Published in final edited form as:

Urol Oncol. 2012 ; 30(4): . doi:10.1016/j.urolonc.2010.05.011.

Recurrent seminomas: Clinical features and biologic implications

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Abstract

Objectives—Certain patients with seminoma and clinically atypical phenotypes—visceral metastases, elevated levels of β human chorionic gonadotropin (β HCG), and/or recurrent disease—have a poor prognosis. The primary goal of this pilot study was to characterize the clinical characteristics and treatment profile of these rare patients. We also wished to test whether these tumors expressed any specific biomarkers that might distinguish them as a unique subtype of seminoma.

Materials and methods—We retrospectively identified 25 patients with a history of seminoma plus visceral metastases, β HCG levels >200 mU/ml, and/or recurrent disease. We reviewed these patients' histories for treatment efficacy and clinical outcome. Tissue samples were available from 6 of those patients, and we studied them for expression of the markers OCT 3/4, PLAP, CD30, TRA-1-60, c-kit, and gp200. We compared our results with the expression of those markers in tissue samples from mixed seminoma/embryonal carcinomas and classic seminomas.

Results—Our analysis suggested that certain chemotherapeutic regimens (such as ifosfamide, paclitaxel, and cisplatin) are efficacious for the treatment of patients with these atypical seminomas. Further, specimens from the atypical seminomas generally had staining profiles that resembled those of classic seminomas and the seminoma components in mixed germ-cell tumors, but the profiles differed from those of the embryonal carcinoma components in the same mixed germ-cell tumors.

Conclusions—Although these atypical seminomas tend to be resistant to chemotherapy, they may still respond to certain chemotherapeutic regimens. Our pilot immunohistochemical study

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also suggested that the unique phenotypes associated with these atypical seminomas do not result from any relationship with embryonal carcinomas. More study is needed to confirm these initial findings.

Keywords

Seminoma; Testicular neoplasms; Embryonal carcinoma; TRA-1-60; gp200

1. Introduction

The clinical course of “atypical” seminomas is believed to be more aggressive than that of classic seminomas [1,2]. For instance, in a Memorial Sloan-Kettering series, 9% of patients with advanced seminoma experienced a relapse at a median time of 16 months after having had a complete remission [3]. Those patients with an elevated β human chorionic gonadotropin (β HCG) concentration had a worse clinical outcome in that study. In a retrospective study conducted at Indiana University, 33% of patients with recurrent seminoma experienced a relapse within 13 months of initiation of salvage chemotherapy. Of these, 88% of patients died from progressive seminoma [4]. In a more recent Memorial Sloan-Kettering study, the 2-year survival rate was 57% for patients with recurrent seminoma who had received conventional-dose ifosfamide-cisplatin combination salvage chemotherapy or high-dose salvage chemotherapy followed by autologous stem-cell rescue; however, only 8% of those patients who had experienced an incomplete response were alive at the last follow-up [5]. Another group, in Marburg, Germany, found that 38% of patients with recurrent seminoma who received high-dose salvage chemotherapy (second or third line) were alive at 4.5 years. Treatment was more likely to fail in those patients with nonpulmonary visceral metastases, short relapse-free intervals, and cisplatin-refractory tumors [6]. Finally, in a study at Institut Gustave Roussy in France, 21% of patients developed recurrent seminoma at a median of 8.8 months. The 5-year overall survival rate after a first recurrence was 33%. In particular, patients with seminoma who had metastasis in the central nervous system or liver at the time of diagnosis had a 5-year survival rate of only 7% [7].

In consideration of all these findings, we speculated that a subtype of seminoma exists which, for our purposes, we have called “atypical,” that may account for the poor outcome in some patients. We have defined atypical seminomas clinically as those that have a propensity to display visceral metastasis (e.g., brain or liver), show evidence of recurrent disease after radiation therapy or chemotherapy, and/or are associated with a relatively high serum concentration of β HCG (i.e., >200 mU/ml). Our main goal in this study was to characterize the treatment profile and clinical characteristics of these rare patients. We also wished to test, as a pilot study, whether these tumors express any specific biomarkers that might distinguish them as a unique subtype of seminoma. Because of their visceral metastases, and according to some intriguing findings in the literature [8], we hypothesized that some atypical seminomas are biologically related to embryonal carcinomas.

