Current Problems in Cancer 44 (2020) 100537

Contents lists available at ScienceDirect

Current Problems in Cancer

journal homepage: www.elsevier.com/locate/cpcancer

Neutrophil-to-lymphocyte ratio in primary mediastinal germ cell tumors: A retrospective analysis of >20 years single institution experience

Lajos Géczi[a], Barna Budai[a,*], Nándor Polk[a], Fruzsina Fazekas[b], István Bodrogi[a], Krisztina Biró[a]

[a] National Institute of Oncology, Budapest, Hungary
[b] Péterfy Hospital, Budapest, Hungary

ABSTRACT

Objectives: To obtain information on outcome stratified by histology, extent and primary treatment patients' data with primary malignant mediastinal germ cell tumors treated between 1998 and 2018 were retrospectively analyzed.
Methods: The primary treatment for localized malignant mediastinal germ cell tumors was neoadjuvant bleomycin + etoposid + cisplatin (BEP) ± surgery (n = 22); or surgery ± adjuvant BEP (n = 16). For disseminated disease (n = 21) first line BEP ± second line chemotherapy were administered. For nonseminomas (NS) the NLR at start of BEP was analyzed in relation to disease-free survival (DFS), progression-free survival (PFS), and overall survival (OS).
Results: After neoadjuvant treatment the 5-year DFS was 100% for seminomas (S), and 63.4% for NS. The 5-year OS was 100% for S, and 76.9% for NS. The 5-year DFS and OS after surgery ± BEP for S was 72.9% and 100%, for NS was 75% and 87.5%, respectively. The 5-year PFS and OS of metastatic patients for S was 60% and 80%, while the median PFS and OS of NS were 5.7 and 11.1 months, respectively. Objective response ($P = 0.006$) and low NLR ($P = 0.043$) were independent prognostic markers of longer OS.
Conclusions: We confirmed the good outcome of BEP-treated S, while NS had poorer prognosis. Previously published prognostic models for NS were validated. Based on NLR and response a new prognostic model was developed.

☆ Funding: None.
☆☆ Conflicts of interest: The authors report no conflicts of interest.
* Correspondence to: Barna Budai, National Institute of Oncology, Ráth Gy. 7-9 1122 Budapest, Hungary.
E-mail address: budai@oncol.hu (B. Budai).

https://doi.org/10.1016/j.currproblcancer.2020.100537

ARTICLE INFO

Keywords: BEP chemotherapy; Neutrophil-to-lymphocyte ratio; Primary mediastinal germ cell tumor; Prognostic model; Survival

Introduction

Mediastinal germ cell tumors (MGCT) account for only 2.2% of all germinal tumors and constitute 25% of all extragonadal tumors.[1] These neoplasms usually occur in adolescent and young adults. At diagnosis the disease extension is metastatic in 41% of cases.[1] Primary germ cell tumors are classified as pure seminomas (S) and nonseminomas (NS). NS include benign and malignant teratoma, choriocarcinoma, yolk sac tumor, embryonal cell carcinoma, and mixed type tumors. Germ cell tumors of the mediastinum are thought to arise as a consequence of an error of migration of germ cells along the urogenital ridge during embryogenesis.[2] Measurement of the serum tumor markers beta-human chorionic gonadotropin (β-HCG) and alpha-fetoprotein (AFP) are indispensable in the management of nonseminomatous germ cell tumors, since approximately 90% of patients with nonseminomatous MGCT will have elevation of 1 or both markers.[3] Primary mediastinal S may occasionally be associated with mild elevation of HCG levels. In addition, lactate dehydrogenase is elevated in approximately 90% of these patients and serial determinations are useful in monitoring the activity of disease. Most masses are localized in the anterior mediastinum, but 3%-8% of tumors arise within the posterior mediastinum.[4] For staging purposes chest and abdominal CT scan should be performed to define the extent of disease, the relationship with the surrounding structures, and the presence or absence of metastases.[5,6] The nonseminomatous germ-cell tumors in young males with mediastinal masses and elevated levels of AFP and β-HCG may be diagnosed without tissue biopsy, and the treatment may be initiated.[3,7] All patients with S or NS should be treated with curative intent, preferably in high-volume centers, since suboptimal treatment leads to a worse outcome.[8] Locally advanced and bulky diseases should be treated initially with cisplatin-based combination chemotherapy (CHT). In NS surgical resection of the residual disease even when tumor markers are persistently elevated has been reported by several authors to be beneficial.[9,10] In spite of that Lemarié et al.[11] already have stated that "Extent of disease remains the most important variable associated with outcome" and ever since others have also demonstrated that the extension (stage) is a significant prognostic marker,[12,13] unfortunately, many publications and amongst them those which large series[14,15] evaluated together patients with localized and metastatic disease. To obtain more information on the outcome stratified by histology, extent, and primary treatment type we retrospectively collected and analyzed the chart data of patients with malignant MGCT. The prognostic factors for nonseminomatous MGCT were also assessed.

Materials and methods

Patients with mediastinal tumor (n = 663) were identified from the electronic database of the institute. There were only 59 primary MGCT, which were included in the analysis. The presence of primary testicular tumor was excluded by clinical and radiographic examination of testes.

