**Original Article**

# Outcome of patients with stage II and III nonseminomatous germ cell tumors: Results of a single center

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## Abstract

**BACKGROUND:** The prognostic factors in nonseminomatous germ cell tumors have been mainly derived from the analysis of stage I tumors. **AIMS:** The aim of this study was to evaluate some prognostic factors and the outcome of patients with stage II and III nonseminomatous germ cell tumors according to risk groups treated between 1993 and 2002. **SETTINGS AND DESIGN:** Patients were retrospectively classified as good, intermediate and poor risk groups according to International Germ Cell Cancer Consensus Group. **MATERIALS AND METHODS:** Biopsy specimens of 58 patients with stage II and III nonseminomatous germ cell tumors were analyzed by means of tumor histopathology, primary localization site of the tumor, relapse sites, initial serum tumor marker levels, the presence of persistent serum tumor marker elevation and the patients' outcome. **STATISTICAL ANALYSIS:** Kruskall Wallis test and Mann-Whitney U test were used to determine the differences between the groups. Kaplan-Meier method was used for survival analysis and log rank test was used to compare the survival probabilities of groups. Cox proportional hazard analysis was used to determine the prognostic factors in univariate and multivariate analysis. **RESULTS:** Five-year overall and disease-free survival rates were calculated as 85% and 75% in stage II; 44% and 29% in stage III cases, respectively. Fifty-seven percent of patients were classified in good risk, 9% in intermediate risk and 27% in poor risk groups. Five-year overall survival rates were 97%, 75% and 7% ($P<0.001$) and disease-free survival rates were 83%, 34% and 7% ($P<0.001$) in good, intermediate and poor risk groups, respectively. Analysis of the prognostic factors revealed that the localization site of the primary tumor ($P< 0.001$), the initial stage of disease ($P< 0.001$), the initial serum AFP level (p: 0.001), the initial $\beta$-HCG level (p: 0.0048), the presence of yolk sac and choriocarcinoma components in tumor (p: 0.003 and p: 0.004), relapse sites of tumor (lung versus other than lung) (p: 0.003), persistent elevation of serum tumor markers ($P<0.001$) were significant prognostic factors in univariate analysis. However, in multivariate analysis, only the localization site of tumor (p: 0.049) and the relapse site (p: 0.003) were found statistically significant. **CONCLUSIONS:** This retrospective study revealed that in advanced stage of nonseminomatous germ cell tumors, the outcome is essentially related with the localization site of the tumor and the relapse site.

**Key words:** Nonseminomatous germ cell tumors, prognostic factors, stage

## Introduction

Germ cell tumors respond generally very well to conventional or to salvage chemotherapy, even in advanced stage or metastatic disease.[1] However, some patients are unable to achieve a complete response.[2] Many prognostic factors including the stage of disease,[3] histopathology,[4] the localization site of the primary

tumor,[5] serum alfa-feto protein (AFP) and β-HCG levels,[6-8] visceral metastasis sites and the number of metastatic sites[6] are examined up-to-date especially in early stage tumors either to preview the outcome or to select the best treatment modality for patients carrying poor prognosis.

In the present study, we retrospectively analyzed some prognostic factors and the outcome of patients with stage II and III nonseminomatous germ cell tumors treated between 1993 and 2002 at our institution.

