RESEARCH ARTICLE

Predictors of Outcome in Patients with Advanced Nonseminomatous Germ Cell Testicular Tumors

Tarkan Yetisyigit[1], Nalan Babacan[2], Yuksel Urun[3], Erdogan Selcuk Seber[3], Sener Cihan[3], Erkan Arpaci[3], Nuriye Yıldırım[3], Sercan Aksoy[3], Burcin Budakoglu[3], Nurullah Zengin[3], Berna Oksuzoglu[3] ,Banu Cicek Yalcin[1], Necati Alkis[3]

Abstract

Background: Predictor factors determining complete response to treatment are still not clearly defined. We aimed to evaluate clinicopathological features, risk factors, treatment responses, and survival analysis of patient with advanced nonseminomatous GCTs (NSGCTs). Materials and Methods: Between November 1999 and September 2011, 140 patients with stage II and III NSGCTs were referred to our institutions and 125 patients with complete clinical data were included in this retrospective study. Four cycles of BEP regimen were applied as a first-line treatment. Salvage chemotherapy and/or high-dose chemotherapy (HDCT) with autologous stem cell transplantation were given in patients who progressed after BEP chemotherapy. Post-chemotherapy surgery was performed in selected patients with incomplete radiographic response and normal tumor markers. Results: The median age was 28 years. For the good, intermediate and poor risk groups, compete response rates (CRR) were, 84.6%, 67.9% and 59.4%, respectively. Extragonadal tumors, stage 3 disease, intermediate and poor risk factors, rete testis invasion were associated with worse outcomes. There were 32 patients (25.6%) with non-CR who were treated with salvage treatment. Thirty-one patients died from GCTs and 94% of them had stage III disease. Conclusions: Even though response rates are high, some patients with GCTs still need salvage treatment and cure cannot be achieved. Non-complete response to platinium-based first-line treatment is a negative prognostic factor. Our study confirmed the need for a prognostic and predictive model and more effective salvage approaches.

Keywords: Advanced disease - germ cell tumor - nonseminomatous germ cell tumor - prognostic factors

Asian Pac J Cancer Prev, **15 (2)**, 831-835

Introduction

Testicular germ cell tumors (GCTs) accounts for only 1-2% of all male neoplasma but GCTs are the most common cancer of young men with the highest incidence in patients aged 15 to 40 years (Devesa et al., 1995; Beyer et al., 2013; Siegel et al., 2013). According to their histological features and serum tumor markers level GCTs are mainly divided into two groups: seminomas (30-45%) and nonseminomas (55-70%). Non-seminomatous type germ cell tumors (NSGCT) are clinically more aggressive (Motzer et al., 2012). GCTs are model for curable solid tumors for more than three decades (Einhorn and Donohue, 1977; S. D. Williams et al., 1987). More than 90% of patients, including those with disseminated disease, are cured with surgery, radiotherapy, and chemotherapy alone or combination of them (Krege et al., 2008; Motzer et al., 2012; Beyer et al., 2013; Siegel et al., 2013). Despite high cure rate, long-term disease free survival (DFS) cannot be achieved in 5-10% of patients and optimal salvage chemotherapy is still unknown for them (Motzer et al., 2012; Beyer et al., 2013). In this retrospective study, our aim was to evaluate clinicopathological features, risk factors, treatment responses, and survival analysis of patient with advanced NSGCTs.

Materials and Methods

Patients' characteristics

All patients who had pathologically confirmed diagnosis of NSGCT and treated between November 1999 and September 2011 at the Departments of Medical Oncology of participating centers (Ankara Dr. Abdurrahman Yurtaslan Education and Research Hospital and Ankara Numune Education and Research Hospital) were included in our retrospective reviews of tumor registry records. One hundred forty male with stage 2 and 3 NSGCT were screened and 125 patients with complete clinical data were included in the study.

Baseline variables including demographic data such as

*[1]Medical Oncology Department, Namık Kemal University Hospital, Tekirdag, [2]Medical Oncology Department, Cumhurriyet University Hospital, Sivas, [3]Department of Medical Oncology, Ankara, Turkey [&]Equal contributors *For correspondence: tyetisyigit@nku.edu.tr*

age, history, physical examination, serum tumor markers, pathologic evaluation, treatment types and outcome data were collected. For staging, American Joint Committee on Cancer (AJCC) TNM system (2010 seventh edition)(Edge SB, 2010) and for risk group assessment International Germ Cell Cancer Collaborative Group Prognostic Classification (IGCCCG) criteria were used("International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers. International Germ Cell Cancer Collaborative Group," 1997).