The primary treatment for localized MGCT was neoadjuvant bleomycin + etoposid + cisplatin (BEP) (n = 22) ± surgery; or surgery (n = 16) ± adjuvant BEP/EP. The treatment for disseminated disease was first line BEP (n = 21). Patients who progressed received further lines of CHT.

The tumor response was controlled according to RECIST 1.1. The level of tumor markers (AFP, β-HCG, lactate dehydrogenase) were measured as indicated in patients with germ line tumors. The treatment of young males with mediastinal masses and elevated serum tumor markers (AFP and β-HCG) was initiated without a tissue biopsy.[7,14] The neutrophil-to-lymphocyte ratio (NLR) at the start of CHT was evaluated as a possible biomarker of survival.[16] For all metastatic NS patients good, intermediate and poor prognostic subgroups were constructed according to the model of Necchi et al.,[17] Fedyanin et al.,[18] Hartmann et al.[19] and by totalizing markers of survival found by Rodney et al.[20] and Liu et al.[12]

The primary objective of this study was to determine the disease-free survival (DFS), progression-free survival (PFS), and overall survival (OS). The survivals were analyzed according to Kaplan-Meier method and by multivariate Cox regression. The objective response (OR) was also assessed. Finding predictive markers was the secondary objective. For all statistical analyses the NCSS program (NCSS 12 Statistical Software (2018). NCSS, LLC. Kaysville, UT) was used. $P < 0.05$ was considered statistically significant.

The Hungarian Medical Research Council (21679-2/2016/EKU) and the Ethical Committee of the institute approved the study.

Results

Clinicopathologic characteristics of patients (n = 59) are presented in Table 1. The histopathologic diagnoses were determined from primary mediastinal biopsy (n = 29) or surgical tissue samples (n = 30).

Efficacy of neoadjuvant therapy

The primary treatment of 22 patients (9 S and 13 NS) was neoadjuvant BEP (3-4 cycles). One patient with S and 3 patients with NS received palliative radiotherapy (RT) before CHT. Patients with S had 100% OR after BEP and further surgery was not necessary. None of these patients progressed during the follow-up (median 97 [95%CI 83-152] months). In case of NS the OR was 77%, while 2 patients presented stable disease and 1 progressed. The pathologic stage after surgery of these patients was ypT0 for 4 patients, <10% of viable tumor tissue remained in 5 patients (and is unknown for 4 patients who had the surgical intervention at other institutes). In 6 patients with NS 2 cycles of EP was administered after surgery. During the follow-up 4 patients (1 after the adjuvant therapy) progressed and 3 died. The DFS at 5 and 10 years was uniformly 100% for S and 63.4% for NS (log rank test $P = 0.062$). The OS at 5, 10, and 15 years was uniformly 100% for S and 76.9% for NS (log rank test $P = 0.133$).

Efficacy of primary surgery ± adjuvant therapy

Surgery as primary treatment (in the S and NS group only 1 and 2 cases were incomplete resections, respectively) was followed by adjuvant BEP in 14 patients (7 S and 7 NS), while for 2 patients (1 S and 1 NS) the adjuvant BEP was not administered. Two patients with S received also adjuvant RT after BEP. Out of these 16 patients (14 BEP-treated and 2 monitored) 2 S and 2 NS progressed and 1 NS died during the follow-up (median 101 [95% CI 81-142] months). The survivals were calculated from the date of surgery. Patients who previously received neoadjuvant treatment were not included. The DFS rate at 5, 10, and 15 years for S was uniformly 72.9%, and for NS was uniformly 75% (log rank test $P = 0.937$), while the OS rate at 5, 10, and 15 years for S was uniformly 100% and for NS was uniformly 87.5% (log rank test $P = 0.317$).

Table 1
Clinicopathologic characteristics of patients with primary MGCT and the prognostic groups for patients with nonseminoma.

Parameters		N (%)
Age, median (range)		29 (16-65) y
BMI, median (range)		24.2 (16-36)
Period from first symptoms to diagnosis		4.4 (0-52) wk
Major symptoms		
Pain		24 (41)
Cough		21 (36)
Fever		15 (25)
Dyspnoe		13 (22)
Gynecomastia		5 (8)
Other		6 (10)
None (screened)		16 (27)
Misdiagnosed at other hospitals		15 (25)
Testes		
Calcification		8 (14)
Cysts		3 (5)
Atrophy, hypoplasia		7 (12)
Histology		
Pure seminoma		22 (37)
Nonseminoma		37 (63)
Yolk sac tumor		11 (30)
Malignant teratoma		9 (24)
Embryonal carcinoma		3 (8)
Choriocarcinoma		1 (3)
Mixed		6 (16)
Not specified*		7 (19)
	Seminoma	Nonseminoma
Stage (Moran-Suster)[6]		
I	9 (41)	8 (22)
II	8 (36)	13 (35)
IIIA	2 (9)	6 (16)
IIIB	3 (14)	10 (27)
Localization of distant metastases at diagnosis		
Lung	1 (5)	10 (27)
Lymph node	2 (9)	2 (5)
Bone	1 (5)	2 (5)
Brain	0 (0)	2 (5)
Liver	0 (0)	1 (3)
Tumor marker levels at the start of therapy		
AFP		
Normal	21 (95)	8 (22)†
High	0 (0)	27 (73)
NA	1 (5)	2 (5)
β-HCG		
Normal	18 (82)	25 (68)
High	4 (18)	9 (24)
NA	0 (0)	3 (8)
LDH		
Normal	10 (45)	7 (19)
High	10 (45)	25 (68)
NA	2 (9)	5 (13)
NLR, median (range)	4.2 (0.7-44.1)	6.3 (2.3-20.1)

