Original Study

A Suggested Prognostic Reclassification of Intermediate and Poor-Risk Nonseminomatous Germ Cell Tumors

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Abstract

In a large series of intermediate and poor risk nonseminomatous germ-cell tumors we were able to identify new prognostic factors and to construct an improved risk classification system. Fewer cycles of cisplatin, etoposide, and bleomycin chemotherapy might be necessary in most cases to attain a cure.

Background: The International Germ Cell Cancer Collaborative Group (IGCCCG) classification has been used since 1997 to allocate metastatic germ cell tumors (GCTs), but its applicability needs an update. We aimed to revisit the outcomes of intermediate and poor risk nonseminomatous GCTs (NSGCTs). **Patients and Methods:** Individual patient-level data from the databases of 2 institutions were collected. Outcomes of consecutive patients who received first-line chemotherapy from 1990 to 2014 were used. The Kaplan–Meier method was used to estimate relapse-free (RFS) and overall survival (OS). Cox regression analyses were used to evaluate potential prognostic factors of RFS and OS univariably. Forward stepwise selection was used to construct a multivariable model. A risk factor (RF) model was then constructed and compared with IGCCCG classification using the concordance statistics (CS). **Results:** A total of 647 patients were identified. Four RFs for OS in the multivariable model were identified: primary mediastinal NSGCT ($P < .001$), brain metastases ($P < .001$), lung metastases ($P = .016$), and age at the time of diagnosis ($P = .003$). CS were improved on the basis of the number of RF (0, 1, 2, and 3 or 4) compared with IGCCCG (RFS: 0.63 vs. 0.58; OS: 0.65 vs. 0.59). For intermediate risk, there were no differences between 3 (n = 25) and 4 cycles of cisplatin, etoposide, and bleomycin (BEP; n = 159) or BEP × 3 + etoposide and cisplatin (EP) × 1 (n = 31) for RFS ($P = .35$) and OS ($P = .061$). **Conclusion:** An improved risk stratification was obtained for intermediate and poor risk GCTs. Our reclassification system might provide an aid for a reclassification attempt of all GCT patients. Our prognostic model might be offered to clinicians to improve their ability to assess patient prognosis, enhance stratification, and inform patients.

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Introduction

Metastatic germ cell tumors (GCTs) account for a total of 40% of all diagnosed patients, and established risk factors for relapse-free (RFS) and overall survival (OS) were on the basis of patient and disease characteristics used to construct the International Germ Cell Cancer Collaborative Group (IGCCCG) classification.[1] However, this classification relied on individual patient-level data of patients who had received treatment in the years 1975 to 1990, and the current standard bleomycin, etoposide, and cisplatin (BEP) combination was not administered in most cases. Since the publication of IGCCCG classification in 1997, 4 cycles of BEP became the standard regimen for intermediate and poor risk GCTs.[2-4] A number of randomized clinical trials of alternative regimens,

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conducted in the past 2 decades, reported incremental survival estimates, compared with those from the IGCCCG publication, in their experimental and standard arms for intermediate and poor risk patients.[5-7] In a pooled analysis of the available results, the median estimates of 5-year OS were 86.9% and 65.5% for intermediate- and poor-risk patients, respectively.[7] This apparent survival improvement with BEP chemotherapy over historical controls is partially the reason why most randomized trials ultimately failed to meet their primary efficacy end point, the exception being represented by the Groupe d'Etude des Tumeurs Urogénitales (GETUG)-13 phase III study.[8] Outside of clinical trials, we have recently presented the single-institution series from Indiana University and the Fondazione IRCCS Istituto Nazionale dei Tumori, and results substantially overlapped.[9-12] Further results of large data sets from tertiary cancer centers are available,[13,14] whereas limited information is available in regard to the evolving outcomes of patients who had received treatment in the community oncology practice.[15]

The prognostic ability of the IGCCCG classification system and its applicability to either clinical trial or 'real world' patients is now questionable. Basically, the need for reducing the total burden of curative chemotherapy for GCT patients is advocated by an increasing number of specialists.

Because of the nature of the available data, our principal aim was to provide an aid for a future reclassification attempt by focusing on selected categories of primary interest. Hence we analyzed patients who were currently classified at high-risk, including evaluations of the therapeutic effect of different strategies in such patients.