## Materials and Methods

### Patients' characteristics

Patients' characteristics are given in Table 1. A total of

**Table 1: Patients characteristics**

| Age | Number (n) | Percentage (%) | Total number |
|---|---|---|---|
| < 20 | 3 | 5 | 58 |
| 20-30 | 51 | 89 | |
| > 30 | 4 | 6 | |
| **Stage** | | | 58 |
| II | 36 | 62 | |
| III | 22 | 38 | |
| **Primary site of tumor** | | | 58 |
| Testicular | 45 | 78 | |
| Retroperitoneal | 10 | 17 | |
| Mediastinal | 3 | 5 | |
| **Histopathology** | | | |
| Embryonal carcinoma | 14 | 24 | |
| Terato carcinoma | 20 | 34 | |
| Mixed germ cell tumor | 19 | 33 | |
| Other | 5 | 9 | |
| **Occurrence of relapse** | | | 23 |
| Stage II | 9 | 15 | |
| Stage III | 14 | 24 | |
| **Location of relapse** | | | 23 |
| Lung | 9 | 15 | |
| Other than lung | 14 | 24 | |
| **Number of death** | | | 17 |
| Stage II | 5 | 9 | |
| Stage III | 12 | 21 | |

58 patients (19-45 years old) with stage II (36 patients) and stage III (22 patients) nonseminomatous germ cell tumors treated with chemotherapy at our university hospital between 1993 and 2002 were retrospectively analyzed. Most of the patients underwent surgery at different centers and then were referred to our center for chemotherapy application. All data were retrieved by the same physician. At initial presentation, clinical staging was done according to AJCC Cancer Staging[9] with computed tomography of the chest, abdomen and pelvis; as well as preoperative serum tumor marker (AFP and β-HCG) levels were noted for each patient. Initial localization sites of the tumor, metastasis sites (lung versus other than lung) and tumor response to first-line chemotherapy were also noted. Patients were classified as good, intermediate and poor risk groups according to International Germ Cell Cancer Collaborative Group (IGCCCG) [Table 1].[10]

### Chemotherapy regimens

All patients were given the same initial BEP chemotherapy (bleomycin 30 mg, days 2, 9 and 16; etoposide 100 mg/m², days 1-5 and cisplatin 20 mg/m², days 1-5) for four cycles. Salvage chemotherapy regimens were applied in relapsed or refractory cases. The same initial salvage chemotherapy was given independent from the relapse sites. Further salvage regimens were applied when needed.

### Follow-up

Patients were assessed periodically by computed tomography of the chest, abdomen and pelvis, by biochemical analysis and by serum tumor marker levels after the last course of chemotherapy. Periodical follow-up exam with computed tomography was done every two months for the first two years, every six months in the third and fourth year and annually thereafter. Patients with residual retroperitoneal lymphadenopathy, despite normal serum tumor marker levels underwent retroperitoneal lymph node dissection along with resection of metastases in selected cases. Response to chemotherapy was assessed as complete response, partial response or progression.

### Histopathologic evaluation

All archival tissue blocks from each tumor were initially checked by hematoxylin and eosin-stained sections to select the representative block with available tissue for immunocytochemical staining. Two same pathologists who did not know the initial stage of disease examined a 4-μm thick section from each formalin-fixed paraffin-embedded tumor.

### Statistics

The differences between the groups were tested using

Kruskall Wallis test and Mann-Whitney U test. The survivals of patients were estimated by using Kaplan Meier method. Log rank test was used to compare survivals of groups. Cox proportional hazard analysis was used to determine the prognostic factors in univariate and multivariate analysis. All statistical calculations were performed with SPSS 10.0 for Windows statistical software package (SPSS Inc., Chicago, IL, USA). A *P* value less than 0.05 was considered statistically significant in all analysis.

## Results

### Patients and histopathologic findings

Thirty-six patients (62%) had stage II and 22 patients (38%) had stage III disease. In 45 patients (78%), the tumor arose from the testis, whereas in 13 patients (22%) from extragonadal sites [in 10 patients (17%) from retroperitoneal areas and from mediastinal areas in three patients (5%)]. Histopathologic examination revealed embryonal carcinoma in 14 patients (24%), teratocarcinoma in 20 patients (34%), mixed germ cell tumors in 19 patients (33%) and other histological types in five patients (9%). Embryonal carcinoma, choriocarcinoma and yolk sac components in the tumor were present in 72%, 19% and 24% of the patients, respectively [Table 2].