(*continued on next page*)

Table 1
(*continued*)

Prognostic groups for patients with nonseminoma	
According to Necchi et al.[17]	
Surgery	
Yes	22 (59)
No	15 (41)
Pathology	
Viable cancer	7 (32)
Necrosis or teratoma	15 (68)
Lung metastases	
Yes	13 (35)
No	24 (65)
Poor	16 (43)
Good	21 (57)
According to Fedyanin et al.[18]	
Age	
$<$ 29 y	20 (54)
$\geq$ 29 y	17 (46)
Tumor size	
$\leq$ 10 cm	14 (38)
$>$ 10 cm	20 (54)
NA	3 (8)
Poor	7 (21)
Good	27 (79)
According to Hartmann et al.[19] [prognostic score]	
Metastases	
CNS	6 (16)[2]
Liver	3 (8)[1]
Lung	18 (49)[1]
High β-HCG	9 (24)[1]
Sum of prognostic scores (+2 for mediastinum)	
2	17 (50)
3	8 (22)
4	5 (14)
5	3 (8)
6	4 (11)
Intermediate[2-3]	25 (68)
Poor [>3]	12 (32)
According to Rodney et al.[20] [prognostic score]	
Extramediastinal extent	
Yes	29 (78) [1]
No	8 (22) [0]
Not yolk sac tumor	
Yes	26 (70) [1]
No	11 (30) [0]
β-HCG $>$ 1000 mIU/ml	
Yes	6 (16) [1]
No	28 (76) [0]
NA	3 (8)
Sum of prognostic scores	
0	2 (6)
1	10 (29)
2	17 (50)
3	5 (15)
According to Liu et al.[12]	
Extramediastinal extent	
No	8 (22)
Yes	29 (78)

(*continued on next page*)

Table 1 (*continued*)

Response rate	
OR (CR/PR)	26 (70)
SD/PD	11 (30)
Poor (no OR)	11 (30)
Medium (OR, extent)	19 (51)
Good (OR, no extent)	7 (19)

AFP, alpha-fetoprotein; BMI, body mass index; CNS, central nervous system; CR, complete response; HCG, human chorionic gonadotropin; LDH, lactate dehydrogenase; NA, not available; NLR, neutrophil-to-lymphocyte ratio; OR, objective response; PD, progressive disease; PR, partial response; SD, stable disease.

* Were categorized as nonseminoma according to elevated AFP levels.

† $P < 0.001$.

Efficacy of first line therapy

At the time of diagnosis 21 patients (5 S and 16 NS) had locally advanced, inoperable metastatic disease and out of them 13 (3 S and 10 NS) had distant spread. They received 3-4 BEP ± 1EP cycles as first line CHT. Two patients (1 S and 1 NS) were metastasectomized and 3 patients with NS were treated by RT prior to the first line CHT. The OR was 60% and 62.5% for S and NS, respectively. One to one patient presented stable disease, while 1 S and 5 NS progressed. The median follow-up was 117 (95%CI 62-126) months. The PFS and OS were calculated from the start of first treatment. The PFS rate at 5, 10, and 15 years for S was uniformly 60%, for NS was 12.5%, 0%, and 0%, respectively (log rank test $P = 0.045$). The median PFS was 5.7 months for NS. The OS rate for S at 5, 10, and 15 years was 80%, 80%, and 40%, respectively, and for NS was uniformly 12.5% (log rank test $P = 0.013$). The median OS was 169.3 and 11.1 months for S and NS, respectively.

Patients who progressed after neoadjuvant or adjuvant therapy received further therapy as follows: S: 1 patient RT and 1 metastasectomy + BEP (1 cycle); NS: 4 patients vinblastine+ifosfamide+cisplatin (VeIP) or etoposide+ifosfamide+cisplatin (VIP) and 2 patients other treatments (metastasectomy, adriamycin-based CHT). After progression further RT, CHT (VeIP, VIP, taxan-based, etc) or surgery was applied for 11 patients.

The OS curves for all patients are presented in Fig. 1. The influence of different parameters on OS was analyzed only for patients with NS, because only very few S cases progressed. The univariate analysis revealed that stage (I,II vs III); extramediastinal extent, OR after surgery + adjuvant CHT or first-line CHT, lung metastasis, surgery and NLR were statistically significant markers of survival. Patients with higher (≥median) NLR had significantly longer OS ($P = 0.014$).

Markers of survival

The prognostic model suggested by Necchi et al.[17] for NS resulted in a highly significant ($P = 6.5 \times 10^{-7}$) difference in OS (Fig. 2A), likewise the Hartmann's[19] model ($P = 1.4 \times 10^{-5}$) (Fig. 2C) and the Fedyanin's model[18] ($P = 0.033$) (Fig. 2B). The number of risk factors reported by Rodney et al.[20] were not associated with OS (data not shown). Significantly different OS curves ($P = 1.4 \times 10^{-4}$) were observed by combination of the 2 survival markers presented by Liu et al.[12] (Fig. 2D).

