

Baseline prognostic factors and post-chemotherapy pathological response in primary mediastinal non-seminomatous germ cell tumors: a single-institution retrospective study

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Abstract

Background:

Primary mediastinal non-seminomatous germ cell tumors (NSGCTs) are classified as poor-risk disease by the International Germ Cell Cancer Collaborative Group (IGCCCG), although prognostic heterogeneity within this rare subgroup remains unclear. Because mediastinal tumors represented a small proportion of the IGCCCG dataset, the applicability of established prognostic factors to mediastinal NSGCTs remains uncertain.

Methods:

Patients with primary mediastinal NSGCTs treated at the National Cancer Center Hospital, Japan, between January 2001 and August 2021 were retrospectively analyzed. Baseline clinical factors, tumor markers, pretreatment D-dimer levels, and post-chemotherapy pathological response were evaluated for associations with relapse-free survival (RFS) and overall survival (OS).

Results:

Among 62 patients with NSGCTs, 3-year RFS and OS were 59.4% and 73.3%, respectively. Conventional tumor markers were not significantly associated with prognosis. Pleural effusion, lung metastasis, non-pulmonary visceral metastasis (NPVM), and elevated D-dimer levels ($\geq 2 \mu\text{g/mL}$) were associated with shorter RFS. Multivariable analysis identified NPVM, lung metastasis, and elevated D-dimer levels as predictors of shorter RFS (hazard ratios, 7.85, 2.83, and 2.73, respectively). The D-dimer association was borderline and exploratory. Among patients undergoing post-chemotherapy resection, pathological response was strongly associated with postoperative RFS: no relapse occurred after pathological complete response ($n = 16$), residual mature teratoma only ($n = 11$) showed intermediate outcomes, and other residual histologies ($n = 20$) showed the poorest outcomes ($p < 0.001$).

Conclusion:

NPVM and lung metastasis were associated with shorter RFS. Elevated pretreatment D-dimer levels may provide additional prognostic information. Post-chemotherapy pathological response was strongly associated with postoperative outcomes.

Introduction

Mediastinal germ cell tumors (GCTs) are rare, accounting for approximately 15% of mediastinal tumors in adults and 1–3% of all GCTs [1]. GCTs are classified into two major histological types: seminomas and non-seminomatous GCTs (NSGCTs). NSGCTs include yolk sac tumor, choriocarcinoma, embryonal

carcinoma, and teratoma [2]. Seminomas with elevated serum alpha-fetoprotein (AFP) levels and mixed GCTs are also clinically classified as NSGCTs.

Although mediastinal GCTs share histological and molecular features with gonadal GCTs, primary mediastinal NSGCTs have distinct biological and clinical characteristics, including an over-representation of yolk sac tumor components, characteristic associations with hematologic malignancies, and a higher prevalence of TP53 alterations [3–5]. Mediastinal NSGCTs also have poorer outcomes than gonadal NSGCTs, and a mediastinal primary site is recognized as an adverse prognostic factor in the International Germ Cell Cancer Collaborative Group (IGCCCG) classification.

GCTs are generally chemotherapy-sensitive, except for teratoma. Seminoma is often curable with chemotherapy alone, whereas standard treatment for poor-risk NSGCTs consists of four cycles of bleomycin, etoposide, and cisplatin (BEP) chemotherapy followed by surgical resection of residual masses [6, 7].

The IGCCCG established a prognostic classification in 1997 based on a large database of patients with GCTs [8] and subsequently updated it in 2021 [9]. The original classification categorized GCTs as good, intermediate, or poor risk, whereas the updated report developed a nomogram. Prognostic factors included mediastinal primary site, non-pulmonary visceral metastasis (NPVM), lung metastasis, and serum tumor markers (AFP, human chorionic gonadotropin [hCG], and lactate dehydrogenase [LDH]). Patients with a mediastinal primary site were uniformly classified as having poor-risk disease. Beyond pretreatment factors, treatment response, assessed by the rate of tumor marker decline, has also been reported to predict prognosis [10].

However, whether these prognostic factors apply to mediastinal NSGCTs remains unclear because most patients in the IGCCCG dataset had testicular primaries, whereas only 3.7% had mediastinal primaries. Few studies have evaluated prognostic factors in mediastinal or extragonadal NSGCTs [11].

This study aimed to identify prognostic factors in mediastinal NSGCTs and determine whether they are consistent with those reported for testicular GCTs, using medical records from the National Cancer Center Hospital in Japan. Evaluated factors included baseline disease extent, tumor markers, and treatment response.

Patients and Methods

Ethical Consideration

This single-institution retrospective cohort study was approved by the local ethics committee of the National Cancer Center (approval number 2012 – 335). Written informed consent was waived because of the retrospective study design.