According to IGCCCG risk groups, 33 patients (57%), nine patients (15%) and 16 patients (27%) were included in good, intermediate and poor risk groups, respectively.

### Uni and multivariate cox proportional hazard modeling results

The most important prognostic factors were found to be the localization site of tumor (gonadal vs extragonadal) (p: 0.001), the stage of disease (*P*<0.001), the initial serum AFP level (p: 0.001), the initial serum β-HCG level (p: 0.0048), the presence of yolk sac and choriocarcinoma component in tumor (p:

0.003 and p: 0.004), the relapse site (lung vs other site than lung) (p: 0.003) and the persistent serum tumor marker elevation (*P*<0.001) in univariate analysis. However, in multivariate analysis, only the localization site of tumor (p: 0.049) and the relapse site (p: 0.003) were the most statistically important prognostic factors to predict the survival [Tables 3 and 4].

### Response status and survival

The median follow-up was 55.3 months (range: 11.07-120.07) and 25.53 months (range: 1.47-113.80) in patients with stage II and III germ cell tumors, respectively. Five-year overall survival rates were calculated as 85% in stage II and 44% in stage III; whereas five-year disease-free survival rates were 75% in stage II and 29% in stage III patients, respectively [Figures 1 and 2]. The five-year overall survival rate and according to risk groups were 97%, 75% and 7% whereas the disease-free survival rate were 83%, 34% and 7% for the same groups, respectively (*P*<0.001, log-rank: 48.91 and *P*<0.001, log rank: 43.02) [Figures 3 and 4].

### Relapse

The relapse has occurred at a median of $51^{st}$ month (4.17-120.07) and at $17^{th}$ month (1.47-113.80) with a percentage of 25% and 63% in stage II and III patients, respectively. The relapse time between the groups was found statistically significant (p: 0.004). Four patients out of nine in stage II and one patient out of 14 in stage III achieved a complete remission after the salvage chemotherapy administration.

Regarding the risk groups, the relapse time was at median $59^{th}$ month (range: 6.27-120.07) in low risk group, at $48^{th}$ month (range: 1.47-6.70) in intermediate risk group and at $10^{th}$ month (range: 3.20-69.57) in high-risk group. The difference on relapse time between the groups was statistically significant (*P*<0.001). The complete response has occurred in 31%, 11% and 0%

## Table 2: Distribution of patients according to stage and prognosis groups

|  | Good prognosis | Intermediate prognosis | Poor prognosis | Total |
| --- | --- | --- | --- | --- |
| n | 33 (57) | 9 (15) | 16 (27) | 58 (100) |
| Embryonal component | 26 (78) | 6 (66) | 15 (94) | 47 (81) |
| Yolk sac component | 4 (12) | 3 (33) | 7 (43) | 14 (24) |
| Chorio component | 3 (9) | 2 (22) | 6 (37) | 11 (19) |
| Stage II | 26 (78) | 5 (55) | 5 (31) | 36 (62) |
| Stage III | 7 (21) | 4 (44) | 11 (69) | 22 (38) |

Figures in parentheses are in percentage

## Table 3: Univariate cox hazard proportional analysis

| Prognostic factor | Hazard ratio | 95% CI | *P* |
|---|---|---|---|
| Alfa-feto protein | 5.06 | 1.99-12.89 | 0.001 |
| β-HCG | 3.15 | 0.90-11.05 | 0.0048 |
| Chorio component | 4.12 | 1.57-10.80 | 0.004 |
| Yolk sac component | 4.29 | 1.62-11.39 | 0.003 |
| Stage of disease | 3.96 | 1.08-10.42 | 0.0005 |
| Tumor localization | 19.63 | 4.50-85.61 | 0.001 |
| Persistent tumor marker elevation | 12.93 | 4.75-35.19 | <0.001 |
| Relapse site | 10.09 | 2.17-47.02 | 0.003 |
| Vascular invasion | 4.24 | 1.48-9.08 | 0.0048 |

HR - Hazard ratio, CI - Confidence interval

## Table 4: Multivariate cox hazard proportional analysis results

| Prognostic factor | Hazard ratio | 95% CI | *P* |
|---|---|---|---|
| Tumor localization site | 4.87 | 1.01-23.87 | 0.0049 |
| Relapse site | 10.09 | 2.17-47.02 | 0.003 |

CI - Confidence interval

of patients with good, intermediate and poor risk patients, respectively.