All variables with $P < 0.1$ in univariate analysis (age, tumor size, and β-HCG besides of the abovementioned parameters) were used in multivariate analysis, while stage, pulmonary metastases and surgery were excluded because of multicollinearity. Two variables proved to be independent markers of OS: OR (hazard ratio = 0.25; 95%CI 0.1-0.7; $P = 0.006$) and NLR (0.34; 0.1-0.96; 0.043). Combination of these variables resulted in significantly different survival curves ($P = 1.0 \times 10^{-4}$) (Fig. 3).

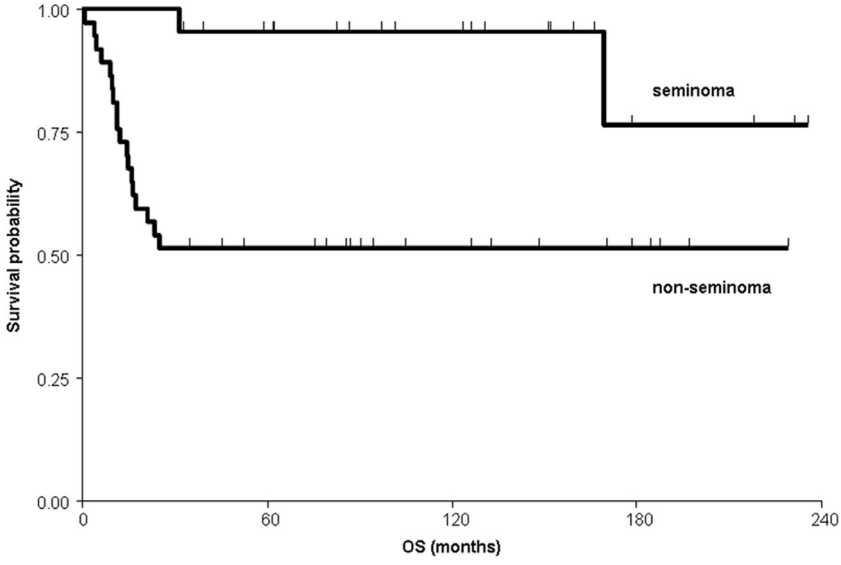

Fig. 1. Overall survival of patients with primary mediastinal germ cell tumor. Log rank test $P = 0.002$. Survival rate at 5, 10, and 15 years for nonseminoma is uniformly 51%, while for seminoma is 95%, 95%, and 76%, respectively.

Discussion

In this retrospective study the clinical features and outcomes of 59 consecutive patients with MGCT, who were treated at our institute over a 20-year period, were analyzed.

The frequency of symptoms in different series is strongly correlated to distribution of histology, and teratomas and S are more frequently discovered incidentally, because these tumors grow slowly.[5,21,22] Our and earlier studies proved that the histologic type is the most important prognostic factor.[14,20,23] S both in localized and in disseminated stage has a better prognosis than NS. All primary NS fall into the poor-risk category of the International Germ Cell Consensus Classification.[24]

Neoadjuvant treatment

Neoadjuvant CHT consisted of 3 BEP/EP cycles. Since 2016, when a study by Ranganath et al.[15] was published VIP is preferred over BEP, because patients are at high risk for bleomycin-related postoperative pulmonary complications.

Our 9 patients with localized S had 100% OR after BEP and further surgery was not necessary and no progression was observed. There are very few studies, which separately investigated a nonmetastatic cohort with S treated with preoperative CHT (Table 2). Lamarié et al.[11] presented nonmetastatic patients receiving primarily cisplatin-based CHT and 30% of patients underwent surgical resection, the others were treated by further RT or CHT. Forty percent of patients relapsed and 30% died. Napieralska et al.[25] reported BEP- and RT-treated patients and after treatment the majority of them presented CR and recurrence occurred only in 1 patient. In a study of Fizazi et al.[26] the patients were treated by platinum-based CHT and subsequent complete surgical resection was done in 33% of patients. Usually the histology in residual mass was necrosis. According to Albany et al.[27] the primary S represents a good-risk disease with a cure rate near 100% when treated with BEP/EP and thus no surgical resection is needed.

