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Advances in Brief

Percentage of Embryonal Carcinoma and of Vascular Invasion Predicts Pathological Stage in Clinical Stage I Nonseminomatous Testicular Cancer[1]

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Abstract

We analyzed 92 clinical stage I nonseminomatous testicular germ cell tumors for primary tumor histological factors that would distinguish true pathological stage I disease (N = 54) from those patients who harbored occult disease and actually were later found to have pathological stage II disease (N = 38). Primary tumor pathological material was analyzed for vascular invasion, lymphatic invasion, tunical invasion, and quantitative determination of percentage of the primary tumor composed of embryonal carcinoma, yolk sac carcinoma, teratoma, and seminoma. Univariate logistic regression analyses revealed that vascular invasion (P = 0.0001), percentage of embryonal carcinoma (P = 0.0001), lymphatic invasion (P = 0.0001), and tunical invasion (P = 0.0013) were higher in pathological stage II and that percentage of teratoma (P = 0.0001) and of yolk sac carcinoma (P = 0.0174) were higher in stage I. Percentage of seminoma was not significant. Individually, these parameters were able to correctly predict occult disease 66.3 to 80.4% of the time. In multivariate logistic regression analysis, only vascular invasion and percentage of embryonal carcinoma remained significant, and a model using these two variables was able to correctly predict stage 85.9% of the time. Vascular invasion and determination of percentage of embryonal carcinoma should be assessed for all clinical stage I nonseminomatous germ cell tumor patients and the model presented herein can be used clinically to predict the likelihood of occult disease and dictate therapy.

Introduction

Although we have made tremendous advances in the care of testicular cancer (1), a major controversy still exists in the case of CSI[3] NSGCT patients (2). Because of inaccuracy in clinical staging, most CSI patients in the United States undergo RPLND, a major abdominal operation to detect occult retroperitoneal metastases that occur in only 30% of cases (3). Up to 10% of men also have occult distant metastases that manifest later despite a negative RPLND (3). Some have advocated observation or surveillance after orchiectomy, however, follow-up studies must be intense and some patients have been harmed or died as a result of the occult metastases not being detected and treated appropriately (4). Over the last few years, primary testis tumor histological risk factors have been discovered that help stratify the risk of occult metastases in the CSI patient (5, 6). The presence/absence of tumor VI and embryonal carcinoma have been most commonly used factors. Although the qualitative presence of embryonal carcinoma component has been a risk factor, our recent preliminary study of quantitating the %EMB in the primary testis tumor was the first to suggest this as a very clinically useful test (7). This report extends our experience now with 92 CSI NSGCT patients by using VI and %EMB and also evaluates other quantitative determination of percentage of teratoma, yolk sac, and seminoma, and determination of lymphatic and tunical invasion. We have developed a multivariate logistic regression model and clinically useful probabilities of occult disease for treatment decisions in CSI patients.

Materials and Methods

Of 192 patients with NSGCT treated at our center between 1980 and 1993, 92 (48%) had CSI disease before RPLND and/or follow-up and form the basis of this study. Eighty-six patients underwent staging RPLND and 5 patients were placed on an observation protocol following orchiectomy and negative staging work-up, and all were disease-free at follow-up intervals ranging from 1 to 10 years. One pathological stage II patient was originally treated as a stage I seminoma at another institution but developed a supraclavicular mass within 1 year of radiation therapy to the retroperitonum. Upon referral to our service review of his original pathology revealed embryonal carcinoma and biopsy of the supraclavicular mass revealed malignant germ cell tumor. The pathological stage II group also included 2 patients with a negative modified RPLND who had disease relapse within 6 months of initial therapy. Final pathological stage for these 92 CSI patients consisted of 54 pathological stage I and 38 pathological stage II cases.

A single pathologist (I. A. S.) reviewed the hematoxylin and eosin slides from the primary tumor and assessed the cases for the presence of VI, lymphatic, and tunical invasion and determination of the %EMB, percentage of yolk sac carcinoma, teratoma, and seminoma as previously described (7, 8).

In order to determine statistically significant risk factors associated with stage II disease, logistic regression was used (9). Initially univariate logistic regression models were developed to determine if percentage of each cell type, VI, lymphatic, and tunical invasion were each a significant risk factor. Multivariate logistic regression was used to determine the "best" set of risk factors for predicting stage II disease. Three different procedures for the selection and/or deletion of variables were used to determine this best set (step forward, step backward, and stepwise) (10). In addition, certain variables were forced into the final multivariate model to see if their inclusion improved predictability.

Logistic regression diagnostics and assessment of sensitivity, specificity, number of stage II cases correctly predicted, the false-positive rate and the false-negative rate were used to validate that the best set of risk factors were indeed determined by the multivariate logistic regression procedures. The condition best was satisfied if the resulting set of multivariate risk factors had passed the diagnostic tests as defined by Hosmer and Lemeshow (9) and produced high sensitivity, high specificity, a high prediction rate, a low false-negative rate, and a low false-positive rate. In addition, if the definition for best was satisfied, the resulting set of risk factors were considered to have clinical utility.

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[3] The abbreviations used are: CSI, clinical stage I; NSGCT, nonseminomatous germ cell tumor; RPLND, retroperitoneal lymph node dissection; VI, vascular invasion; %EMB, percentage of embryonal carcinoma.