Patients and Methods

Patient Population

Two retrospective data sets of first-line chemotherapy for IGCCCG intermediate- and poor-risk metastatic nonseminomatous GCTs (NSGCTs) were jointly analyzed. Data on relevant patient, treatment, and outcome results were reported. Patients had to be treated between 1990 and 2014 and should have received chemotherapy and possible additional surgery at 1 of the 2 centers. The number of cases with pure seminomatous histology was too low to allow reliable statistical analyses and these cases were then excluded. The data were deidentified and provided in a Microsoft Excel Mac Word version 2011 (Redmond, WA) spreadsheet by the investigators and statistical analyses were done externally by a senior statistician (G.R.P.). The study was conducted after the institutional review board approval of the 2 institutions.

Statistical Analysis

Descriptive statistics were used to summarize baseline characteristics, treatments, and outcomes. The Kaplan–Meier method was used for estimation of time to event outcomes such as RFS and OS. Cox proportional hazards regression was used to investigate prognostic factors of RFS and OS. Each selected factor was investigated univariately. Categorization of some factors was performed (eg, α-fetoprotein [AFP] and human chorionic gonadotropin [HCG]) on the basis of a priori defined cut points. A separate multivariable model was constructed using stepwise selection for each of RFS and OS outcomes.

A risk stratification was proposed by counting the number of adverse risk factors, defined by the factors' inclusion in the multivariable model, exhibited by each patient. For ordinal categories such as lung metastases and retroperitoneal metastases according to size, risk factor was categorized as any versus none. Age was initially analyzed as a continuous variable in univariable and multivariable models. However, risk factor categorization was performed on the basis of a cutoff age of 30 years, which is approximately the median, because no obvious cutoff was detected and the maximum log-rank test χ^2 value was observed for values near 30. Some groups of risk factors were combined because of small numbers.

Retroperitoneal metastases factor was observed to be confounded with tumor primary. Notably, more than 98% of patients with no retroperitoneal metastases had a mediastinal primary disease, as expected, whereas $<$ 1% of patients who had a retroperitoneal metastases had a mediastinal primary disease. As a result, retroperitoneal metastases was omitted as a potential factor from multivariable models.

Discrimination ability was evaluated using the concordance statistic (c-statistic), and then compared between models on the basis of the proposed risk stratification with IGCCCG classification. Bootstrap sampling, using 2000 replicates, was performed to evaluate the performance of this comparison. Bootstrapping is widely regarded as a superior method to split-sample validation (ie, where data are split into a development and validation data set).[16] Calibration of the risk stratification model was then assessed by comparing the 2-year OS between risk groups on the basis of bootstrap samples. Logistic regression was used to determine the odds of having viable GCTs among patients who had a post-chemotherapy retroperitoneal lymph node dissection (PC-RPLND). The log-rank and χ^2 tests were used to compare differences in outcomes between intermediate risk patients who had received 3 versus 4 cycles of BEP versus 3 cycles of BEP followed by 1 cycle of etoposide and cisplatin (EP) chemotherapy. All tests and confidence intervals (CIs) were 2-sided and statistical significance was defined at the $\alpha = 0.05$ level. All tests were performed using SAS version 9.2 (SAS Institute Inc, Cary, NC). C-statistics and plots were prepared using R version 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient, Disease, Treatment Characteristics, and Outcomes

Patient characteristics, treatments, and outcomes of the 647 patients included in this analysis are summarized in Table 1. Median (range) age of patients was 27 years (13-60), 232 (35.9%) patients had an intermediate-risk and 415 (64.1%) a poor-risk GCT according to the IGCCCG stratification. Elevated HCG levels (ie, HCG $\geq$ 5000 IU/L) were significantly more frequent in patients with testicular primary tumor ($P < .001$) as well as in those with brain ($P < .001$), liver ($P = .041$), and lung metastases ($P < .001$). Conversely, no significant association was found between elevated AFP levels and distribution of patient and disease characteristics.

There were 302 patients (46.7%) who received PC-RPLND, 45 of them (14.9%) showing a pathologically viable residual disease. Median follow-up was 86.7 months. RFS outcomes are presented in Supplemental Table 1 and Supplemental Figure 1A in the online