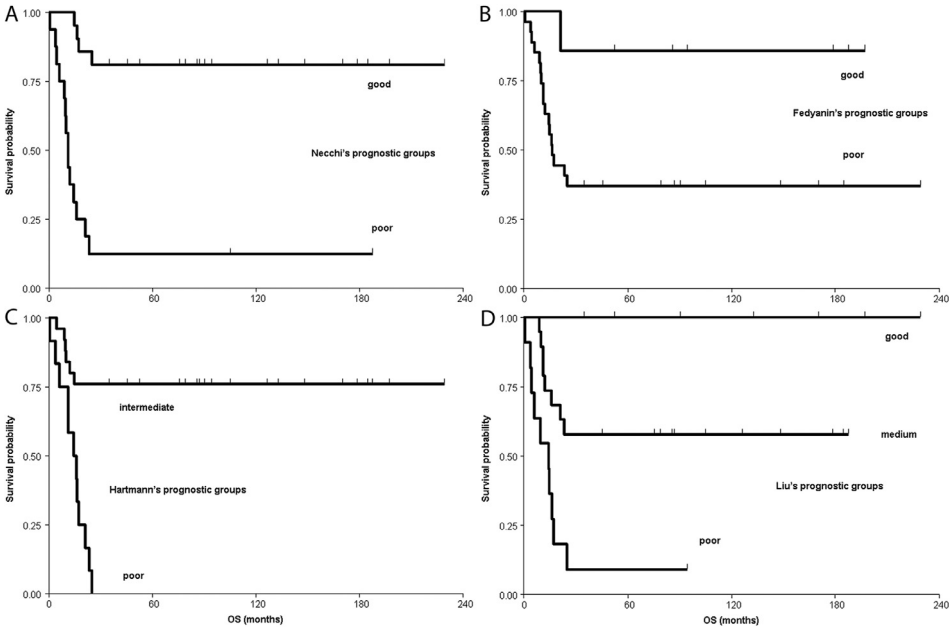

Fig. 2. Overall survival (OS) according to Necchi's (A), Fedyanin's (B), Hartmann's (C), and Liu's (D) prognostic model for patients with NS. Log rank test (A) $P = 6.5 \times 10^{-7}$; (B) $P = 0.033$; (C) $P = 1.4 \times 10^{-5}$; (D) $P = 1.4 \times 10^{-4}$.

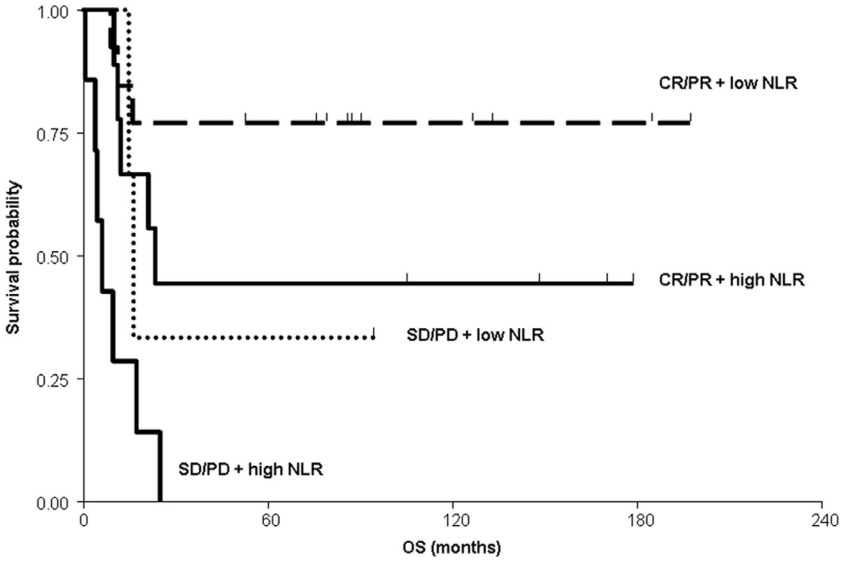

Fig. 3. Overall survival (OS) according to median neutrophil-to-lymphocyte ratio (NLR) and best response of patients with nonseminoma. Log rank test $P = 3.5 \times 10^{-4}$; survival rate at 5, 10, and 15 years for CR/PR + low NLR is uniformly 77%, for CR/PR + high NLR is uniformly 44.4%. CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

Table 2
Response and survival of patients with MGCT in our study and literature.

Seminoma				Nonseminoma				
Study	N	OR %	5-y OS %	Study	n	OR %	5-y OS %	mOS Months
Localized disease (stage I, II)								
Neoadjuvant CHT ± surgery								
[11]	10	90	84	[13]	<35		66	
[25]	8	88	100	[22]	56		63	
[26]	6	100	83	[28]	24		65	
This	9	100	100	[29]	16		80	
				[30]	11	91	64	
				[32]	5		60*	
				this	13	77	77	
Surgery ± adjuvant therapy								
[4]	7		86	[13]	<35		69	
[11]	8		100	[33]	14		21	8
[25]	8		100	this	8		88	NR
[26]	5		100					
This	8		100					
Metastatic disease (stage IIIA, IIIB)								
First line CHT								
[35]	15		67	[13]	<26		37	
[36]	5		100	[20]	6		17†	
This	5		95	[22]	19		26	
				[28]	28		36	9.6
				[29]	5		59	
				[37]	14		43	
				this	16		13	11.1

BEP, bleomycin + etoposid + cisplatin; CHT, chemotherapy; mOS, median OS; NR, not reached; OR, objective response; OS, overall survival.
* 4-year OS.
† 2-year progression-free survival.

The mainstay of treatment of nonmetastatic locally advanced (primarily inoperable) NS is cisplatin-based CHT, followed by surgery.[28] In a study of Wang et al. all patients (Moran-Suster's stage I/II) received platinum-based CHT as first treatment.[13] Our higher rate of 5-year OS may be due to the adjuvant CHT applied to 46% of patients. In a series of NS from Indiana University the initial treatment was cisplatin-based CHT and only those patients underwent surgical resection who did not achieved CR and adjuvant EP was administered if residual cancer was identified.[22] In a study by Sarkaria et al.[28] patients (Moran-Suster's stage I/II) were treated preoperatively with cisplatin-based CHT, however, the OS was measured from time of surgery and 4.5 months was the median interval from start of CHT to surgery and no further adjuvant treatment was reported. The 5-year OS rate was similar in our study to those reported by Kang et al,[29] where all except 1 patient received preoperative cisplatin-based CHT. The patients with nonmetastatic NS reported by Dulmet et al.[30] received preoperative PVB and for all with partial response (n = 6, 54.5%) salvage CHT was administered. Despite that the 5-year OS rate remained relatively low (Table 2), which may be explained by the frequent (91%) presence of yolk sac tumor (component) with poor prognosis.[31] Kay et al.[32] reported patients with nonmetastatic disease receiving preoperative cisplatin-based CHT. Forty percent of them died early (<3 month, because of surgical complications and postoperative brain metastases), but the others had long (>48 months) OS. CHT facilitated tumor removal in 2 patients whose disease has been previously declared inoperable.