This study was approved by the institutional medical ethics review board and conducted according to Helsinki Declaration and good clinical practice.

Treatment

All patients were treated with three to four cycles of BEP regimen (bleomycin 30 mg, days 2,9, and 16;etoposide 100mg/m2 days1-5; and cisplatin 20 mg/m^2 days 1-5) according to their disease stage as first line treatment. Salvage chemotherapy and/or high-dose chemotherapy (HDCT) with autologous stem cell transplantation were applied in relapsed or refractory cases. In addition, surgery was performed in selected patients for postchemotherapy residual mass.

Evaluation of response and outcomes

After completion of the allocated chemotherapy, patients with normal levels of tumor markers and with no clinical or radiologic evidence of residual disease were classified as complete responders and were monitored without further therapy. Patients in whom markers normalized, but who showed evidence of residual mass, underwent surgery, unless the histologic examination showed viable cancer cells these patients also were classified as complete response. Progression free survival was defined as the time from diagnosis until relapse, disease progression or death, whichever occurred first. Overall survival (OS) was defined as the time from diagnosis until death from any cause or lost to follow-up.

Statistical analysis

The values are expressed as median or percentage, as appropriate. For comparison of the groups, Kruskal-Wallis analysis or chi-square tests were used. When between-group significance was determined, data were compared in pairs using the Mann-Whitney U test. Univariate and multivariate analysis was used to identify the risk factors for disease free survival and overall survival. All statistical analyses were performed using SPSS software (version 16.0; SPSS Inc., Chicago, IL, USA). All tests were two-tailed and a p value of less than 0.05 was considered significant.

Results

One hundred and twenty-five patients with NSGCT were included in this study. The median age was 28 years (range: 17-57). The most common symptom was painless mass, which 62.1% of patients (77 patients) had at presentation. While 110 patients (88%) had primary gonadal tumors, 15 patients (12%) had extra gonadal disease. Baseline demographic features are summarized in Table 1. The distribution of the histopathological characteristics of the primary tumor is summarized in Table 2.

Of these patients, 57 (45.4%) had stage 2 and 68 (54.4%) had stage 3 disease.According to IGCCCG risk classification 65 patients (52%) had good risk,28 (22.4%) patients had intermediate risk and 32(25.6%) patients had poor risk disease. Regional and non-regional lymphadenopathy was documented in 46.4% and 7.2% of patients, respectively. In addition, 27.2% patients presented with lung metastases and 19.2% had extra pulmonary metastatic lesions.

Response

After radical orchiectomy all patients were given platinum based combination chemotherapy (123 patients were treated with BEP and two patients with EP). In all cohort, complete response rate (CRR) was 74.45 (93

Table 1. Patient Characteristics

Variables		n
Median age, years (range)		28 (17-57)
Painless mass as presenting symptom n;%		77; 62.1
Time to diagnosis, median months (range)		2 (1-24)
Primary tumor	Gonadal n;%	110; 88
	Extra-Gonadal n;%	15; 12
Stage	Stage 2 n;%	42; 33.6
	Stage 3 n;%	83; 66.4
Risk stratification	Good n;%	65; 52.0
	Intermediate n;%	28; 22.4
	Poor n;%	32; 25.6
Metastatic disease	Regional n;%	58; 46.4
	Non Regional LAP n;%	9; 7.2
	Pulmonary n;%	34; 27.2
	Extra pulmonary n;%	24; 19.2
Metastatic disease	Thoracic n;%	34; 27.2
	Extra Thoracic n;%	24; 19.2
Postoperative treatment modalities		
	RT n;%	
	EP n;%	2; 1.6
	BEP n;%	123; 98.4
Response to Treatment	Complete response	93; 74.5
	Non complete response	32; 24.7
	Unknown	1; 0.8
OS median months (range)		24 (0-143)
PFS median months (range)		17 (0-143)

Table 2. Histopathological Characteristics of Patient Tumors

Pure	n=36	% 30,5
Embriyonal	16	44.40%
Yolk sac	13	36.1%
Teratoma	5	13.8%
Choriocarcinoma	2	5.5%
Mixed	n=82	69.4%
Seminoma	34	17.2%
Teratoma	54	27.4%
Embriyonal	60	30.4%
Yolk sac	44	22.3%
Choriocarcinoma	5	2.5%

