Correlation Between Primary Tumor Pathologic Features and Presence of Clinical Metastasis at Diagnosis of Testicular Seminoma

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OBJECTIVES To compare several risk factors in the testicular biopsy of patients with pure seminoma with and without clinical metastasis at diagnosis.

METHODS We performed a retrospective study of patients with pure seminoma. The retroperitoneum was staged with computed tomography and the thorax with simple radiography and/or computed tomography, taking into account the original reports and clinical stage. The previous reports and original pathology plates were reviewed by pathologists who were unaware of the clinical stage of the patients. Patients with beta-human chorionic gonadotropin greater than 800 mUI/mL were excluded.

RESULTS A total of 86 patients had sufficient data and comprised the study cohort. Of the 86 patients, 62 had clinical Stage I (72%), 20 had Stage II (23%), and 4 had Stage III (5%). On univariate analysis, tumor size greater than 4 cm ($P = 0.0135$), testicular vascular invasion ($P = 0.0042$), rete testis invasion ($P = 0.0002$), tunica albuginea penetration ($P = 0.00001$), base of the spermatic cord invasion ($P = 0.0002$), epididymis invasion ($P = 0.001$), and vascular invasion of the cord ($P = 0.024$) were predictive of metastasis. On multivariate analysis, tumor size greater than 6 cm (odds ratio 6.9, 95% confidence interval 1.3 to 35, $P = 0.02$) and rete testis invasion (odds ratio 6.1, confidence interval 1.2 to 30, $P = 0.025$) remained as important predictors of metastasis (tumor size less than 6 cm was not significant on multivariate analysis).

CONCLUSIONS The results of this study have demonstrated that rete testis invasion and tumor size correlate independently with the presence of clinical metastasis at diagnosis of testicular seminoma. UROLOGY 70: 777–780, 2007. © 2007 Elsevier Inc.

Approximately 45% of germ cell testicular cancers are pure seminomas, and most patients (70% to 80%) present with clinical Stage I.[1] This means that nearly one third of all cases of germ cell testicular cancer are pure seminomas in clinical Stage I. After orchiectomy, these patients have traditionally been treated with radiotherapy, most recently using a reduced field directed only at para-aortic lymph nodes, which is less toxic.[2] Nevertheless, long-term studies have demonstrated that patients with seminoma treated with radiotherapy have a greater risk of developing a second malignancy.[3]

Nearly 100% of patients with Stage I seminoma who undergo surveillance are cured.[4–6] The prognostic factors for relapse have been analyzed to be able to select a treatment in accordance with the individual risk of each patient.[7]

The objective of this study was to compare the various risk factors as determined from the testicular biopsy of patients with pure seminoma, with and without clinical metastasis at diagnosis, as another approach to the problem of deciding on radiotherapy or surveillance for patients with clinical Stage I.

MATERIAL AND METHODS

This was a retrospective study of patients with pure seminoma[8] who underwent radical orchiectomy from January 1996 to December 2005.

Clinical Information

The diagnostic procedures included physical examination, testicular ultrasonography, and tumor markers. Staging was done using the TNM classification of malignant tumors of 2002.[9] The

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Table 1. Comparison of numeric variables in testicular seminoma with and without clinical metastasis

Variable	Total	Metastasis (%)		*P* Value
		Yes	No	
Age (yr)	34.8 ± 8.11	32.8 ± 7.08	35.6 ± 8.39	0.1457
Tumor size (cm)	4.3 ± 2.67	6.8 ± 2.84	4.2 ± 2.29	0.0001
Mitoses/10 HPF (n)	15.8 ± 9.58	18.8 ± 8.74	14.6 ± 9.71	0.0847

HPF = high power field.
Data presented as mean ± standard deviation.

retroperitoneum was staged with computed tomography and the thorax with simple radiography and/or computed tomography, taking into account the findings of the original reports. During the entire study period, lymph nodes greater than 10 mm were considered abnormal. Three patients with two or more lymph nodes of 7 to 8 mm within the primary zone of metastasis (left tumors, para-aortic and preaortic lymph nodes; and right tumors, precaval, intercaval-aortic, and preaortic lymph nodes) were considered to have metastasis, maintaining the clinical opinion at diagnosis. Patients with beta-human chorionic gonadotropin greater than 800 mUI/mL were excluded from the study.

Pathologic Information

The previous reports and the original pathologic plates were reviewed by two pathologists who were unaware of the clinical stage of the patients. The operative testicular pieces had been fixed in formalin and embedded in paraffin. At least one section was made per centimeter of the major axis of the tumor, with the entire tumor processed for those that were less than 3 cm. Samples were taken of the epididymis, the base, and three levels of the spermatic cord. The paraffin blocks were sectioned and stained with hematoxylin-eosin. The following possible risk factors were analyzed: tumor size, number of mitoses per 10 high-power fields (400×), necrosis (groups of tumor cells with coagulation necrosis; the presence of isolated apoptotic cells was not considered), testicular vascular invasion (tumor cells within lymphatic or venous vessels at the testicular level), rete testis invasion (tumor cells in contact with or between the ducts of the rete testis), penetration of the tunica albuginea (tumor cells in the entire thickness of the albugineal layer; partial penetration was not considered), invasion of the epididymis (tumor cells in contact with or between the epididymal duct), invasion of the base of the spermatic cord (tumor cells in contact with the adipose tissue of the spermatic cord adjacent to the testis), and vascular invasion of the cord (tumor cells within the lymphatic or venous vessels of the cord at any of the three levels examined).