Primary surgery ± adjuvant therapy

In our study surgery as, primary treatment (47% for all localized S) was followed by adjuvant BEP for all but 1 patients. Two patients with S received also adjuvant RT. No patients died during the study period. Lamarié et al.[11] presented nonmetastatic patients with S who primarily underwent surgery. They received adjuvant RT (88%) and/or CHT (25%) and remained disease-free during follow-up of 17-92 months (Table 2). In a study by Takeda et al.[4] patients with localized S postoperatively received RT (86%) and CHT (14%) and only 1 patient died after relapse at 29 months. Fizazi et al.[26] reported about patients treated by surgery and adjuvant cisplatin-based CHT (60%) or RT (40%). In another study by Napieralska et al.[25] surgery was followed by BEP (75%) and/or RT (75%). All patients responded with CR and only 25% of patients relapsed.

Albeit primary CHT and primary surgery followed by CHT both result in good survival rates, therefore, it seems that surgery does not play a role in the definitive treatment of localized S.[7]

In our study NS patients underwent surgery as primary treatment (38% of all localized NS) and 87.5% of them received adjuvant CHT (Table 2). Wang et al.[13] found that the 5-year OS for localized disease treated primarily by surgery (further CHT not specified) was 71.4% for R0 and 62.5% for R1/2. A median OS of 8 months could be calculated from data reported by Kolodzejski et al.[33] for patients with nonmetastatic NS treated primarily by surgical resection, however, the 71.4% of patients received postoperative CHT and/or 28.5% RT. The short survival may also be due to the relative high rate of yolk sac tumor (component) (43%) and incomplete resections (36%), moreover the modern CHT was available only for a part of patients.

Comparing the outcome for the post- vs preoperative CHT for localized NS patients it seems that in our study the postoperative CHT had some advantage (25% vs 30.8% relapses; 12.5% vs 23% deaths; 87.5% vs 77% 5-year OS, respectively). The histologic pattern for the 2 groups was different (eg the presence of yolk sac tumor [component] with poor prognosis[31] was 37.5% vs 46.2%, respectively [data not shown]). Similar results were reported by Liu et al.[34] however, the stage of disease was not reported. We suggest comparative investigations in larger series with homogeneous stage and histology.

Primary chemotherapy of metastatic patients

The S patients with disseminated disease had a worse prognosis than their localized counterparts (Table 2). These metastatic patients received first line BEP. One patient was metastasectomized. Nichols et al.[35] reviewed patients with advanced S treated by cisplatin-based CHT. Among them 47% presented distant metastases. Eighty percent of patients responded favorably and 67% are long survivors, while 33% with persistent or recurrent disease died. Jain et al.[36] followed-up for a median of 20 months patients treated by cisplatin-based CHT completed by surgical resection in 60% of patients and RT in 40% of cases.

Since the histologic diagnosis was made by needle biopsy and tumor markers, we could not rule out the possibility of NS elements, (especially in widespread disease) which can worsen the outcome. In a large cohort[14] resection of residual mass of mediastinal S after chemotherapy in 1 patient demonstrated mature teratoma, which indicates the initial presence of nonseminomatous elements.

Metastatic NS patients had a dismal outcome (Table 2). Rodney et al.[20] reported only the 2-year PFS rate and the median time to progression for newly diagnosed patients with metastases (some had undergone postchemotherapy resection of a residual mediastinal mass). For the whole cohort of 11 patients the median time to progression was even shorter (9.2 months). The 5-year OS rates in some studies[22,28,29,37] were higher than our results. In all above studies postchemotherapy surgery was applied. The 5-year OS rate in another study[13] was also longer than our results, while the 5-year PFS rates were comparable (11% and 13%), however, the exact number of patients and the resection rate after CHT were not detailed. The median OS reported

for the largest series[28] is similar to our findings. In our study for the entire NS group the OS at 5 years was 51%, which result is comparable to the best results of above studies.

Prognostic markers

We could validate 4 published prognostic models for NS.[12,17-19] Numerous findings suggested that inflammation has an important role in carcinogenesis and disease progression.[38] Among other serum level of CRP or albumin, hematologic markers of systemic inflammatory response, such as absolute white-cell count or NLR were found to be prognostic markers.[39] For testicular germ cell cancer several studies[16,40] investigated NLR as a predictive marker and the lower NLR was in strong correlation with longer survival. This is the first time that NLR was demonstrated to be a prognostic marker of OS in patients with primary mediastinal NS.

Acknowledgment

The authors thank Professor Dr. Attila Patócs for critical reading and useful suggestions.