Patients

Patients diagnosed with primary mediastinal GCTs between January 2001 and August 2021 at the National Cancer Center Hospital were included. Patients with an apparent gonadal primary tumor or non-mediastinal extragonadal primary tumor were excluded. All GCTs were pathologically confirmed, and seminomas with elevated AFP levels were classified as NSGCTs.

Assessment

Clinical data were retrospectively obtained from medical records and radiological images. Baseline characteristics included age, sex, laboratory data, tumor size, metastatic status, and pathological findings. Follow-up data included tumor marker levels and outcomes, including relapse date, death date, and last follow-up. The predicted time to normalization (TTN) of tumor markers was calculated using a logarithmic formula. Favorable TTN was defined as < 9 weeks for AFP and < 6 weeks for hCG, according to Fizazi et al. [10].

Tumor markers (AFP, hCG, and LDH) were categorized using cutoffs based on the IGCCCG risk classification [8]: AFP, 1,000 ng/mL; hCG, 5,000 mIU/mL; and LDH, 1.5 times the upper limit of normal (ULN).

Pretreatment D-dimer levels were measured at the initial visit before chemotherapy and were available for 46 of 62 patients with mediastinal NSGCTs. Because no universally accepted prognostic cutoff for D-dimer has been established, patients were dichotomized at 2.0 µg/mL. This threshold was selected because it was clinically interpretable, approximately balanced the cohort, was close to the cohort median, and had been used in previous prognostic studies of solid tumors [12, 13]. D-dimer analyses were performed as complete-case analyses.

Pathological response after post-chemotherapy surgical resection was categorized into three groups based on prognostic classifications established in previous studies of testicular and mediastinal NSGCTs [14–16]: (1) pathological complete response (pCR), defined as no viable tumor cells of any histology in the resected specimen; (2) residual mature teratoma only, defined as mature teratoma without viable germ cell tumor cells, immature teratoma, or somatic-type malignancy; and (3) others, defined as residual viable germ cell tumor, immature teratoma, or somatic-type malignancy, with or without mature teratoma or necrotic tissue.

Relapse-free survival (RFS) was defined as the time from diagnosis to relapse, progression after initial treatment, or death from any cause, whichever occurred first. Overall survival (OS) was defined as the time from diagnosis to death from any cause. Among patients who underwent post-chemotherapy surgical resection, postoperative RFS and OS were additionally defined using the date of surgery as the time origin.

Treatment data included first-line chemotherapy regimen, subsequent regimens, timing of surgery relative to chemotherapy, and reasons for not undergoing surgical resection.

Statistical analysis

RFS and OS were estimated using the Kaplan–Meier method. Hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated using univariate and multivariable Cox proportional hazards models. Variables associated with shorter RFS in univariate analysis at $p < 0.05$ (NPVM, lung metastasis, elevated D-dimer levels, and pleural effusion) were considered clinically relevant prognostic factors and included in multivariable Cox models for both RFS and OS. Given the limited number of events and exploratory nature of the study, multivariable models were interpreted cautiously. Models including D-dimer used complete-case analyses.

For post-chemotherapy pathological response, the three groups were compared using Kaplan–Meier analysis and the log-rank test for trend, reflecting the ordinal nature of the categorization. Because no relapse occurred in the pCR group, HR estimation using a three-group Cox model was not feasible. Outcomes were therefore presented descriptively with the log-rank trend test statistic.

All P-values were two-sided, and P-values < 0.05 were considered statistically significant. Analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [17]. Kaplan–Meier curves were generated using EZR, and figures were assembled using Microsoft PowerPoint (Microsoft Corporation, Redmond, WA, USA).

Results

Patient characteristics

The cohort included 29 patients with seminoma and 62 with NSGCTs (Table 1). The median age at diagnosis was 29 years in both groups. Compared with patients with seminoma, those with NSGCTs more frequently had lung metastasis, pleural effusion, and elevated D-dimer levels and were substantially more likely to undergo surgical resection after chemotherapy. Detailed baseline characteristics are presented in Table 1.