Table 3. Factors Influencing Complete Response

Variables	CR	Non-CR	p
Median age, years (range)	28(17-49)	27(17-55)	0.840
Median Time to diagnosis , months (range)			
2(1-24)	2(1-24)	0.658	
Primary tumor			
Gonadal n;%	55;98.2	55;79.7	0.001*
Extra-Gonadal n;%	1;1.8	14;20.3	
Stage			
Stage 2 n;%	30;71.4	12;28.6	<0.001*
Stage 3 n;%	26;31.3	57;68.7	
Risk stratification			
Good n;%	40;61.5	25;38.5	
Intermediate n;%	11;39.3	17;60.7	<0.001*
Poor n;%	5;15.6	27;84.4	
Metastatic disease			
Lung metastasis	13;38.2	21;61.8	0.059
Extra thoracic metastasis	6;17.6	28;82.4	
Embryonal carcinoma component			
Absent	41;51.9	38;48.1	0.081
Present	14;35	26;65	
LDH levels			
Normal	26;33.8	51;66.2	0.005*
High	17;65.4	9;34.9	
Median OS months, (range)	30(2-143)	17(0-134)	0.007*
Median PFS months, (range)	25(2-143)	7(0-88)	<0.001*

*statistically significant

Table 4. Univariate Analysis of Factors Influencing 5 Year DFS

Variables		n	p
Stage	Stage 2	83	<0.001*
	Stage 3	33	
Age	<35	49	0.891
	>35	54	
Risk stratification	Good	70	
	Intermediate	23	<0.001*
	poor	33	
Rete testis invasion	Absent	57	0.079
	Present	39	
Primary tumor location	Gonadal	57	<0.001*
	Extra gonadal	0	
β HCG levels	Normal	58	0.543
	High	46	
LDH levels	Normal	64	0.104
	High	51	
Embryonal carcinoma component			
	Absent	35	0.131
	Present	61	

*statistically significant

patients), non-CRR was 25.5% (32 patients), and in one patient response was unknown. CRR according to good,intermediate and poor risk groups were 84.6%,67.9% and 59.4% ,respectively. The CRR was significantly lower in patients with extragonadal tumors, stage 3 disease, intermediate and poor risk factors, rete testis invasion, elevated LDH levels ($p<0.05$). In addition, complete response was significantly correlated with both PFS and OS ($p<0.05$). There were no statistically significant relapse rates differences between the risk groups ($p>0.05$).

Outcome

The median OS was 24 months and 5 and 10 years OS rates were 67% and 63% respectively. Stage, risk group, presence of rete testis invasion and extragonadal disease were significantly associated with OS (Table 4). The median PFS was 17 months and 5-10 years PFS rates were 50%-33%, respectively. In univariate analysis, advanced stage having poor risk factors, and extragonadal disease were associated with PFS (Table 3). Embryonel carcinoma component was associated worse overall survival rates. Presence of rete testis invasion demonstrated a nonsignificant trend association with the PFS (p 0.079).

Table 5. Univariate Analysis of Factors Influencing 5 Year Overall Survival

Variables		n	p
Stage	Stage 2	92	<0.001*
	Stage 3	55	
Age	<35	65	0.748
	>35	74	
Risk stratification	Good	86	
	Intermediate	50	<0.001*
	poor	46	
Rete testis invasion	absent	74	0.049*
	present	63	
Primary Tumour Size	<4cm	85	0.057
	>4cm	59	
Lymphovascular invasion	absent	85	0.210
	present	63	
Primary tumor location	Gonadal	57	0.001*
	Extragonadal	0	
AFP levels	Normal	83	0.088
	High	63	
LDH levels	Normal	86	0.095
	High	66	
Embryonal component	absent	51	0.007*
	present	71	

*statistically significant

Thiry-two patients were considered as non complete responders. Among these, 10 patients were operated for residual disease. Post-operative pathological examination revealed viable tumors in 5 patients and teratoma in the remaining 5 patients. Twenty-two patients in the incomplete responders group received various salvage therapies; mainly TIPE and VIP chemotherapy regimens. In addition 5 patients received autolog bone marrow transplantation.

During the follow up period, 31 patients died (2 patients had stage 2 and 29 patients had stage 3 disease). Seven,10 and 14 patients had good, intermediate, poor risk factors, respectively.8(%25,5)patients had extragonadal disease and 23 (%74,5)patients had primary gonadal disease. 12 (%38) patients who had complete response and 19 (%62) patients with incomplete response died at the end of study period.

