Outcomes of Surveillance Protocol of Clinical Stage I Nonseminomatous Germ Cell Tumors—Is Shift to Risk Adapted Policy Justified?

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Purpose: We evaluated the potential risk factors for disease relapse in patients with clinical stage I nonseminomatous germ cell tumors treated with surveillance and reevaluated our treatment of these patients.

Materials and Methods: A total of 211 consecutive patients with clinical stage I nonseminomatous germ cell tumors treated with surveillance after orchiectomy between 1993 and 2005 were included in this retrospective study. Risk factors evaluated were presence of vascular invasion, proportion of embryonal carcinoma, age, tumor size, preoperatively increased serum α-fetoprotein and the absence of yolk sac component.

Results: Of the 211 patients 66 (31.3%) had disease relapse. Recurrence ranged from 2 to 32 months after orchiectomy (median 6). A total of 52 (78.8%) cases of relapse were diagnosed in year 1 of followup, 11 (16.7%) during year 2 and only 3 cases were diagnosed thereafter. The first evidence of relapse was most commonly the increase in serum tumor markers alone (28.8%) or in combination with other modalities (66.7%, overall 95.5%). While 40.9% of patients with more than 50% embryonal carcinoma had disease relapse, the relapse rate was 20.8% in patients with less than 50% embryonal carcinoma ($p = 0.002$). Relapse rates in patients with and without vascular invasion were 75.5% and 17.9%, respectively ($p = 0.000$). The relapse rates were 6.1% and 75.7% in patients with no risk factors (no vascular invasion and less than 50% embryonal carcinoma) and 2 risk factors (vascular invasion and more than 50% embryonal carcinoma), respectively ($p < 0.001$). Multivariate analysis revealed that vascular invasion was the most powerful predictor of relapse (OR 16.350, 95% CI 5.582–47.893). Disease-free and disease specific survival rates were 97.6% at a median followup of 75 months.

Conclusions: In light of our results we suggest that all patients with vascular invasion should receive chemotherapy. However, patients with no risk factors and those with more than 50% embryonal carcinoma but without vascular invasion should be on surveillance after orchiectomy since the relapse rate is less than 30%. Although strict followup in the first year is justified, followup schemas may be reassessed for the frequency of radiological investigations.

Key Words: testicular neoplasms, recurrence, risk factors

The standard treatment of patients with clinical stage I NSGCT of the testis following orchiectomy remains controversial since patients with CSI NSGCT have excellent survival either with RPLND,[1] surveillance[2] or primary chemotherapy.[3] Even with modern staging techniques with CTA and monitoring of serum tumor markers, approximately 30% of patients with clinical stage I nonseminomatous testicular germ cell tumors have occult metastatic disease and will have relapse if they are only observed and followed up after orchiectomy. If RPLND is performed disease staging will be more accurate but many patients will have undergone unnecessary surgery and, despite histologically verified negative lymph nodes, 10% to 17% will have metastases[4] outside the surgical boundaries. Moreover, 50% to 55% of patients who are given primary chemotherapy after orchiectomy will be over treated. Because of the inaccuracy of clinical staging methods and the risk of metastasis, clinical research focusing on the development of prognostic risk factors remains one of the most important clinical challenges. In previous studies vascular invasion and the percentage of embryonal carcinoma in an orchiectomy specimen have been identified as significant histopathological risk factors for disease relapse.[5–10] We report on the results of a surveillance program for CSI NSGCT and an analysis of prognostic factors for relapse to revisit our treatment of these patients.

PATIENTS AND METHODS

Of 251 total patients who were offered surveillance treatment at 2 institutes 64 patients missed at least 1 visit. These 64 patients were invited by telephone, and of them 24 responded and were evaluated for relapse. Thus, 211 available patients with CSI NSGCT from SB Tepecik Research and

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TABLE 1. *Patient characteristics*

	No. Pts (%)
Age:	
30 or Younger	130 (61.6)
Older than 30	81 (38.4)
Relapse	66 (31.3)
AFP (preop, abnormal)*	127 (71.3)
Death	5 (2.4)
Presence of yolk sac component	47 (22.3)
Vascular invasion present	49 (23.2)
Presence of EC (more than 50%)	110 (52.1)
Cm^3 primary tumor vol:*	
Greater than 3	98 (67.6)
3 or Less	47 (32.4)
Condition:	
Histopathology	
Teratoma	13 (6.2)
EC	41 (19.4)
Mixed germ cell	85 (40.3)
Yolk sac	8 (3.8)
Teratocarcinoma	64 (30.3)

* We could find partial results in some cases.