For instance, several reports have suggested that the presence of certain markers can differentiate an atypical seminoma from a classic seminoma. In particular, 1 report noted that some seminomas exhibit a molecular profile that is more similar to that of embryonal carcinomas than it is to that of classic seminomas [8]. The markers that were used to distinguish between the seminomas in that microarray study included CD30. Additionally, seminomas have been reported to express the gp230 glycoform of a tumor-specific glycoprotein that is associated with terminal differentiation, whereas nonseminomas express gp200, an embryonic version of the same glycoprotein [9]. Further, expression of the

embryonal marker TRA-1-60 in seminoma may distinguish atypical seminomas and elucidate the origin of these tumors [10].

As such, we retrospectively evaluated the clinical characteristics and treatment profiles of patients with atypical seminomas in this study. We also report the results of our pilot study of immunohistochemical staining (for the markers OCT 3/4, PLAP, CD30, TRA-1-60, c-kit, and gp200) of all available archived tissues from these patients; we compared the results with those from mixed seminoma/embryonal carcinoma and classic seminoma tissues.

2. Materials and methods

2.1. Source of clinical data

The records from 301 men with seminoma diagnosed from July 28, 1995, through August 9, 2006 are available in the data and information system called Genitourinary Research Unlimited (GURU) in the Department of Genitourinary Medical Oncology at The University of Texas M. D. Anderson Cancer Center. From among those records, we identified 25 patients who had been diagnosed with a primary testicular seminoma plus at least 1 of the following 3 requirements: evidence of visceral metastases (e.g., in the brain, liver, or bone); development of recurrent disease after chemotherapy or radiotherapy; serum β HCG concentration of >200 mU/ml at the time of diagnosis or recurrence. Their serum α fetoprotein concentration must be within normal limits at the time of diagnosis or recurrence and there must be no pathologic evidence of nonseminomatous tumor. Patients with extragonadal seminomas were excluded from this study. A chart review was completed for each patient.

The patients' clinical histories and laboratory results were collected from their medical records and from M. D. Anderson Cancer Center's data-management computer system (NETPASS or ClinicStation). Survival data were obtained from the medical records or from the Social Security Death Index interactive search website (<http://ssdi.genealogy.rootsweb.com/>). For the purposes of this study, those patients whose medical records indicated no evidence of disease for more than 5 years were defined as having been cured of their atypical seminomas. Patients were considered to have stable atypical seminomas if there was no evidence of any active or progressive disease. Overall survival time was determined from the time of diagnosis to the time of death.

2.2. Source of tissue specimens

Archived tumor samples from 6 of the 25 patients we identified were available for our study. For comparison, we also obtained tissues from patients with classic seminomas, which had been archived from January 1, 2001, through December 31, 2006. Owing to the requirements of our institutional review board (IRB), we were permitted to use only those tissue samples that had been collected at our own institution; as a result, we could use only 4 of the 10 archived specimens of classic seminomas that we identified. We also extended our search to include tissues that had been archived from January 1, 1950 through December 31, 2006, and found 10 specimens from patients with mixed germ cell tumor; 7 of those specimens contained embryonal carcinoma with at least 5% seminoma. All of the tissues we collected (except for that from 1 of the 4 patients with classic seminoma) contained viable tumor.

Written informed consent to use their clinical data and archived specimens had been obtained from all patients when they were seen at M. D. Anderson, and the laboratory protocol for this study was approved by our IRB.

All clinical review and staining were completed during the summer of 2008.

2.3. Immunohistochemical testing

In summary, as noted above, archived tissue blocks were available for 6 of the 25 patients we identified as having atypical seminoma according to our criteria. In addition, tissues for use as comparisons were available from 3 patients with classic seminomas and from 7 with mixed embryonal carcinomas.