## Discussion

The aims of our study were to examine primarily the outcome and secondarily the prognostic factors in stage II and III nonseminomatous germ cell tumors.

In our study, we found that, five-year overall survival rates were 85% and 44% and five-year disease-free survival rates were 75% and 29% in patients with stage
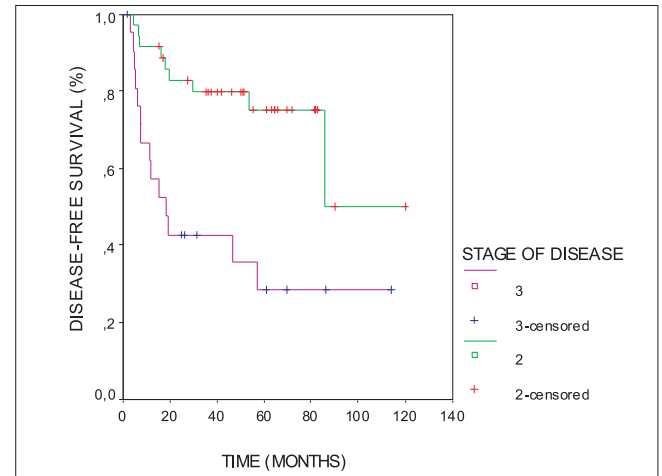


Figure 2: Disease-free survival probability of patients according to stage of disease
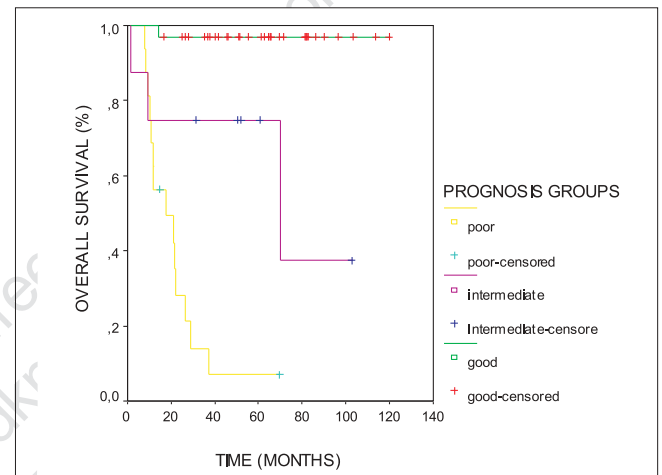


Figure 3: Overall survival probability of patients according to risk groups
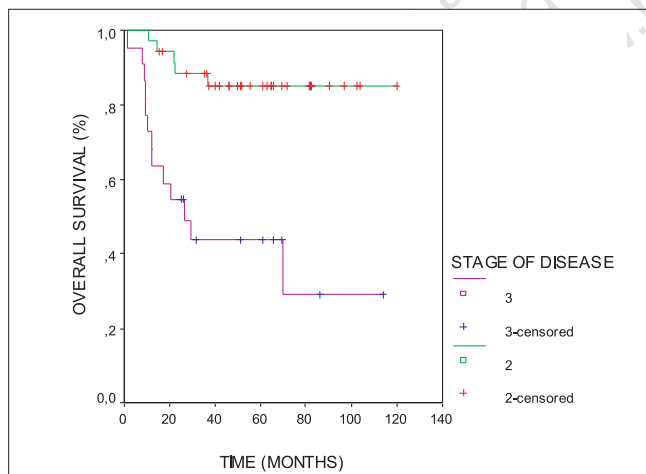