Discussion

The data from this study show that extragonadal disease, stage 3 disease, intermediate and poor risk factors, and rete testis invasion were associated with response rate, PFS, and OS.

Standard treatment of advanced NCGCTs is platinum

based chemotherapy (Williams et al., 1987; Nichols et al., 1991; Horwich et al., 1997; de Wit et al., 1998). Although the GCTs are highly treatable disease with platinum based combination regimens, cure cannot be achieved in 20-30% of patients with advanced disease with first line chemotherapy (Ataergin et al., 2007; Keskin et al., 2012). The role of more intensive treatment and as well as high dose treatment with stem cell rescue have been investigated as a first-line treatment. Despite higher toxicity none of these experimental regimens as part of first-line therapy improves outcome in patients with advanced disease and this approach is currently not recommended for patients poor risk (Kaye et al., 1998; Droz et al., 2007; Motzer et al., 2007; Daugaard et al., 2011). As expected, treatment outcomes are significantly associated with patients risk group (International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers. International Germ Cell Cancer Collaborative Group, 1997). Ten percent of patients with good risk group and 20% of intermediate risk group did not have CR, as compared to 50% of the patients with poor prognosis (International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers. International Germ Cell Cancer Collaborative Group, 1997; Mazumdar et al., 2001). In our multicenter study which included patients with stage 2 and 3 NSGCTs, 5 years OS rates were 92% and 55% and 5 years DFS rates were 83% and 33%, respectively. According to good, intermediate, and poor risk group statification, CRRs were 84.6%, 67.9%, and 59.4%, respectively. These results are compatible with previous studies (Ataergin et al., 2007; Keskin et al., 2012).

Trials after announcement of IGCCCG criteria in 1997 have aimed to identify predictive and prognostic factors for the 20-30% of the patients group who did not have complete remission and who died because of their disease. In the literature published before 1997 in which factors influencing complete response were searched, elevation of levels of tumor markers, especially beta HCG and AFP(Droz et al., 1988; Hanson et al., 1993; Schmoll and Beyer, 1998; Stoter et al., 1987),non-pulmonary metastasis and retroperitoneal tumor size (Javadpour and Young, 1986; Aass et al., 1991; Hanson et al., 1993) were reported as predictive factors. In a recently published retrospective study, rate of decline of tumor marker levels is also reported to have a predictive value (Keskin et al., 2012). In our study, we observed that having extragonadal tumor, stage 3 disease, intermediate and poor risk factors, a high serum LDH level had an inverse relationship with obtaining complete response ($p<0.05$). It is also noteworthy to note that complete responders had significantly longer PFS and OS.

We did not observe any major differences regarding relapse rates between different risk groups. One plausible explanation could be that the size of the study group was not large enough to detect such a difference. Retrospective nature of the study could also have obscured our observations.

Presence of rete testis invasion has been associated with post-orchiectomy relapse in patients with early stage GCTs (Kamba et al., 2010; Vogt et al., 2010; Warde et al., 2002), in present study it was found to be inversely correlated with complete response ($p=0.049$). Additionally this factor was observed to be significantly associated with decreased overall survival. We conclude that rete testis invasion should be assessed in larger multicenteric studies as a potential prognostic factor in advanced disease.

Van djick 2004 (van Dijk et al., 2004) and Kolmansberger (Kollmannsberger et al., 2000) have criticized IGCCCG classification for the lack of definition of risk factors responsible for treatment response. Also in line with these observations scoring systems which include factors predicting complete response have been proposed (Hartmann et al., 2002). Such scoring systems may have the advantage of selecting patients in intermediate and poor risk groups who may carry a different prognosis.

The effect of non pulmonary metastasis on prognosis comes forward as the most important bad prognostic factor at Kollmansberger, van Dijck and Hartman's studies (Hartman et al., 2002; Kollmannsberger et al., 2000; van Dijk et al., 2004). However we failed to find such a significant correlation in our study group. We speculated that the relatively small number of patients having non pulmonary metastatic disease have prevented us from reaching any meaningful observation. Although the presence of embryonal component was inversely associated with complete response, this was not statistically significant ($p=0.091$).As reported previously, presence of embryonal carcinoma was related with poor survival rates in our cohort (Javadpour and Young, 1986; Sweeney et al., 2000; Pohar et al., 2003; Williams et al., 2011).