Standard hematoxylin and eosin staining was performed on each of the samples. Immunohistochemical staining for OCT 3/4, PLAP, CD30, c-kit, and gp200 was performed by using a DAKO Autostainer (DAKO North America Inc., Carpinteria, CA) with AEC as the chromogen. TRA-1-60 stains were done manually. Sections of the tumors were cut at 5- μ m thickness, deparaffinized according to standard procedures, and labeled with antibodies against OCT 3/4 (goat polyclonal antibody, 1:300; sc-8626; Santa Cruz Bio-technology, Inc., Santa Cruz, CA), PLAP (mouse monoclonal antibody, 1:25; MS-734-R7; Lab Vision Products, Fremont, CA), CD30 (mouse monoclonal antibody, 1:20; SIG-3325; Signet [Covance Company], Princeton, NJ), TRA-1-60 (mouse monoclonal antibody, 1:100; ab16288; Abcam Inc., Cambridge, MA), c-kit (CD117) (polyclonal rabbit anti-human antibody, 1:100; DAKO), and gp200 (mouse monoclonal antibody, 1:50; M3632; DAKO).

For OCT 3/4, antibody incubation required 30 minutes after pretreatment with avidin for 20 minutes and biotin for 20 minutes to block nonspecific binding to endogenous biotin. For c-kit, epitope retrieval was done for 15 minutes in citrate buffer; for CD30, in Tris-EDTA buffer for 20 minutes; and for PLAP, TRA-1-60, and gp200, for 20 minutes in citrate buffer. All were incubated at 100°C.

Positive control tissues were stained with each set of antibodies in parallel with our test tissues: embryonal carcinoma was used as a positive control for TRA-1-60, and renal-cell carcinoma and rete testis tissues for gp200 [11,12]; standard positive controls were used for the remaining antibodies. Tissue staining without the primary antibody was used as the negative control for gp200 and TRA-1-60, and standard negative controls were used for the other antibodies. DAB was used to bring out color, and hematoxylin was the counterstain.

An Olympus BX41 microscope was used to analyze the slides at 200 $\times$ magnification. The results of the immunohistochemical analysis were arbitrarily defined as positive if more than 50% of the tumor cells showed robustly positive staining; as focally positive, if 5% to 50% of the tumor cells showed positive staining; and as negative, if less than 5% of the tumor cells showed positive staining.

3. Results

3.1. Clinical characteristics

The clinical characteristics of the 25 patients we identified as having had atypical seminoma are summarized in Table 1. The median age of the patients at the time of diagnosis was 34 years, and the median β HCG concentration was 343 mU/ml. Of the 25 patients total, 14 (56%) were defined as atypical due to β HCG >200 mU/ml, 15 (60%) were defined as atypical due to visceral metastases, and 15 (60%) because of later recurrence. Fifteen (60%) patients had at least 2 of the 3 above criteria.

Table 2 presents the characteristics of the metastases that had been identified among those 25 patients. Almost all patients (88%) had had tumor in the retroperitoneal lymph nodes (RPLNs); the patients without RPLN metastases had been pretreated with radiation for their clinical stage I or II diseases. The second most common site of metastasis was the liver (32%), followed by lymph nodes other than the RPLNs (i.e., cervical, pelvic, and supraclavicular; 24%). Among the patients with β HCG concentrations >200 mU/ml, 39%

had metastases in “atypical” locations, ranging from hilar/mediastinal lymph nodes to visceral organs.

The number of chemotherapy regimens given and the clinical outcome of the 25 patients with atypical seminoma are summarized in Table 3. Table 4 lists the number of chemotherapy courses and the types of chemotherapy regimens given to these patients. In addition, this table depicts the amount and location of radiation given and surgery performed. To determine which regimens might be efficacious for the treatment of atypical seminomas, we separated patients who had received 3 or more regimens of chemotherapy from those who had received 2 or fewer regimens. We considered those patients who had received both etoposide-cisplatin (EP) and bleomycin-etoposide-cisplatin (BEP) to have been treated with 1 chemotherapy regimen. All patients initially received cisplatin-based chemotherapy (EP or BEP). Several patients subsequently received salvage cisplatin-based chemotherapy (ITP, ATP, CISCA). No patient in this study received high-dose chemotherapy with stem cell support.