Table 1
Patient characteristics

Variable	Seminoma (n = 29)	NSGCT (n = 62)	P-value
Age, median (IQR), years	29 (24–41)	29 (25–37)	0.482
Sex, male/female	29/0	57/5	0.173
Primary tumor size, median (IQR), mm	85 (71–112)	103 (85–121)	0.084
Lung metastasis, n (%)	1 (3.4)	13 (21.0)	0.033
Pleural effusion, n (%)	3 (10.3)	19 (30.6)	0.039
Non-pulmonary visceral metastasis, n (%)	0 (0)	5 (8.1)	0.173
AFP, median (IQR), ng/mL	2.7 (1.7–3.8)	6141.0 (620.9–15094.5)	< 0.001
hCG, median (IQR), mIU/mL	8.2 (2.7–27.1)	4.0 (0.2–51.6)	0.490
LDH, median (IQR), IU/L	246 (192–441)	386 (253–502)	0.051
D-dimer, median (IQR), µg/mL	0.8 (0.5–1.1)	1.8 (1.0–4.0)	0.003
Post-chemotherapy surgical resection, n (%)	8 (27.6)	47 (75.8)	< 0.001
Predominant histology of NSGCTs, n			
Yolk sac tumor	—	37	
Teratoma	—	7	
Choriocarcinoma	—	5	
Seminoma with elevated AFP	—	5	
Embryonal carcinoma	—	2	
Other	—	6	
Mixed histology (containing teratoma), n	—	17 (12)	
AFP, alpha-fetoprotein; hCG, human chorionic gonadotropin; IQR, interquartile range; LDH, lactate dehydrogenase; NSGCT, non-seminomatous germ cell tumor. Percentages for lung metastasis, pleural effusion, non-pulmonary visceral metastasis, and post-chemotherapy surgical resection were calculated among patients with available data.			

Among patients with NSGCTs, yolk sac tumor was the predominant histology in 37 patients, followed by teratoma (n = 7), choriocarcinoma (n = 5), seminoma with elevated AFP (n = 5), embryonal carcinoma (n = 2), and other non-seminomatous histologies (n = 6). Mixed histology, defined as > 1 histological

component identified before chemotherapy, was observed in 17 patients; 12 had teratoma as one component (Table 1).

Treatment course in patients with mediastinal NSGCTs

Of the 62 patients with mediastinal NSGCTs, 61 received first-line cisplatin-based chemotherapy: BEP in 55, VIP (etoposide, ifosfamide, and cisplatin) in 5, and EP in 1; 1 patient received no chemotherapy. Seventeen patients received second-line or later chemotherapy for refractory or relapsed disease, including VIP in 11, TIP (paclitaxel, ifosfamide, and cisplatin) in 2, and other regimens in 4.

Overall, 50 patients underwent surgical resection. Of these, 47 underwent post-chemotherapy resection and were included in the pathological response analysis. Three patients were excluded because surgery was performed before chemotherapy ($n = 2$) or without chemotherapy ($n = 1$). Among the 47 patients included in the analysis, surgery followed first-line chemotherapy in 42, second-line chemotherapy in 2, and third-line chemotherapy in 3. Among the 12 patients who did not undergo surgical resection, the reasons were refractory disease ($n = 8$), poor general condition or clinical inoperability ($n = 3$), and other clinical reasons ($n = 1$).

Survival outcomes

The median follow-up duration among surviving patients was 160 months for seminoma and 113 months for NSGCTs. Most patients with seminoma remained alive without recurrence, whereas those with NSGCTs had substantially poorer outcomes (Fig. 1). The 3-year RFS and OS rates were 96.6% (95% CI 78.0–99.5%) and 96.6% (95% CI 78.0–99.5%) for seminoma, compared with 59.4% (95% CI 46.0–70.4%) and 73.3% (95% CI 59.6–83.1%) for NSGCTs, respectively. Compared with seminoma, NSGCT was associated with significantly worse RFS (HR 15.44, 95% CI 2.09–113.9, $p = 0.007$) and OS (HR 9.23, 95% CI 1.22–69.69, $p = 0.031$) by Cox regression.

Univariate analysis of prognostic factors in NSGCTs

Univariate Cox regression results are summarized in Table 2. Among factors reflecting disease extent, pleural effusion (RFS HR 2.35, 95% CI 1.08–5.09, $p = 0.031$; OS HR 4.66, 95% CI 1.69–12.86, $p = 0.003$), lung metastasis (RFS HR 3.36, 95% CI 1.49–7.59, $p = 0.004$; OS HR 2.76, 95% CI 0.94–8.07, $p = 0.064$), and NPVM (RFS HR 6.69, 95% CI 2.37–18.94, $p < 0.001$; OS HR 10.65, 95% CI 3.00–37.74, $p < 0.001$) were associated with worse outcomes (Fig. 2).