References

1. Alanee SR, Feldman DR, Russo P, et al. Long-term mortality in patients with germ cell tumors: Effect of primary cancer site on cause of death. *Urol Oncol*. 2014;32 26.e9-26.e15. doi:10.1016/j.urolonc.2012.09.003.
2. McKenney JK, Heerema-McKenney A, Rouse RV. Extragonadal germ cell tumors: A review with emphasis on pathologic features, clinical prognostic variables, and differential diagnostic considerations. *Adv Anat Pathol*. 2007;14:69–92. doi:10.1097/PAP.0b013e31803240e6.
3. Gilligan TD, Seidenfeld J, Basch EM, et al. American Society of Clinical Oncology Clinical Practice Guideline on uses of serum tumor markers in adult males with germ cell tumors. *J. Clin. Oncol.*. 2010;28:3388–3404. doi:10.1200/JCO.2009.26.4481.
4. Takeda S, Miyoshi S, Ohta M, et al. Primary germ cell tumors in the mediastinum. *Cancer*. 2003;97:367–376. doi:10.1002/cncr.11068.
5. Moran CA, Suster S. Primary germ cell tumors of the mediastinum: I. Analysis of 322 cases with special emphasis on teratomatous lesions and a proposal for histopathologic classification and clinical staging. *Cancer*. 1997;80:681–690. doi:10.1002/(SICI)1097-0142(19970815)80:4⟨691::AID-CNCR7⟩3.0.CO;2-Q.
6. Weissferdt A, Moran CA. Staging of primary mediastinal tumors. *Adv Anat Pathol.*. 2013;20:1–9. doi:10.1097/PAP.0b013e31827b6619.
7. Ginsberg RJ. Mediastinal germ cell tumors: The role of surgery. *Semin Thorac Cardiovasc Surg.*. 1992;4:51–54.
8. Yonemori K, Kouno T, Ando M, et al. Influence of suboptimal treatment in patients with mediastinal primary non-seminomatous germ cell tumors. *Oncology*. 2010;78:34–39. doi:10.1159/000288647.
9. Radaideh SM, Cook VC, Kesler KA, et al. Outcome following resection for patients with primary mediastinal non-seminomatous germ-cell tumors and rising serum tumor markers post-chemotherapy. *Ann Oncol*. 2009;21:804–807. doi:10.1093/annonc/mdp516.
10. De Latour B, Fadel E, Mercier O, et al. Surgical outcomes in patients with primary mediastinal non-seminomatous germ cell tumours and elevated post-chemotherapy serum tumour markers. *Eur J Cardiothorac Surg*. 2012;42:66–71. doi:10.1093/ejcts/ezr252.
11. Lemarié E, Assouline PS, Diot P, et al. Primary mediastinal germ cell tumors. Results of a French retrospective study. *Chest*. 1992;102:1477–1483. doi:10.1378/chest.102.5.1477.
12. Liu TZ, Zhang DS, Liang Y, et al. Treatment strategies and prognostic factors of patients with primary germ cell tumors in the mediastinum. *J Cancer Res Clin Oncol*. 2011;137:1607–1612. doi:10.1007/s00432-011-1028-7.
13. Wang J, Bi N, Wang X, et al. Role of radiotherapy in treating patients with primary malignant mediastinal non-seminomatous germ cell tumor: A 21-year experience at a single institution. *Thorac Cancer*. 2015;6:399–406. doi:10.1111/1759-7714.12190.
14. Bokemeyer C, Nichols CR, Droz JP, et al. Extragonadal germ cell tumors of the mediastinum and retroperitoneum: Results from an international analysis. *J Clin Oncol*. 2002;20:1864–1873. doi:10.1200/JCO.2002.07.062.
15. Ranganath P, Kesler KA, Einhorn LH. Perioperative morbidity and mortality associated with bleomycin in primary mediastinal nonseminomatous germ cell tumor. *J Clin Oncol*. 2016;34:4445–4446. doi:10.1200/jco.2016.69.8910.
16. Jankovich M, Jankovichova T, Ondrus D, et al. Neutrophil-to-lymphocyte ratio as a predictor of preoperative tumor staging in testicular germ cell tumors. *Bratislava Med J*. 2017;118:510–512. doi:10.4149/BLL_2017_098.
17. Necchi A, Giannatempo P, Lo Vullo S, et al. A prognostic model including pre- and postsurgical variables to enhance risk stratification of primary mediastinal nonseminomatous germ cell tumors: The 27-year experience of a referral center. *Clin Genitourin Cancer*. 2015;13. doi:10.1016/j.clgc.2014.06.014.
18. Fedyanin M, Tryakin A, Mosyakova Y, et al. Prognostic factors and efficacy of different chemotherapeutic regimens in patients with mediastinal nonseminomatous germ cell tumors. *J Cancer Res Clin Oncol*. 2014;140:311–318. doi:10.1007/s00432-013-1567-1.