We found that 4 of the 25 patients (16%) had died from their atypical seminoma. Two other patients had been cured of their atypical seminoma but had died from other causes: 1 from complications of lung transplantation for pulmonary fibrosis secondary to bleomycin toxicity and the other from a secondary malignancy of advanced pancreatic cancer. Ten of the 15 patients (67%) with atypical seminoma who had had metastases in “atypical” sites (mostly visceral organs) had experienced recurrences. Four of those 15 patients (27%) had died. In addition, nine of 15 (60%) patients with atypical seminoma who had experienced posttreatment recurrences had had atypical metastases, and 4 of those 15 patients (27%) had died. Further, 9 of the 14 patients (64%) who had had high β HCG concentrations had also experienced recurrences. None of the patients who had had high β HCG concentrations died from their seminomas. Although the seminomas in 4 of 5 patients who had had both high β HCG concentrations and metastases in atypical sites recurred after initial radiotherapy or chemotherapy, the disease had been cured or remained stable after further treatments.

3.2. Immunohistochemical studies

Tables 5, 6, and 7 summarize the immunohistochemical staining results for the atypical seminomas, classic seminomas, and mixed embryonal carcinomas and seminomas, respectively. Fig. 1 shows representative photomicrographs of the stained tumor specimens from 2 of the 6 patients with atypical seminomas for whom we had archived specimens. Overall, for each of the 6 markers we studied, both the “atypical” and classic seminomas had a staining profile of OCT 3/4+, PLAP+, CD30–, TRA-1-60–, c-kit+, and gp200–, whereas that for the embryonal carcinoma components of the mixed tumors was OCT 3/4+, PLAP–, CD30+, TRA-1-60+, c-kit–, and gp200–.

3.2.1. OCT 3/4—All tumor tissues had strongly positive nuclear staining for OCT 3/4.

3.2.2. PLAP—The membrane and cytoplasm of the seminoma tissues generally stained positively for PLAP (range, 20%–80%), although overall, the staining was only weakly to moderately positive, and not all portions of the tumor cells stained positively.

3.2.3. CD30—None of the seminoma tissues, including the seminoma components of mixed embryonal carcinomas, stained positively for CD30. The embryonal components, on the other hand, showed strongly positive staining for CD30 in the membrane.

3.2.4. TRA-1-60—No pure seminoma tissues stained positively for TRA-1-60, but the cytoplasm of the embryonal carcinoma tissues stained strongly positively for this marker.

The seminoma components of 2 of the 7 mixed embryonal carcinomas had focal or diffusely positive cytoplasmic staining for TRA-1-60.

3.2.5. c-kit—All seminoma tissues stained strongly positively for c-kit (CD117) in the membrane and cytoplasm of tumor cells, although the embryonal carcinoma tissues did not stain positively.

3.2.6. gp200—All tissues were negative for gp200 staining, although the positive controls, renal-cell carcinoma and rete testis, had luminal and membrane staining.

4. Discussion

Although classic seminomas are generally considered to be predictable and curable, some atypical seminomas seem to behave like nonseminomas and are lethal. Of our 25 patients with atypical seminoma who experienced visceral metastases, elevated β HCG concentration, and/or disease recurrence after therapy, 4 (16%) died from their disease. Thus, despite the relative drug resistance of atypical seminomas, some respond to salvage chemotherapies.

It is of interest to discover what therapeutic approach or chemotherapy regimens may improve the management and clinical outcome of patients with refractory seminomas. About 60% of our patients with atypical seminomas experienced a recurrence after their initial chemotherapy. Comparing the results of treatment of those patients who had survived their atypical seminoma and had undergone at least 3 regimens of chemotherapy (i.e., patients 4, 10, and 16) with those who had undergone fewer than 3 regimens (Table 4) suggests that a salvage regimen comprising paclitaxel, ifosfamide, and cisplatin (ITP) [13] may be an important therapeutic option for the treatment of atypical seminomas. Other regimens, such as doxorubicin, paclitaxel, and cisplatin (ATP) [14] and actinomycin D, cyclophosphamide, and etoposide (ACE) [15], may also be useful for the treatment of this potentially intractable and lethal tumor.