Table 2

Univariate Cox regression analysis of prognostic factors in patients with mediastinal NSGCTs (n = 62)

Variable	RFS		OS	
	HR (95% CI)	P	HR (95% CI)	P
Pleural effusion	2.35 (1.08–5.09)	0.031	4.66 (1.69–12.86)	0.003
Lung metastasis	3.36 (1.49–7.59)	0.004	2.76 (0.94–8.07)	0.064
Non-pulmonary visceral metastasis	6.69 (2.37–18.94)	< 0.001	10.65 (3.00–37.74)	< 0.001
Primary tumor size $\geq$ 100 mm	1.79 (0.78–4.11)	0.173	2.49 (0.80–7.73)	0.114
AFP $\geq$ 1000 ng/mL	0.56 (0.25–1.26)	0.163	0.48 (0.17–1.32)	0.156
hCG $\geq$ 5000 mIU/mL	1.31 (0.45–3.80)	0.623	1.80 (0.51–6.35)	0.360
LDH $\geq$ 1.5 $\times$ ULN	1.96 (0.84–4.59)	0.121	2.91 (0.92–9.18)	0.068
Elevated D-dimer ($\geq$ 2 μ g/mL)	2.60 (1.03–6.54)	0.042	3.15 (0.97–10.25)	0.057
Favorable TTN	1.02 (0.44–2.37)	0.958	1.45 (0.47–4.49)	0.522
AFP, alpha-fetoprotein; CI, confidence interval; hCG, human chorionic gonadotropin; HR, hazard ratio; LDH, lactate dehydrogenase; OS, overall survival; RFS, relapse-free survival; TTN, time to normalization of tumor markers; ULN, upper limit of normal. D-dimer analyses included patients with available data (n = 46).				

Conventional tumor markers, including AFP ($\geq$ 1,000 ng/mL), hCG ($\geq$ 5,000 mIU/mL), and LDH ($\geq$ 1.5 $\times$ ULN), did not significantly predict prognosis. Given the high prevalence of yolk sac tumors and elevated AFP levels, higher tumor marker thresholds were additionally explored. However, alternative thresholds, including AFP $\geq$ 10,000 ng/mL and LDH $\geq$ 2.5 $\times$ ULN, the latter used in the IGCCCG Update model [9], did not materially improve prognostic stratification for RFS or OS (Supplementary Table S1). In contrast, elevated D-dimer levels ($\geq$ 2 μ g/mL) were associated with shorter RFS (HR 2.60, 95% CI 1.03–6.54, p = 0.042) and showed a similar trend for OS (HR 3.15, 95% CI 0.97–10.25, p = 0.057) (Fig. 2).

Primary tumor size and predicted TTN of tumor markers were not significantly associated with prognosis.

Multivariable analysis

In multivariable Cox regression including pleural effusion, lung metastasis, NPVM, and elevated D-dimer levels, three variables remained independently associated with shorter RFS: NPVM (HR 7.85, 95% CI 1.40–44.09, p = 0.019), lung metastasis (HR 2.83, 95% CI 1.01–7.97, p = 0.048), and elevated D-dimer levels (HR 2.73, 95% CI 1.00–7.44, p = 0.050) (Table 3). The association with elevated D-dimer levels was borderline. Pleural effusion was not associated with RFS after adjustment (HR 0.98, 95% CI 0.30–3.22, p

= 0.970). None of the variables reached statistical significance in the OS model, likely because of the limited number of OS events.

Table 3

Multivariable Cox regression analysis of prognostic factors in patients with mediastinal NSGCTs with complete data for all variables (n = 46)

Variable	RFS		OS	
	HR (95% CI)	P	HR (95% CI)	P
Non-pulmonary visceral metastasis	7.85 (1.40–44.09)	0.019	2.90 (0.42–20.24)	0.283
Lung metastasis	2.83 (1.01–7.97)	0.048	2.92 (0.62–13.77)	0.176
Elevated D-dimer (≥ 2 $\mu\text{g/mL}$)	2.73 (1.00–7.44)	0.050	1.90 (0.50–7.15)	0.344
Pleural effusion	0.98 (0.30–3.22)	0.970	3.00 (0.64–14.11)	0.164
CI, confidence interval; HR, hazard ratio; OS, overall survival; RFS, relapse-free survival. The multivariable Cox proportional hazards model included the four variables shown.				

Pathological response after post-chemotherapy resection

Among the 47 patients who underwent post-chemotherapy surgical resection, pathological findings were classified as pCR (n = 16), residual mature teratoma only (n = 11), or others (n = 20). None of the 16 patients with pCR experienced postoperative relapse, compared with 3 patients in the residual mature teratoma only group and 11 in the others group. Kaplan–Meier curves demonstrated a stepwise prognostic hierarchy across the three groups for postoperative RFS and OS (Fig. 3).

