGCCCG Update database. Patients in the IGCCCG database underwent first-line chemotherapy with at least three cycles of cisplatin-based chemotherapy. Only patients with nonseminomatous or mixed testicular GCC without nonpulmonary visceral metastases (NPVM) for whom preorchiectomy and postorchiectomy STM data were available were included in the analysis. Seminomas with elevated AFP were classified as nonseminoma. Pure seminomas without AFP elevation were excluded. Patients who received chemotherapy >90 d after orchiectomy were considered as having metachronous disease after surveillance and were also excluded. Progression-free survival (PFS) was defined as time from the start of chemotherapy to disease progression, death, or last follow-up. Overall survival (OS) was defined as time from the start of chemotherapy to death or last follow-up. Patients lost to follow-up were censored at the date of last contact.

Of the total population of 9575 men, only 744 met the eligibility criteria for our study. The primary reason for exclusion was lack of information necessary for calculating the preorchiectomy IGCCCG prognostic group from 21 of 30 participating institutions (Supplementary material). Median follow-up from the start of chemotherapy to either death or loss to follow-up (n = 9575; 1351 events) was estimated using the reverse Kaplan-Meier method as 5.35 yr (interquartile range [IQR] 2.58–9.55). There were notable differences between the included and excluded groups (Supplementary material). Patients who were included had lower median AFP (30.1 vs 43.4 ng/ml) and HCG (48.0 vs 68.0 U/l) levels before orchiectomy. In addition, the eligible patients had better PFS and OS in comparison to the patients who were excluded (Supplementary material). However, as this was an unplanned retrospective analysis and as patients with NPVM and primary mediastinal nonseminoma had to be excluded from the analysis, these results were expected. Furthermore, it is important to highlight that only a small percentage of the eligible group (2.2%) consisted of patients from trials, whereas a significant proportion of the ineligible group (25.4%) were participants in clinical trials.

We finally included 744 men with a median age of 29 yr (IQR 24–35) fulfilling the inclusion criteria, of whom 449 (60%) had good, 237 (32%) had intermediate, and 58 (8%) had poor IGCCCG prognosis. The median time from orchiectomy to chemotherapy was 26 d (IQR 16–40). At 3 yr, the PFS and OS rates for the overall cohort were 87% and 93%, respectively. If preorchiectomy instead of prechemotherapy STM results had been used, assignment of the IGCCCG prognostic group would have been incorrect for 169/744 patients (22%; Table 1), while no change in IGCCCG group would have been observed for 575/744 patients (78%). Higher IGCCCG classification leading to overtreatment would have occurred for 122/44 patients (16%). Lower IGCCCG classification leading to undertreatment would have occurred for 47/744 patients (6%). The P-B κ value was 0.6593 (95% confidence interval [CI] 0.6141–0.7044).

As expected, among the cohort of 575 men without a change in IGCCCG prognosis group, a better PFS rate at 3 yr was observed for the good prognosis group (93.8%, 95% CI 90.6–95.9%) than for the IGCCCG intermediate/poor prognosis group (82.3%, 95% CI 77.1–86.4%). Owing to the

Table 1 – Reclassification of the IGCCCG prognosis group if preorchiectomy results (column 1) were used instead of prechemotherapy results (columns 2–4)[a]

Preorchiectomy	Prechemotherapy, *n* (%)			
	Good	Intermediate	Poor	Total
Good	342 (46)	31 (4)	1 (0.1)	374 (50)
Intermediate	97 (13)	191 (26)	15 (2)	303 (41)
Poor	10 (1)	15 (2)	42 (5.6)	67 (9)
Total	449 (60)	237 (32)	58 (8)	744 (100)

IGCCCG = International Germ Cell Cancer Collaborative Group.

[a] No reclassification would be observed for 575 men (green). Higher IGCCCG classification leading to overtreatment would be observed for 122 men (16%; red). Lower IGCCCG classification leading to undertreatment would be observed for 47 men (6%; yellow).