The value of using an elevated β HCG concentration to identify patients with “atypical seminomas” is still unclear. Although more than half of our patients later experienced a recurrence, all of them who had had seminomas and β HCG concentrations of >200 ng/dl were cured of their seminoma. Thus, our results indicate that high β HCG concentration is not a predictor of poor prognosis in patients with atypical seminoma. This matches the inconclusive findings published earlier by other investigators. For example, the authors of a case report about a patient with an exceedingly high β HCG concentration pointed out that such an elevated level may in fact point to a better response to chemotherapy [16]. Similarly, Weissbach et al. that β HCG had no influence on the prognosis provided standard therapy was given [17]. However, these findings disagree with those of Mencil et al. [1] in the Memorial Sloan-Kettering series, in which an elevated β HCG concentration correlated with an increased risk of death. Further investigation is needed for clarification of this point.

The results of our pilot immunohistochemical studies suggest that the atypical seminomas we identified for this study did not have an underlying biologic link to embryonal carcinomas. However, perhaps it is not a surprise that atypical seminomas are not related to embryonal carcinomas. After all, seminomas with embryonal features respond well to chemotherapy [18]. We now speculate that these atypical seminomas are more closely related to other types of nonseminomas than they are to embryonal carcinomas. Such a link may explain the clinical characteristics of our atypical seminomas and, more importantly, may lead us to discover a useful marker for identifying this unique subtype of seminoma [19]. Further studies need to be performed to test this alternative hypothesis.

One limitation of this study is that we were unable to procure tissues from all of the patients with atypical seminomas for our analysis because most did not have specimens stored at our institution. However, the tissues we did procure were from patients whose clinical histories were representative of those of all patients. Another limitation is the retrospective nature of this study. Although a prospective study would have been preferable, the frequency of atypical seminomas is low, and our criteria for identifying them are untested. Nevertheless, we hope that the results of this exploratory study may help us establish a platform for the development of future studies to further elucidate the clinical features and biologic implications of atypical seminomas.

5. Conclusions

In conclusion, we have confirmed that there are clinically relevant “atypical” seminomas that are more virulent than “classic” seminomas are. This subtype of seminoma tends to be associated with the presence of visceral metastases and disease recurrence but is not associated with elevated β HCG concentrations. The pilot immunohistochemical results further suggest that this subtype does not resemble embryonal carcinoma. Additional studies need to be performed to elucidate the origin and nature of atypical seminomas and to discover pertinent biomarkers that may distinguish these tumors from classic seminomas.

Acknowledgments

The authors acknowledge supported for this study in part by the National Institutes of Health through M. D. Anderson’s Cancer Center Support Grant CA016672 and by David M. Carmine’s Cancer Research Fund to A.B. The authors thank Karen Phillips, ELS, for her gracious help in editing this paper. They also thank Hank Adams for his help in imaging; Delores Richards, Casha Broussard, Erin Home, and Cherie Perez for help with tissue requests; Anh Hoang and Odilia Leon for their excellent laboratory techniques in validation and staining; the Histology Core Laboratory; and Rosaly General and Penafrañcia Zoha for their excellent care of patients.

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Fig. 1.

Photomicrographs show results of immunohistochemical analyses from 2 representative patients' tissues. Patient no. 2 (left) had had chemotherapy-resistant disease and died; patient no. 24 (right) was alive with no evidence of disease at the time of our analysis.

Table 1

Clinical characteristics of the 24 patients with “atypical” seminomas

Patient no.	Age at dx (year)	β HCG conc. at dx (mU/ml)	Primary site testis? (Y/N)	Size of RPLN met (cm)	Abnormal met site? (Y/N)	Disease status	Recurrence (Y/N)	Survival (month to last follow-up)
1	40	3	N	ND	Y	NC	Y	19.3
2	35	4.4	N	11.5	Y	NC	Y	19.2
3	52	ND	Y	18	Y	NC	Y	35.5
4	26	151,967	Y	5	Y	Cured	Y	26.3
5	31	ND	Y	6	Y	NC	Y	45.9
6	69	29	Y	ND	Y	Cured	N	86.0
7	41	274	N	17	N	Stable	Y	89.0
8	29	10,385	Y	4	N	Stable	Y	34.1
9	33	400	Y	8.9	N	Stable	N	13.5
10	32	37,000	Y	9.1	Y	Stable	Y	37.1
11	40	18.8	Y	ND	Y	Stable	N	47.3
12	26	2	Y	ND	Y	Stable	Y	58.8
13	31	Very elevated	Y	ND	Y	Cured	Y	49.1
14	44	4.2	Y	ND	Y	Cured	N	129.3
15	21	<1	Y	RPLN irradiated	Y	Cured	N	150.8
16	37	23,322	Y	Extensive	Y	Cured	Y	18.6
17	39	3,179.7	Y	1.5	N	Cured	N	78.4
18	25	1,671	Y	4.5	N	Cured	Y	9.8
19	27	286	Y	1.4	N	Cured	Y	1.4
20	34	37,167	Y	14.5	N	Cured	Y	48.7
21	37	400	Y	3.5	N	Cured	N	8.5
22	30	211	Y	2.4	N	Stable	N	16.2
23	40	512	Y	RPLN irradiated	Y	Cured	N	40.8
24	28	<2	Y	ND	Y	Cured	N	20.9
25	48	69	Y	5.8	N	Stable	Y	28.8
Median	34	343		5.8				35.5
Min.	21	<1		1.4				1.4
Max.	69	151,967		18				150.8