Because pathological response could be assessed only in patients who underwent surgery, it should be interpreted as a post-treatment prognostic factor rather than a baseline risk stratification measure. The log-rank test for trend demonstrated a significant monotonic association between pathological response and outcome (postoperative RFS: $\chi^2 = 12.3$, df = 1, $p < 0.001$; postoperative OS: $\chi^2 = 7.2$, df = 1, $p = 0.007$). The same trend was observed in a sensitivity analysis restricted to 42 patients who underwent surgery after first-line chemotherapy (postoperative RFS: $\chi^2 = 12.3$, df = 1, $p < 0.001$; postoperative OS: $\chi^2 = 6.7$, df = 1, $p = 0.010$).

Discussion

Primary mediastinal NSGCTs are rare malignancies with poor outcomes, and prognostic data specific to this subgroup remain limited. In this single-institution retrospective study of 62 patients with mediastinal NSGCTs treated between 2001 and 2021, NPVM and lung metastasis were associated with shorter RFS, while elevated pretreatment D-dimer levels showed a borderline independent association with shorter RFS. These findings suggest that metastatic burden and coagulation-related markers may refine prognostic assessment within this uniformly poor-risk population. Among patients who underwent post-

chemotherapy surgical resection, pathological findings were strongly associated with postoperative outcomes: pCR and residual mature teratoma only were associated with favorable outcomes, whereas residual viable germ cell tumor, immature teratoma, or somatic-type malignancy was associated with worse outcomes. Although elevated hCG has been reported as an adverse prognostic factor in extragonadal NSGCTs [11], neither hCG nor conventional serum tumor markers (AFP and LDH) reached statistical significance in this cohort. Non-conventional parameters such as D-dimer may therefore provide additional prognostic information in this rare population.

NPVM was an independent adverse prognostic factor for RFS. It has consistently been recognized as one of the strongest prognostic factors in metastatic NSGCTs in both the original IGCCCG classification [8] and the IGCCCG Update model [9], in which it has the highest hazard ratio among the included variables. The present findings, based on a cohort restricted to mediastinal NSGCTs, are consistent with these reports and reinforce the prognostic importance of NPVM in this subgroup.

Lung metastasis was also independently associated with shorter RFS. Although mediastinal NSGCTs are uniformly classified as poor risk in the IGCCCG classification regardless of other factors, the IGCCCG Update model demonstrated that lung metastasis provides additional adverse prognostic information across the metastatic NSGCT population [9]. The present findings support this observation and suggest that lung metastasis may identify a particularly unfavorable subgroup even within the uniformly poor-risk population of mediastinal NSGCTs.

Elevated pretreatment D-dimer levels (≥ 2.0 $\mu\text{g/mL}$) were associated with shorter RFS in both univariate and multivariable analyses and showed a similar trend for OS. Given the limited number of patients with available D-dimer data and the empirically selected cutoff, this finding should be considered hypothesis-generating. Although the 2.0 $\mu\text{g/mL}$ threshold was not derived from a disease-specific validation cohort, comparable cutoffs have been used in prognostic studies of other malignancies [12, 13]. Elevated D-dimer levels have been associated with poor outcomes in various solid tumors [18], but their prognostic value in GCTs, including testicular GCTs, remains unclear. The observed association may reflect characteristics of mediastinal disease. These tumors frequently invade or compress mediastinal structures, including the great vessels and pericardium [19]. Such intrathoracic tumor burden, together with the procoagulant activity of malignant cells [18], may activate coagulation and increase D-dimer levels independently of overt thromboembolism. All measurements were obtained before chemotherapy, and no overt pulmonary embolism was detected on contrast-enhanced chest CT at diagnosis. However, routine contrast protocols rather than dedicated CT pulmonary angiography or DVT-protocol imaging were used; therefore, subclinical thromboembolism cannot be excluded. Given the limited sample size, exploratory design, and absence of a disease-specific threshold, both the prognostic association and optimal D-dimer cutoff require validation in independent cohorts.

Among patients who underwent post-chemotherapy surgical resection, pathological findings were strongly associated with postoperative outcomes. No patient with pCR experienced relapse during follow-up, patients with residual mature teratoma only had intermediate outcomes, and patients in the

“others” group, including those with residual viable germ cell tumor, immature teratoma, or somatic-type malignancy, had the poorest outcomes. This three-tiered hierarchy, with pCR being most favorable, residual mature teratoma intermediate, and viable malignancy least favorable, is consistent with previous findings in testicular NSGCTs [14, 20, 21] and mediastinal NSGCTs [15, 16, 22], providing further evidence from a Japanese single-institution cohort.