Two study groups were defined for the comparisons: (a) patients without evidence of metastasis (clinical Stage I) and (b) patients with clinical metastasis (clinical Stage II and III).

Statistical Analysis

To compare the numerical variables (age, tumor size, and number of mitoses), Student's *t* test was used. To compare the different risk factors (categorical variables) with the presence or absence of metastasis, either the chi-square test or Fisher's exact test was used (the latter was used when an event presented in fewer than 5 cases). The odds ratio was calculated when any statistically significant association was found. The multivariate analysis was performed with the logistical regression method. The information was processed with the Stata, version 8.1, program (Stata, 2003), and statistical significance was defined as $P < 0.05$.

RESULTS

Of the 98 patients with testicular seminoma during the study period, 86 (88%) were included in the study. The excluded patients lacked either pathologic plates or the original radiologic records. The included patients had nearly complete pathologic information (6.2% missing data).

Of the 86 patients, 62 had clinical Stage I (72%), 20 had Stage II (23%; Stage IIA in 8, Stage IIB in 5, and Stage IIC in 7), and 4 had Stage III (5%). All the patients with clinical Stage I underwent retroperitoneal radiotherapy. The patients with metastasis had significantly larger tumors, but the greater number of mitoses observed was not significant (Table 1).

On univariate analysis, seven of the nine risk factors studied were significantly more frequent in patients with metastatic seminoma: tumor size greater than 4 cm, testicular vascular invasion, rete testis invasion, penetration of the tunica albuginea, invasion of the base of the spermatic cord, invasion of the epididymis, and vascular invasion of the cord (Table 2). Of the 86 patients, 21% did not present with any of the seven significant risk factors. Of those 21%, only 1 patient had metastasis (clinical Stage IIA, with two lymph nodes of 8 mm within the primary zone of metastasis).

On multivariate analysis, only tumor size greater than 6 cm and rete testis invasion were significantly more common in metastatic seminoma, and albugineal penetration almost attained statistical significance (Table 3). Tumors less than 6 cm were not significant on multivariate analysis. Table 4 lists the sensitivity, specificity, accuracy, and positive and negative predictive values of the risk factors that were significant on multivariate analysis.

COMMENT

This was a retrospective study from which less than 15% of the patients in the series were excluded and a complete range of pathologic characteristics of the primary testicular tumor was analyzed. The study had the bias of clinical staging of the retroperitoneum with computed tomography; nearly 15% to 20% of patients with Stage I

Table 2. Comparison of risk factors by univariate analysis

Risk Factor	Total (%)	Metastasis (%)		*P* Value	Odds Ratio	95% CI
		Yes	No			
Tumor size (cm)						
>4	55	77	47	0.0135	3.868	1.304–11.362
>5	36	68	24	0.0002	6.714	2.347–19.156
>6	26	59	15	0.00001	8.506	2.867–25.301
Tumor necrosis	52	59	49	NS	—	—
Testicular vascular invasion	47	73	37	0.0042	4.571	1.583–13.108
Rete testis invasion	44	77	32	0.0002	7.366	2.410–22.298
Albuginea penetration	25	59	12	0.00001	10.317	3.297–32.343
Base of cord invasion	19	45	9	0.0002	8.666	2.581–28.981
Epididymis invasion	14	36	5	0.001*	10.285	2.568–40.516
Vascular invasion of cord	13	27	7	0.024*	4.968	1.322–18.583
≥30 Mitoses/10 HPF	9	14	7	NS*	—	—

CI = confidence interval; HPF = high power field; NS = not significant.
* Fisher's exact test.

Table 3. Logistic regression analysis between presence of metastasis and significant risk factors (multivariate analysis)

Risk Factor	Odds Ratio	*P* Value	95% CI
Tumor size >6 cm	6.901	0.020	1.359–35.036
Rete testis invasion	6.157	0.025	1.261–30.049
Albuginea penetration	4.907	0.056	0.963–25.000
Epididymis invasion	3.711	0.238	0.421–32.705
Vascular invasion of cord	1.924	0.543	0.234–15.811
Base of cord invasion	1.492	0.706	0.186–11.968
Testicular vascular invasion	0.414	0.371	0.060–2.852

CI = confidence interval.