dx = diagnosis; β HCG = human chorionic gonadotropin; RPLN = retroperitoneal lymph node; met = metastasis; ND = no data; NC = not cured.

Table 2

Clinical characteristics of metastases

Site	No. (%)
Primary	
Seminoma	22 (88)
Not found ^a	3 (12)
Metastasis	
RPLN	22 (88)
Liver	8 (32)
Cervical, pelvic, supraclavicular LN	6 (24)
Lung	4 (16)
Adrenal	3 (12)
Bone	3 (12)
Brain	2 (8)
Mediastinal mass	1 (4)
Pleural mass	1 (4)

RPLN =retroperitoneal lymph node; LN =lymph node.

^aNot found: sonographic examination of the testes showed microlithiasis suggestive of a burned-out tumor.

Table 3

Summary of therapy responses

Total no. of chemotherapeutic regimens given ^a	No. (%) patients with "atypical" seminoma	Disease status		Mean survival time to last follow-up (month)	
		% Cured	% Stable	% Not cured	
1	10 (40)	70	30	0	59.2
2	7 (28)	57	43	0	33.0
3	1 (4)	0	100	0	89.0
4	2 (8)	50	50	0	31.7
5	4 (16)	25	0	75	23.1
7	1 (4)	0	0	100	45.9

^aThose patients who had received both etoposide/cisplatin and bleomycin/etoposide/cisplatin were considered to have undergone only one chemotherapy regimen.

Table 4

Patient characteristics: therapy received, including chemotherapy regimens (types and number of cycles), radiotherapy (dosage), and surgery

Patient no.	Status	EP	BEP	ATP	ITP	VIP	CTX/Carbo	VeIP	ACE	Other	XRT (Gy)	Location of XRT	Type of surgery
Patients who underwent 3 or more types of chemotherapy (n)													
4	Cured	1	3		2				1	2 IAG			RPLND
16	Cured		2	1	1	2			1				
10	Stable		4	3 ^a	3					1 Cytosan/VP16	NK	Brain	
7	Stable		4	3						3 CTX/CDDP	36	RPLN	
1	NC	2	4	4						4 POMB, 1 GC/IFN, 1 CTX/CDDP			
2	NC		4	4		1	1			1 CTX/CDDP	49.6	RPLN, pelvis	RPLND
3	NC	3		3		1	5			1 BOP	25	Mediastinum, RPLN	RPLND
5	NC	4		3	1			2	2	2 POMB, 1 Gem/Oxal	23.4	RPLN	
Patients who underwent 1 or 2 types of chemotherapy (n)													
6	Cured	4	1										
9	Stable		4										
11	Stable	4											
14	Cured						5				30	Pelvis	
15	Cured							5			NK	RPLN	
17	Cured						4						
21	Cured	4											
22	Stable		4										
23	Cured	4									20	RPLN	
24	Cured	4											
8	Stable	4			4						NK	RPLN	
12	Stable	4						1			20	RPLN	Metastectomy (lung)
13	Cured		2			4							
18	Cured	4			3								
19	Cured	4			3								
20	Cured	4			2						26/27	Supraclavicular/RPLN, pelvis	
25	Stable		4		2								