Although mature teratoma is intrinsically chemoresistant and may grow during or after chemotherapy, complete surgical resection is generally curative because of its essentially benign histologic nature, supporting its classification as a favorable pathological response [19]. In contrast, somatic-type malignancy has limited responsiveness to standard GCT chemotherapy, making surgical resection the mainstay of treatment, although chemotherapy may benefit selected patients with histologically restricted transformation [23, 24]. Kesler et al. also reported shorter survival among patients with teratoma with stromal atypia in residual mediastinal masses than among those with teratoma without atypia [16]. The small number of patients with these histologies in the present cohort (immature teratoma, n = 2; somatic-type malignancy, n = 2) precluded dedicated subgroup analyses. However, their classification with viable germ cell tumor in the “others” group was supported by their known biological behavior and prognostic implications.

This study has several limitations. First, this retrospective single-institution study had a relatively small sample size, limiting the number of variables that could be reliably included in multivariable models. The limited number of OS events also reduced the statistical power of the multivariable OS analysis and may explain why no candidate variable reached statistical significance. The small number of events relative to covariates further indicates that these analyses should be interpreted cautiously and not considered a validated prognostic model. Second, pathological response could be assessed only in patients who underwent surgical resection (n = 47), introducing potential selection bias. This analysis was therefore performed separately rather than incorporated into the multivariable model for the entire NSGCT cohort. Radiological response rates and quantitative tumor shrinkage during chemotherapy were not systematically collected. Consequently, relationships among radiological response, resectability, pathological response, and postoperative outcomes could not be fully assessed. Third, patients were treated over 20 years (2001–2021), during which changes in diagnostic modalities and supportive care may have influenced outcomes, although the main chemotherapy regimens for NSGCTs remained largely consistent. Fourth, pretreatment D-dimer levels were available for only 46 of 62 patients and were analyzed using complete cases. The empirical cutoff used in this exploratory analysis also requires validation in independent, preferably prospective, cohorts.

In conclusion, NPVM and lung metastasis were associated with shorter RFS in patients with mediastinal NSGCTs. Elevated pretreatment D-dimer levels may provide additional prognostic information, but this hypothesis-generating finding requires independent validation. Post-chemotherapy pathological response, particularly pCR or residual mature teratoma only, was strongly associated with favorable outcomes. These findings reinforce the prognostic relevance of metastatic burden while suggesting that D-dimer may provide additional information beyond the current IGCCCG classification. Larger,

prospective, multi-institutional studies are warranted to validate these findings and establish their clinical utility.

Declarations

Conflicts of interest / Competing interest

The authors declare no conflicts of interest.

Ethics approval

This study was approved by the local ethics committee of the National Cancer Center (approval number 2012 – 335). Written informed consent was waived because of the retrospective study design.

Consent to participate

Not applicable. Written informed consent was waived because of the retrospective study design.

Consent for publication

Not applicable.

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Author contributions

Y.A., Y.H. and T.Sh. designed the study, collected the data, and performed data analysis and interpretation. K.T., H.T., T.Sa., T.Y., M.H., A.S., S.K., H-S.O., A.M., Y.K., K.S., E.N., M.Y., Y.Y., Y.F., and K.Y. contributed to manuscript drafting and critical revision. All authors read and approved the final manuscript.