Figure 1: Overall survival probability of patients according to stage of disease
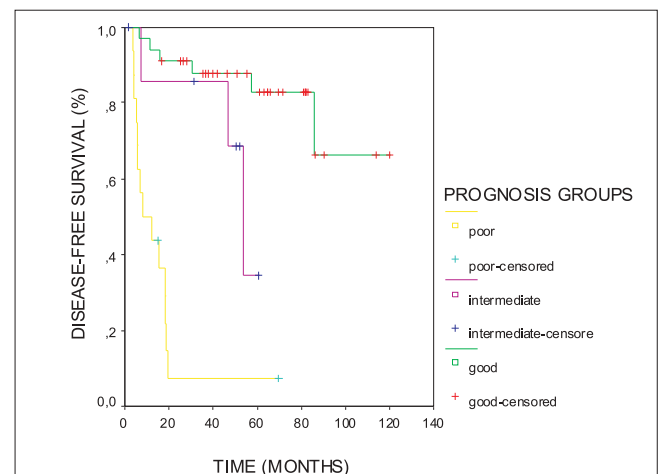


Figure 4: Disease-free survival probability of patients according to risk groups

II and III disease, respectively. However, according to risk groups, five-year overall survival rates were 97%, 75% and 7%; and five-year disease-free survival rates were 83%, 34% and 7% in good risk, intermediate risk and poor risk groups, respectively. This data shows that the outcome of patients was closely related with risk groups.

According to new IGCCCG classification system, primary mediastinum-originated tumors, nonpulmonary visceral metastases or the presence of elevated tumor markers were associated with poor prognosis.[10] Mediastinum-originated tumors were shown to have the worst prognosis and the prognosis for retroperitoneum-originated germ cell tumors is accepted as intermediate risk.[1] Patients with metastasis other than lung have been reported to have a five-year survival of less than 50%.[10] Our study also revealed that patients with tumors of extragonadal origin (22% of all patients) had poor prognosis; and mediastinum-originated tumors had the worst prognosis. All patients with extragonadal origins have died within the first twelve months after the last chemotherapy due to progression.

On the other hand, we also found the relapse site as an important risk factor. Lung metastasis developed in 39% of patients and visceral organ metastasis other than lung developed in 61% patients. Five-year survival rate was 78% in the group with lung metastasis; while no patients achieved remission in the group with visceral organ metastasis and died at their 37th month of follow-up.

Histopathologic components were also assessed by many investigators as significant prognosticators to determine the risk for metastasis in germ cell tumors.[11-18] In our study, only yolk sac or choriocarcinoma components in tumor were determined as significant prognosticator in univariate analysis (p: 0.003 and p: 0.004).

AFP and β-HCG levels were found to be closely related to clinical stage and bulky disease.[19] Although, cut-off values are varied in different trials, preoperative increased levels of serum tumor markers predicted the prognosis.[20] In our study, the cut-off value was accepted as 1000 U/ml and 10.000 mU/ml for AFP and β-HCG, respectively. On these values, these tumor markers were found to be important prognostic factors by only univariate analysis (p: 0.001 and $P<0.001$).

Persistent elevation of serum tumor markers was estimated to be crucial in assessing the refractoriness of tumor to treatment and the risk of relapse.[21] In our study, 11 patients had persistent serum tumor marker elevation; and all of them have died at a median time of 18 months due to progression. Our study showed that persistent elevation of serum tumor markers was a significant prognostic factor in univariate analysis ($P<0.001$) but not in multivariate analysis (p: 0.59).

In summary, although our study retrospectively examined the patients most of whom underwent their surgery at different centers, their survival rates according to risk groups are similar to the current literature data and the outcome of patients with advanced stage nonseminomatous germ cell tumors is closely related with the localization site and the relapse site of the tumor. Further large prospective randomized studies may identify different prognostic factors in these patients along with responsiveness to different chemotherapy regimens applicable in poor risk patients.

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