EP =etoposide/cisplatin; BEP =bleomycin/etoposide/cisplatin; ATP =doxorubicin/paclitaxel/cisplatin; ITP =ifosfamide/paclitaxel/cisplatin; VIP =etoposide/ifosfamide/cisplatin; CTX/Carbo =cyclophosphamide/carboplatin; VeIP =vinblastine/ifosfamide/cisplatin; ACE =actinomycin D/cyclo-phosphamide/etoposide; XRT =radiotherapy; IAG =ifosfamide/doxorubicin/gemcitabine; RPLN (D) =Retroperitoneal lymph node (dissection); CTX/VP16 =Cyclophosphamide/etoposide; NK =Not known; CTX/CDDP =cyclophosphamide/cisplatin; NC =not cured; POMB =cisplatin/vincristine/methotrexate/bleomycin; GC/IFN =Gemcitabine/cisplatin/alpha-interferon; BOP =Bleomycin/vincristine/cisplatin; Gem/Oxal =gemcitabine/oxaloplatin; CISCA/VB =cyclophosphamide/doxorubicin/cisplatin–vinblastine/bleomycin.

^a An attenuated schedule of ATP was given because of poor tolerance (bone marrow suppression) to the treatment.

Table 5
Immunohistochemical characteristics of available tumor specimens from patients with “atypical” seminomas

Patient no.	Date of orchiectomy	Site of specimen	OCT 3/4	PLAP	CD30	TRA-1-60	c-kit	gp200	Patient status	Survival (month) ^a
1	4/2/1999	Liver	+	+	-	-	+	ND	Died	19.3
2	7/7/2000	Left para-aortic LN	+	+	-	-	+	ND	Died	19.2
		Large RPLN mass	+	+	-	-	+	ND		
		Para-aortic LN	+	+	-	-	+	-		
11	8/13/2002	Testis	+	-	-	-	+	-	Living	47.3
14	5/16/1997	Testis	+	F+	-	-	+	-	Living	129.3
		RPLN	+	+	-	-	+	ND		
17	12/8/1999	Testis	+	+	-	-	+	-	Living	78.4
24	8/9/2006	Testis	+	F+	-	-	+	-	Living	20.9

ND =no data; LN =lymph node; RPLN =retroperitoneal lymph node; F+ = focally positive staining.

^aMedian survival time, 34.1 months.

Table 6

Immunohistochemical characteristics of available tumor specimens from patients with “classical” seminomas

Patient no.	Source of specimen	Immunohistochemical staining result						
		OCT 3/4	PLAP	CD30	TRA-1-60	c-kit	gp200	
25	Right orchiectomy	NT	NT	NT	NT	NT	NT	
26	Right orchiectomy	+	+	-	-	+	-	
27	Left orchiectomy	+	+	-	-	+	-	
28	Left orchiectomy	+	+	-	-	+	-	

NT = no tumor on sample slide.

Table 7

Immunohistochemical characteristics of available tumor specimens from patients with mixed “embryonal” carcinoma and seminoma tumors

Patient no.	Source of specimen	Component	OCT 3/4	PLAP	CD30	TRA-1-60	c-kit	gp200
29	Left orchiectomy	Embryonal	+	F+	+	NA	-	-
		Seminoma	+	+	-	-	+	-
30	Left orchiectomy	Embryonal	+	+	+	+	-	-
		Seminoma	NT	NT	NT	NT	+ Intratubular carcinoma	NT
31	Left orchiectomy	Embryonal	+	F+	+	+	-	-
		Seminoma	+	+	-	-	+	-
32	Right orchiectomy	Embryonal	+	-	+	+	Wk+	-
		Seminoma	+	+	-	-	F+	-
33	Left orchiectomy	Embryonal	+	-	D+	D+	-	-
		Seminoma	+	+	F+	F+	+	-
34	Right orchiectomy	Embryonal	+	+	+	-	-	-
		Seminoma	+	+	-	-	+	-
35	RPLND	Embryonal	NT	NT	NT	NT	NT	NT
		Seminoma	+	F+	-	F+	Wk+	-

F+ = focally positive staining; NA = not available; NT = no tumor on sample slide; Wk+ = weakly positive staining; D+ = diffusely positive staining.