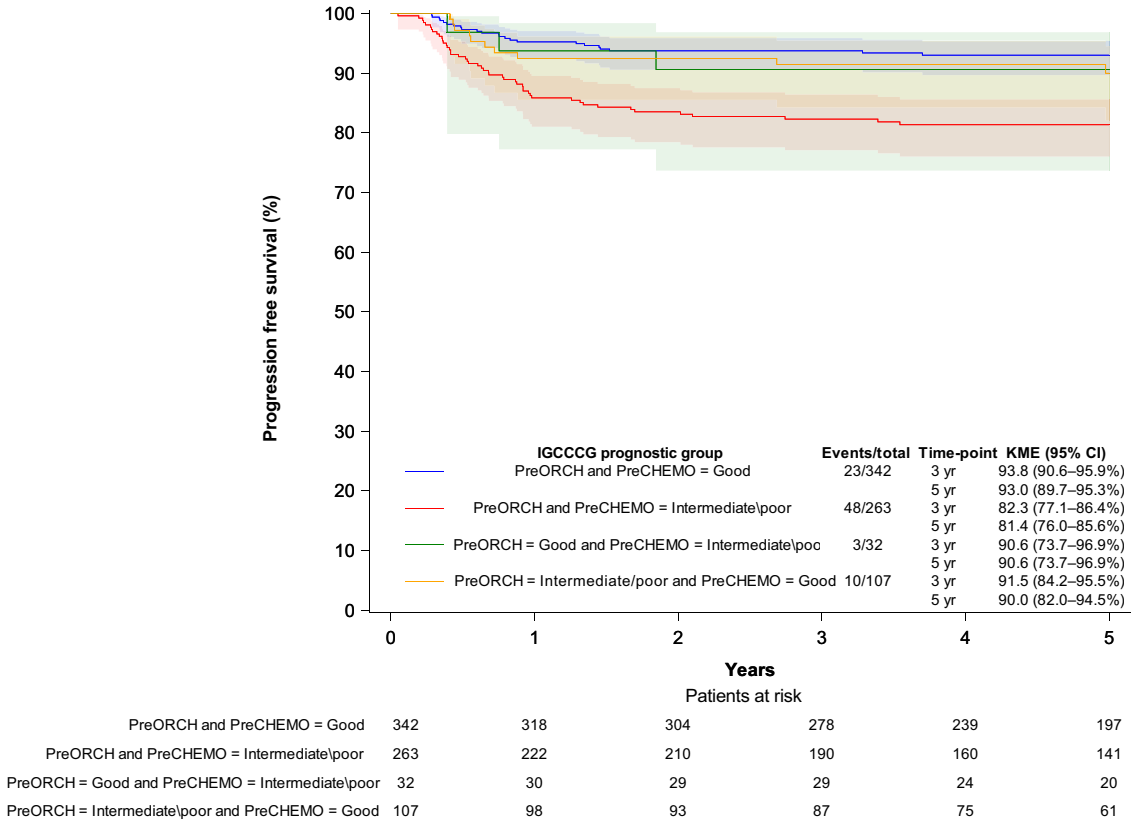

Fig. 1 – Kaplan-Meier curves for progression-free survival stratified by International Germ Cell Cancer Collaborative Group (IGCCCG) classification according to preorchiectomy (PreORCH) or prechemotherapy (PreCHEM) marker levels. KME = Kaplan-Meier estimate; CI = confidence interval.

limited number of events in the small subgroups, we were not able to conduct any robust PFS analyses for the 169 men with IGCCCG group incorrectly assigned using preorchiectomy STM levels (Fig. 1).

Increases in STM levels after orchiectomy indicate that progressing metastases continue to excrete STMs into the circulation and are producing more STMs than the primary tumor that was removed. Thus, patients might move from the good to the intermediate or from the intermediate to the poor prognosis IGCCCG category after orchiectomy and should be treated accordingly. By contrast, decreases in STM levels after orchiectomy indicate that a considerable amount of STMs originated from the primary testicular tumor. Interestingly, approximately 10% of our cohort showed a STM decline according to STM half-life times (AFP ~6 d, HCG ~3 d, LDH ~1 d), which suggests that the primary testicular tumor and not metastases was the main contributor to STM expression. For men classified in the IGCCCG intermediate/poor prognosis groups who did not have any NPVM before orchiectomy and experienced a decrease in STMs after surgery, repeated measurements before initiating chemotherapy could potentially reclassify them as having good IGCCCG prognosis. This reclassification is significant because patients who are categorized incorrectly as having intermediate/poor instead of good IGCCCG prognosis tend to receive overtreatment with four cycles of BEP instead of three, leading to greater short- and long-term side effects of chemotherapy.

This study was an exploratory analysis of the largest metastatic GCC series, but the retrospective approach is an inherent limitation. Because data collection for the IGCCCG Update did not primarily address the question for the present analysis, our results include only a subset of patients with complete preorchiectomy and postorchiectomy STM data and may thus not be representative. In addition, this analysis does not apply to patients with a very high tumor load and/or life-threatening metastases who require immediate upfront chemotherapy and orchiectomy after completion of first-line treatment.

Nevertheless, our results indicate that up to one in four men with metastatic GCC and no NPVM would be exposed to overtreatment or undertreatment if preorchiectomy instead of prechemotherapy STM results were used for IGCCCG prognostic group assignment. This reinforces the recommendations in international guidelines. Prechemotherapy STM results remain the reference point for IGCCCG prognostic classification and should be clearly specified in national and international guidelines.

Author contributions: Jörg Beyer 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: Fankhauser, Jandari, Collette, Gillessen, Beyer.
Acquisition of data: Fankhauser, Tandstad, Jiang, De Giorgi, Sweeney, Terbuch, Chovanec, Huddart, Bokemeyer.
Analysis and interpretation of data: Fankhauser, Jandari, Collette, Gillessen, Beyer.
Drafting of the manuscript: Fankhauser, Beyer, Gillessen.
Critical revision of the manuscript for important intellectual content: Collette.
Statistical analysis: Jandari, Collette.
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Administrative, technical, or material support: Collette, Gillessen.
Supervision: Beyer, Collette, Gillessen.
Other: None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euros.2023.08.008.

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