Training Hospital and Hacettepe University Hospital treated with surveillance between January 1993 and May 2005 were included in this retrospective study. After undergoing radical orchiectomy cases were clinically staged with CXR, CT of the chest and abdomen, and repeated serum tumor marker analysis. All patients with normalized markers according to the half-life of the markers and normal tomography were offered surveillance. For the prediction of risk factors we used the previously published cutoff values of these parameters, that is the absence or presence of VI, 50% or more vs less than 50% EC, age, primary tumor size (cutoff 3 cm), presence of abnormal serum AFP levels before orchiectomy and presence of YS component. Vascular invasion was documented when tumor adhered to a vessel wall or almost completely filled a space lined with flat endothelial cells. We used the term vascular invasion to indicate the presence of venous or LI with no distinction between venous and lymphatic structures. Followup consisting of clinical history, physical examination, tumor markers and CXR was performed every 2 months in year 1, every 3 months in year 2, every 6 months in year 3 and annually thereafter. Computerized tomography of the abdomen and thorax were performed every 4 months in the first year, 6 months in the second year and annually thereafter. Disease recurrence was defined as serum tumor marker increase and/or tumor growth seen on radiographic study. The patients with disease relapse received mostly 3 courses of BEP chemotherapy and supplementary surgical resection of any residual disease after chemotherapy. The chi-square test and Fisher's exact test were used for univariate analysis. Multivariate logistic regression analysis with stepwise selection was performed for variables.

RESULTS

Median patient age was 28 years (range 2 to 56). These patients were followed for a median of 75 months after orchiectomy (mean 87.7, range 12 to 148). Disease progression occurred in 66 patients (31.3%) and was observed 2 to 32 months following orchiectomy (median 6 months). Of 62 patients who had relapse 52 (78.8%) were diagnosed within 12 months, 11 (16.7%) had relapse during the second year and the rest after 24 months of followup. Tumor dimensions were available for evaluation in 145 patients, with 47 (32.4%) having a tumor less than 3 cm and 98 (67.6%) greater than 3 cm. Serum AFP levels before orchiectomy were available in 178 patients. AFP was increased in 127 (71.3%) patients. Primary histopathological findings were teratoma in 13 patients (6.2%), EC in 41 patients (19.4%), mixed germ cell tumors in 85 patients (40.3%), YS in 8 patients (3.8%) and teratocarcinoma in 64 patients (30.3%). More than 50% of EC was found in 110 (52.1%) patients. Vascular invasion was detected in 49 (23.2%) patients. Patient characteristics are summarized in table 1.

Neither age at orchiectomy nor preoperative AFP levels were significantly associated with the risk of relapse. Furthermore, tumor dimensions and the presence of YS component were not found to be significant on univariate analysis. Two factors were determined as significant risk factors for relapse, that is more than 50% EC and the presence of

TABLE 2. *Univariate and multivariate analyses of variables in terms of relapse*

	Relapse		Univariate Analysis (p value)	Multivariate Analysis (p value)
	% No	% Yes		
AFP:				
Normal	70.6	29.4	0.859	Not significant
High	68.5	31.5		
% EC:				
Greater than 50	59.1	40.9	0.002	0.045 (OR 2.583, 95% CI 1.020–6.540)
Less than 50	79.2	20.8		
VI:				
Present	24.5	75.5	0.000	<0.001 (OR 16.350, 95% CI 5.582–47.893)
Absent	82.1	17.9		
VI absent & less than 50% EC (no risk factor)	93.9	6.1	0.000	<0.001
VI present or greater than 50% EC (1 risk factors)	64.1	35.9		
VI present & greater than 50% EC (2 risk factors)	24.3	75.7		
Yolk sac elements:				
Present	59.6	40.4	0.153	0.701 (OR 1.258, 95% CI 0.390–4.053)
Absent	71.3	28.7		
Age:				
Younger than 31	71.5	28.5	0.287	0.859 (OR 1.091, 95% CI 0.418–2.845)
Older than 30	64.2	35.8		
Primary tumor vol (cm^3):				
3 or Less	72.4	27.6	0.696	0.828 (OR 1.118, 95% CI 0.407–3.070)
Greater than 3	68.1	31.9		