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Data availability

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

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Figures

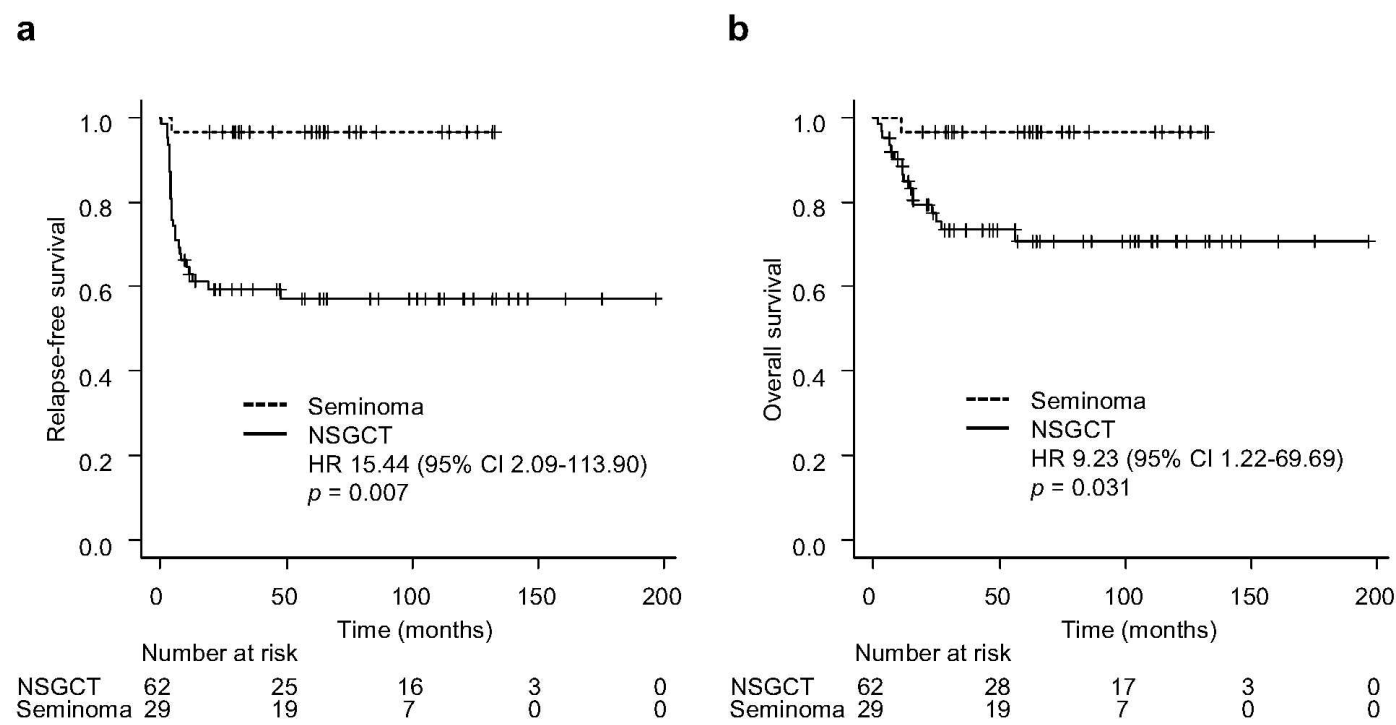


Figure 1

Kaplan–Meier survival curves of patients with mediastinal germ cell tumors. (a) Relapse-free survival in patients with seminoma (n = 29) and non-seminomatous germ cell tumors (NSGCTs, n = 62). (b) Overall

survival in the same groups. Hazard ratios and P-values were calculated using Cox proportional hazards regression