In conclusion, though GCTs are a highly curable disease, some patients still have a poor prognosis and optimum salvage treatment for those is still unknown. This situation gives a big responsibility on treating physicians to provide an accurate and precise treatment to their patients. Scoring system and molecular based markers are still needed to predict the patient group who don't give a complete response to chemotherapy.

References

Aass N, Klepp O, Cavallin-Stahl E, Dahl O, Wicklund H, et al (1991). Prognostic factors in unselected patients with nonseminomatous metastatic testicular cancer: a multicenter experience. *J Clin Oncol*, **9**, 818-26.

Ataergin S, Ozet A, Arpaci F, et al (2007). Outcome of patients with stage II and III nonseminomatous germ cell tumors: results of a single center. *Indian J Cancer*, **44**, 6-11.

Beyer J, Albers P, Altena R, et al (2013). Maintaining success, reducing treatment burden, focusing on survivorship: highlights from the third European consensus conference on diagnosis and treatment of germ-cell cancer. *Ann Oncol*, **24**, 878-88.

Daugaard G, Skoneczna I, Aass N, et al (2011). A randomized phase III study comparing standard dose BEP with sequential high-dose cisplatin, etoposide, and ifosfamide (VIP) plus stem-cell support in males with poor-prognosis germ-cell cancer. An intergroup study of EORTC, GTCSG, and Grupo Germinal (EORTC 30974). *Ann Oncol*, **22**, 1054-61.

de Wit R, Stoter G, Sleijfer DT, et al (1998). Four cycles of BEP vs four cycles of VIP in patients with intermediate-prognosis

metastatic testicular non-seminoma: a randomized study of the EORTC Genitourinary Tract Cancer Cooperative Group. European Organization for Research and Treatment of Cancer. *Br J Cancer*, **78**, 828-32.

Devesa SS, Blot WJ, Stone BJ, et al (1995). Recent cancer trends in the United States. *J Natl Cancer Inst*, **87**, 175-82.

Droz JP, Kramar A, Biron P, et al (2007). Genito-Urinary Group of the French Federation of Cancer. Failure of high-dose cyclophosphamide and etoposide combined with double-dose cisplatin and bone marrow support in patients with high-volume metastatic nonseminomatous germ-cell tumours: mature results of a randomised trial. *Eur Urol*, **51**, 739-746.

Droz JP, Kramar A, Ghosn M, et al (1988). Prognostic factors in advanced nonseminomatous testicular cancer. A multivariate logistic regression analysis. *Cancer*, **62**, 564-8.

Edge SB BD, Compton CC (2010). AJCC Cancer Staging Manual. New York, NY: Springer.

Einhorn LH, Donohue J.(1977). Cis-diamminedichloroplatinum, vinblastine, and bleomycin combination chemotherapy in disseminated testicular cancer. *Ann Intern Med*, **87**, 293-8.

Hanson PR, Belitsky P, Millard OH, Lannon SG. (1993). Prognostic factors in metastatic nonseminomatous germ cell tumours. *Can J Surg*, **36**, 537-40.

Hartmann JT, Nichols CR, Droz JP, et al (2002). Prognostic variables for response and outcome in patients with extragonadal germ-cell tumors. [Multicenter Study]. *Ann Oncol*, **13**, 1017-28.

Horwich A, Sleijfer DT, Fossa SD, et al (1997). Randomized trial of bleomycin, etoposide, and cisplatin compared with bleomycin, etoposide, and carboplatin in good-prognosis metastatic nonseminomatous germ cell cancer: a Multiinstitutional Medical Research Council/European Organization for Research and Treatment of Cancer Tria. *J Clin Oncol*, **15**, 1844-52.

International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers. International Germ Cell Cancer Collaborative Group (1997). *J Clin Oncol*, **15**, 594-603.

Javadpour N, Young JD, (1986). Prognostic factors in nonseminomatous testicular cancer. J Urol, 135, 497-499.

Kamba T, Kamoto T, Okubo K, et al (2010). Outcome of different post-orchiectomy management for stage I seminoma: Japanese multi-institutional study including 425 patients. *Int J Urol*, **17**, 980-7.