19. Hartmann JT, Nichols CR, Droz JP, et al. Prognostic variables for response and outcome in patients with extragonadal germ-cell tumors. *Ann Oncol*. 2002;13:1017–1028. doi:10.1093/annonc/mdf176.
20. Rodney AJ, Tannir NM, Siefker-Radtke AO, et al. Survival outcomes for men with mediastinal germ-cell tumors: The University of Texas M. D. Anderson Cancer Center experience. *Urol. Oncol.*. 2012;30:879–885. doi:10.1016/j.urolonc.2010.08.005.
21. Kalhor N, Moran CA. Primary germ cell tumors of the mediastinum: A review. *Mediastinum*. 2018;2:4. doi:10.21037/med.2017.12.01.
22. Ganjoo KN, Rieger KM, Kesler KA, et al. Results of modern therapy for patients with mediastinal nonseminomatous germ cell tumors. *Cancer*. 2000;88:1051–1056. doi:10.1002/(sici)1097-0142(20000301)88:5⟨1051::aid-cncr15⟩3.0.co;2-r.
23. Dechaphunkul A, Sakdejayont S, Sathitruangsak C, et al. Clinical characteristics and treatment outcomes of patients with primary mediastinal germ cell tumors: 10-years' experience at a single institution with a bleomycin-containing regimen. *Oncol Res Treat*. 2016;39:688–694. doi:10.1159/000452259.
24. International Germ Cell Cancer Collaborative Group. International Germ Cell Consensus Classification: A prognostic factor-based staging system for metastatic germ cell cancers. *J Clin Oncol*. 1997;15:594–603. doi:10.1200/JCO.1997.15.2.594.
25. Napieralska A, Majewski W, Osewski W, et al. Primary mediastinal seminoma. *J Thorac Dis*. 2018;10:4335–4341. doi:10.21037/jtd.2018.06.120.
26. Fizazi K, Culine S, Droz JP, et al. Initial management of primary mediastinal seminoma: Radiotherapy or cisplatin-based chemotherapy? *Eur J Cancer*. 1998;34:347–352. doi:10.1016/S0959-8049(97)10021-1.
27. Albany C, Kesler K, Cary C. Management of residual mass in germ cell tumors after chemotherapy. *Curr Oncol Rep*. 2019;21:5. doi:10.1007/s11912-019-0758-6.
28. Sarkaria IS, Bains MS, Sood S, et al. Resection of primary mediastinal non-seminomatous germ cell tumors: A 28-year experience at memorial sloan-kettering cancer center. *J Thorac Oncol*. 2011;6:1236–1241. doi:10.1097/JTO.0b013e31821d513e.
29. Kang CH, Kim YT, Jheon SH, et al. Surgical treatment of malignant mediastinal nonseminomatous germ cell tumor. *Ann. Thorac. Surg.*. 2008;85:379–384. doi:10.1016/j.athoracsur.2007.09.011.
30. Dulmet EM, Macchiarini P, Suc B, et al. Germ cell tumors of the mediastinum. A 30-year experience. *Cancer*. 1993;72:1894–1901. doi:10.1002/1097-0142(19930915)72:6⟨1894::AID-CNCR2820720617⟩3.0.CO;2-6.
31. Liu B, Lin G, Liu J, et al. Primary mediastinal yolk sac tumor treated with platinum-based chemotherapy and extended resection: Report of seven cases. *Thorac Cancer*. 2018;9:491–494. doi:10.1111/1759-7714.12591.
32. Kay PH, Wells FC, Goldstraw P. A multidisciplinary approach to primary nonseminomatous germ cell tumors of the mediastinum. *Ann Thorac Surg*. 1987;44:578–582. doi:10.1016/S0003-4975(10)62138-8.
33. Kołodziejski L, Duda K, Niezabitowski A, et al. Occurrence of malignant non-germ cell components in primary mediastinal germ cell tumours. *Eur J Surg Oncol*. 1999;25:54–60. doi:10.1053/ejso.1998.0600.
34. Liu Y, Wang Z, Peng ZM, et al. Management of the primary malignant mediastinal germ cell tumors: experience with 54 patients. *Diagn Pathol*. 2014;9:33. doi:10.1186/1746-1596-9-33.
35. Nichols CR, Roth B, Loehrer PJ, et al. Mediastinal germ cell tumors. *Adv Biosci*. 1994;91:113–117. doi:10.1016/B978-0-08-042198-8.50030-3.
36. Jain KK, Bosl GJ, Bains MS, et al. The treatment of extragonadal seminoma. *J Clin Oncol*. 1984;2:820–827. doi:10.1200/JCO.1984.2.7.820.
37. Fizazi K, Tjulandin S, Salvioni R, et al. Viable malignant cells after primary chemotherapy for disseminated nonseminomatous germ cell tumors: Prognostic factors and role of postsurgery chemotherapy—Results from an international study group. *J Clin Oncol*. 2001;19:2647–2657. doi:10.1200/JCO.2001.19.10.2647.
38. Colotta F, Allavena P, Sica A, et al. Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. *Carcinogenesis*. 2009;30:1073–1081. doi:10.1093/carcin/bgp127.
39. Huang ZL, Luo J, Chen MS, et al. Blood neutrophil-to-lymphocyte ratio predicts survival in patients with unresectable hepatocellular carcinoma undergoing transarterial chemoembolization. *J Vasc Interv Radiol*. 2011;22:702–709. doi:10.1016/j.jvir.2010.12.041.
40. Fankhauser CD, Sander S, Roth L, et al. Systemic inflammatory markers have independent prognostic value in patients with metastatic testicular germ cell tumours undergoing first-line chemotherapy. *Br J Cancer*. 2018;118:825–830. doi:10.1038/bjc.2017.467.