Table 4. Sensitivity, specificity, accuracy, and positive and negative predictive values of risk factors significant on multivariate analysis

Risk Factor	Sensitivity	Specificity	Accuracy	PPV	NPV
Tumor size >6 cm	0.59	0.85	0.79	0.59	0.85
Rete testis invasion	0.77	0.68	0.71	0.49	0.89
Tumor size >6 cm or rete testis invasion	0.81	0.56	0.63	0.40	0.89
Tumor size >6 cm plus rete testis invasion	0.62	0.98	0.88	0.93	0.88

PPV = positive predictive value; NPV = negative predictive value.

testicular seminoma have microscopic, subclinical metastasis and have disease relapse after orchiectomy if they undergo surveillance.[10] Because all the patients with clinical Stage I disease in this series underwent retroperitoneal radiotherapy, it was not possible for us to know which patients would have developed a relapse if they had only undergone observation. Another source of bias was the inclusion of 3 patients with retroperitoneal lymph nodes less than 10 mm categorized as clinical Stage IIA. This decision was made to maintain the clinical opinion at diagnosis. Nevertheless, if these patients were excluded, no changes occurred in the univariate or multivariate analysis. Also, if the threshold size for lymph nodes to be considered pathologic is reduced when staging the retroperitoneum with computed tomography, the sensitivity increases but so does the false-positive rate.[11] Despite these limitations, we believe this study has provided useful information about the pathologic factors involved in the development of metastasis in testicular seminoma in countries where it is very difficult to carry out a protocol of surveillance for patients with clinical Stage I, given that a poor adherence to the follow-up protocol is assumed.

According to the information available to us, only two previous studies have specifically compared the pathologic characteristics of patients presenting with seminoma with and without metastasis. Marks and colleagues,[12] in a series of 57 patients (28 with retroperitoneal metastasis) staged with computed tomography and/or lymphangiography and/or endovenous pyelography, found that only vascular invasion was significantly more common in patients with metastasis ($P = 0.03$); invasion of the tunica albuginea and rete testis almost achieved statistical significance ($P = 0.07$ and $P = 0.08$, respectively). Sato and coworkers,[13] in a series of 100 patients (9 with retroperitoneal metastasis) for whom the method of staging the retroperitoneum was not indicated, found that tumor size and the preoperative lactate dehydrogenase level were significant predictors of Stage II disease. On univariate analysis, our study showed 7 of 9 risk factors to be significantly more frequent in metastatic seminoma, a difference that can be explained first by how the staging was performed and, second, by the inclusion of patients with large retroperitoneal metastasis and su-

Table 5. Prognostic factors for relapse of stage I seminoma managed by surveillance

Study	Patients (n)	Follow-up (yr)	Significant Prognostic Factors
Horwich *et al.,*[4] 1992	103	5.2 (1.2–11.8)	Vascular invasion
von der Maase *et al.,*[5] 1993	261	4.0 (0.5–5.6)	Univariate analysis Tumor size Histologic subtype Necrosis Rete testis invasion Multivariate analysis Tumor size (≥6 cm)
Warde *et al.,*[6] 1997	201	6.1 (1.3–12.3)	Univariate analysis Tumor size Age Vascular invasion Multivariate analysis Tumor size (>6 cm) Age (≥35 yr)
Warde *et al.,*[7] 2002 (pooled analysis)	638	7.0 (0.02–17.5)	Univariate analysis Tumor size Rete testis invasion Vascular invasion Multivariate analysis Tumor size (>4 cm) Rete testis invasion

Data in parentheses are ranges.

pradiaphragmatic metastasis in our study. Nevertheless, when we excluded the data of patients with pulmonary metastases from our study, the only factor that lost significance on univariate analysis was vascular invasion of the spermatic cord, with no changes on multivariate analysis.

Several studies have been performed of patients with Stage I testicular seminoma who underwent surveillance, in which different prognostic factors for relapse were evaluated. Table 5 shows the significant results of the largest published series.[4–7] Warde and colleagues, in a combined analysis of four clinical series that included 638 patients with Stage I seminoma who underwent surveillance, found that tumor size greater than 4 cm and rete testis invasion were the only two independent prognostic factors for relapse, in accordance with our results obtained by comparing patients with and without clinical metastasis at diagnosis. The TNM classification of malignant tumors of 2002 did not consider rete testis invasion as a high pT stage, which perhaps requires revision. The rete testis is a communicating network of seminal channels that traverses the testicular mediastinum, which is in close contact with the lymphatic and blood vessels, and could facilitate the mechanisms of metastasis. However, it would be interesting to know the role of the penetration of the tunica albuginea, epididymal invasion, and invasion of the base of the spermatic cord (factors not analyzed in the previously cited studies) in predicting for relapse in patients with Stage I testicular seminoma who undergo surveillance, for which it is necessary to perform a prospective study.

CONCLUSIONS

The results of this study have demonstrated that rete testis invasion, as well as tumor size, correlated independently with the presence of clinical metastasis at the diagnosis of testicular seminoma. Because of limitations in the clinical staging of testicular seminoma, a prospective study that includes patients with Stage I who undergo surveillance would help to determine the real utility of analyzing a complete range of the pathologic characteristics of the primary tumor for the prediction of metastasis.

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