Kaye SB, Mead GM, Fossa S, et al (1998). Intensive induction-sequential chemotherapy with BOP/VIP-B compared with treatment with BEP/EP for poor-prognosis metastatic nonseminomatous germ cell tumor: a Randomized Medical Research Council/European Organization for Research and Treatment of Cancer study. *J Clin Oncol*, **16**, 692-701.

Keskin S, Ekenel M, Basaran M, Bavbek S (2012). Predictive value of marker half-life in relapsed and nonrelapsed nonseminomatous germ cell testicular tumor patients undergoing chemotherapy. [Comparative Study]. *Am J Clin Oncol*, **35**, 369-72.

Kollmannsberger C, Nichols C, Meisner C, et al (2000). Identification of prognostic subgroups among patients with metastatic 'IGCCCG poor-prognosis' germ-cell cancer: an explorative analysis using cart modeling. *Ann Oncol*, **11**, 1115-20.

Krege S, Beyer J, Souchon R, et al (2008). European consensus conference on diagnosis and treatment of germ cell cancer: a report of the second meeting of the European Germ Cell Cancer Consensus Group (EGCCCG): part II. *Eur Urol*, **53**, 497-513.

Mazumdar M, Bajorin DF, Bacik J, et al (2001). Predicting outcome to chemotherapy in patients with germ cell tumors: the value of the rate of decline of human chorionic gonadotrophin and alpha-fetoprotein during therapy. *J Clin Oncol*, **19**, 2534-41.

Motzer RJ, Agarwal N, Beard C, et al (2012). National Comprehensive Cancer, N. Testicular cancer. [Practice Guideline]. *J Natl Compr Canc Netw*, **10**, 502-35.

Motzer RJ, Nichols CJ, Margolin KA, et al (2007). Phase III randomized trial of conventional-dose chemotherapy with or without high-dose chemotherapy and autologous hematopoietic stem-cell rescue as first-line treatment for patients with poor-prognosis metastatic germ cell tumors. *J Clin Oncol*, **25**, 247-56.

Nichols CR, Williams SD, Loehrer PJ, et al (1991). Randomized study of cisplatin dose intensity in poor-risk germ cell tumors: a Southeastern Cancer Study Group and Southwest Oncology Group protocol. *J Clin Oncol*, **9**, 1163-72.

Pohar KS, Rabbani F, Bosl GJ, et al (2003). Results of retroperitoneal lymph node dissection for clinical stage I and II pure embryonal carcinoma of the testis. *J Urol*, **170**, 1155-8.

Schmoll HJ, Beyer J (1998). Prognostic factors in metastatic germ cell tumors. [Review]. *Semin Oncol*, **25**, 174-85.

Siegel R, Naishadham D, Jemal A. (2013). Cancer statistics, 2013. *CA Cancer J Clin*, **63**, 11-30.

Stoter G, Sylvester R, Sleijfer DT, et al (1987). Multivariate analysis of prognostic factors in patients with disseminated nonseminomatous testicular cancer: results from a European Organization for Research on Treatment of Cancer Multiinstitutional Phase III Study. *Cancer Res*, **47**, 2714-8.

Sweeney CJ, Hermans BP, Heilman DK, Foster RS, Donohue JP, et al (2000). Results and outcome of retroperitoneal lymph node dissection for clinical stage I embryonal carcinoma--predominant testis cancer. *J Clin Oncol*, **18**, 358-62.

van Dijk MR, Steyerberg EW, Stenning SP, Dusseldorp E, Habbema JD (2004). Survival of patients with nonseminomatous germ cell cancer: a review of the IGCC classification by Cox regression and recursive partitioning. *Br J Cancer*, **90**, 1176-83.

Vogt AP, Chen Z, Osunkoya AO. (2010). Rete testis invasion by malignant germ cell tumor and/or intratubular germ cell neoplasia: what is the significance of this finding? *Hum Pathol*, **41**, 1339-44.

Warde P, Specht L, Horwich A, et al (2002). Prognostic factors for relapse in stage I seminoma managed by surveillance: a pooled analysis. [Meta-Analysis]. *J Clin Oncol*, **20**, 4448-52.

Williams SB, Kacker R, Winston D, et al (2011). Predictors of positive retroperitoneal lymph nodes in patients with high risk testicular cancer. *J Urol*, **186**, 2245-8.

Williams SD, Birch R, Einhorn LH, et al (1987). Treatment of disseminated germ-cell tumors with cisplatin, bleomycin, and either vinblastine or etoposide. *N Engl J Med*, **316**, 1435-40.