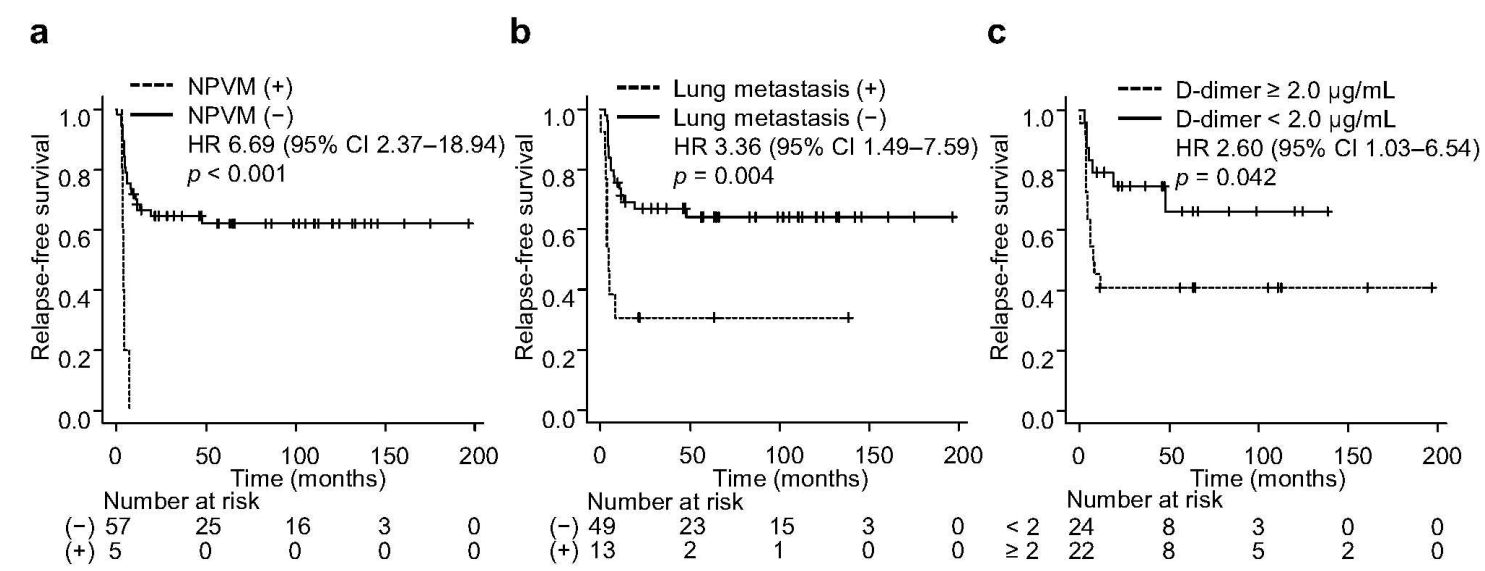


Figure 2

Kaplan–Meier curves for relapse-free survival in patients with mediastinal NSGCTs ($n = 62$), stratified by independent prognostic factors identified in multivariable Cox regression. (a) Presence of non-pulmonary visceral metastasis (NPVM). (b) Presence of lung metastasis. (c) Elevated D-dimer levels (≥ 2 $\mu\text{g/mL}$ vs. < 2 $\mu\text{g/mL}$). Hazard ratios and P-values were calculated using Cox proportional hazards regression. Panels A and B include all patients with mediastinal NSGCTs ($n = 62$), whereas panel C includes patients with available pretreatment D-dimer data ($n = 46$)

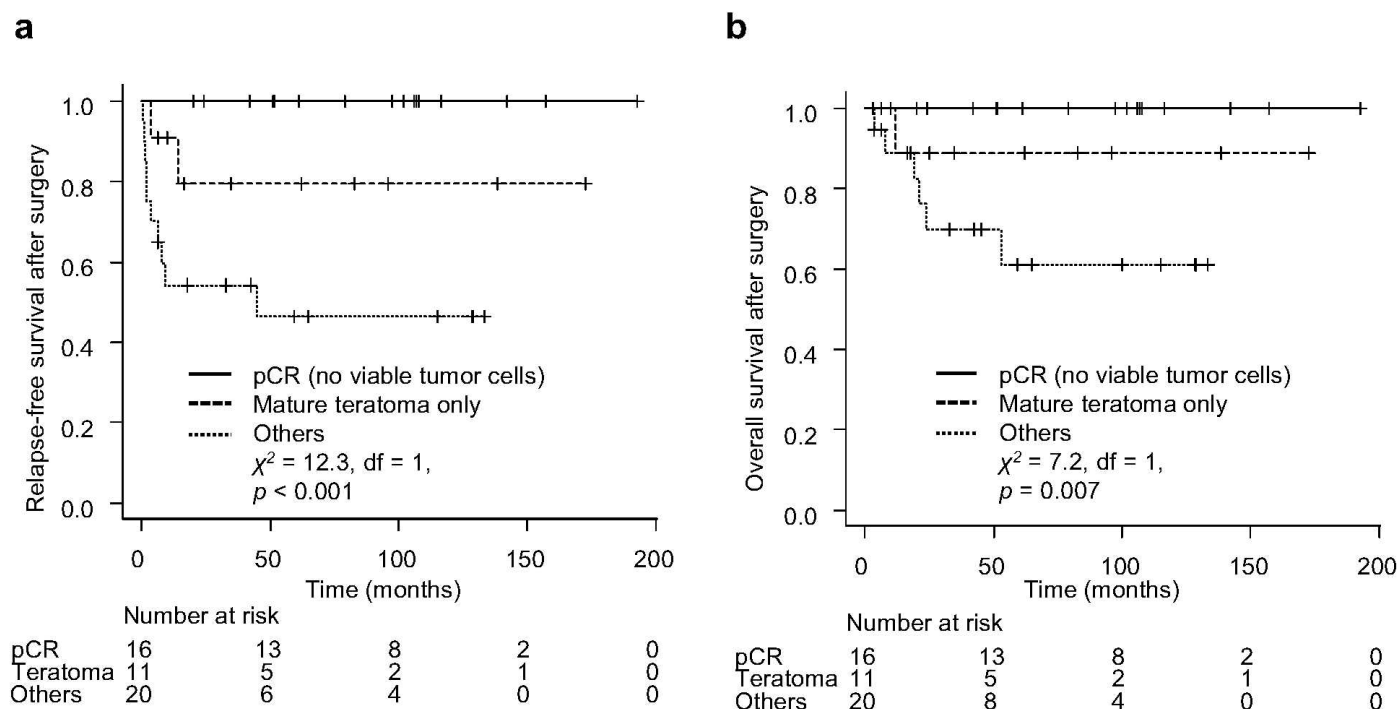


Figure 3

Kaplan–Meier survival curves of patients with mediastinal NSGCTs who underwent post-chemotherapy surgical resection (n = 47), stratified by pathological response. (a) Postoperative relapse-free survival. (b) Postoperative overall survival. pCR, pathological complete response (no viable tumor cells; n = 16); Mature teratoma only, residual mature teratoma without other components (n = 11); Others, residual viable germ cell tumor, immature teratoma, or somatic-type malignancy (n = 20). P-values were calculated using the log-rank test for trend

Supplementary Files

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