Results and Discussion

For our 92 CSI NSGCT patients all of whom had RPLND and follow-up defining true pathological stage, Table 1 documents mean (median) quantitative histology for pathological stage I versus stage II. Most striking differences were seen for percentage of embryonal carcinoma and vascular invasion. For the 38 stage II (upstaged occult disease) patients, mean %EMB was 74.6%, and 76% had VI compared to 29.9 and 16% for stage I cases, respectively. In general, percentage of teratoma, yolk sac carcinoma, and seminoma were higher in stage I and lymphatic and tunical invasion were more common in stage II. Univariate logistic regression statistical analysis (Table 2) revealed that all these factors with the exception of percentage of seminoma were statistically significant and were able to individually correctly predict occult stage II disease from 66 to 80% of the time. Vascular invasion was the best single risk factor (80.4% correct) with percentage of embryonal carcinoma also quite predictive (77.2%). In the multivariate logistic regression analysis, percentage of embryonal carcinoma and vascular invasion remained significant, whereas the other factors did not, and the model including both VI and %EMB was able to predict occult disease 85.9% of the time (Table 2).

Based on these data, we were able to create a multivariate logistic regression model for the probability (Pr) of occult stage II disease based on VI (0 = No, 1 = Yes) and %EMB (1–100 continuous variable):

$$\mathrm{Pr}^{\text{occult disease}} = \frac{e^{\{-3.0839 + 0.0341\,[\%\mathrm{EMB}] + 2.0778\,[\mathrm{VI}]\}}}{1 + e^{\{-3.0839 + 0.0341\,[\%\mathrm{EMB}] + 2.0778\,[\mathrm{VI}]\}}}$$

Table 3 provides the calculated clinically useful probabilities of occult disease for various %EMB values with and without VI. These probabilities range from a 92% risk of occult disease in a patient with pure embryonal carcinoma and VI to a 4% risk in a man without embryonal components and no VI.

The mere presence or absence of embryonal carcinoma component in the primary tumor of CSI NSGCT had been known to be a risk factor for occult disease since the mid-1980s (5, 6). In 1989, Wishnow *et al.* (11) were the first to study the percentage of embryonal carcinoma in CSI NSGCT. In 89 CSI surveillance-treated patients, there were no relapses when %EMB was <80% and there was no VI; however, when %EMB was >80%, or VI was present, or preoperative α-fetoprotein was >80 ng/dl, relapses occurred in 46% of patients. The study was interesting but did not apply rigorous statistics or multivariate risk analysis. Allhoff *et al.* (12) studied 50 CSI patients by using semiquantitative %EMB of two categories: <50% and ≥50%, which was significant by univariate analysis ($P = 0.036$) for relapse on surveillance. Vascular invasion was not included and %EMB was not used as a continuous variable. McLeod *et al.* and the Testicular Cancer Intergroup Study (3) also analyzed semiquantitative embryonal carcinoma (pure, mixed, and absent embryonal elements) in 352 CSI patients. This was significant in the multivariate model but this semiquantitative approach was only able to correctly predict occult disease in 73%. Most recently, in a preliminary study of flow cytometric parameters to predict occult disease in a small cohort of 36 CSI patients, we found that the continuous variable of %EMB and VI were able to correctly predict occult disease in 81% (7).

We feel that our study has very important implications for the care of the CSI NSGCT patient. No longer should patients be offered RPLND or surveillance without regard to a careful analysis of the primary tumor histology. All CSI NSGCT patients should have their primary tumor pathology material reviewed by an experienced reference pathologist who can perform quantitative histological assessment. We have found that measurement of the percentage of embryonal carcinoma and assessment for presence/absence of vascular invasion are the two most important determinants. The logistic regression model using these two variables provided herein yields clinically useful probabilities for occult disease. These probabilities can be used clinically to assist the health care provider and patient in deciding on the most appropriate therapy.

Table 1 *Quantitative histology in clinical stage I NSGCT cohort by final pathologic stage*

	Pathologic stage	
	I	II
Patients, *N* (%)	54 (58.7)	38 (41.3)
% EMB	28.3	30.7
Mean (median) SD	29.9 (28)	74.6 (94.0)
% TER[a]	32.4	25.5
Mean (median) SD	47.3 (45)	16.1 (2.5)
% YS	15.5	7.1
Mean (median) SD	11.7 (5.0)	4.6 (0.5)
% SEM	22.1	14.4
Mean (median) SD	9.3 (0)	4.5 (0)
VI present (%)	9 (16%)	29 (76%)
LI present (%)	3 (5%)	17 (45%)
TI present (%)	5 (9%)	15 (39%)

[a] %TER, percentage of teratoma; % YS, percentage of yolk sac carcinoma; %SEM, percentage of seminoma; LI, lymphatic invasion; TI, tunical invasion.

Table 2 *Univariate and multivariate statistical analysis of quantitative histological factors to predict occult disease in clinical stage I NSGCT*

Variable	P^a	Sensitivity (%)	Specificity (%)	Correct (%)	False positive (%)	False negative (%)
VI	0.0001	76.3	83.3	80.4	23.7	16.7
%EMB	0.0001	65.8	85.2	77.2	24.2	22.0
%TER[b]	0.0001	71.0	77.8	75.0	30.8	20.7
%YS	0.0174	57.9	72.2	66.3	40.5	29.1
LI	0.0001	44.7	94.4	73.9	15.0	29.2
TI	0.0013	39.5	90.7	69.6	25.0	31.9
% SEM	0.2565	NA	NA	NA	NA	NA
% EMB + VI[c]	0.0002	86.8	85.2	85.9	19.5	9.8
	0.0004					

[a] Significance by logistic regression.
[b] %TER, percentage of teratoma; %YS, percentage of yolk sac carcinoma; LI, lymphatic invasion; TI, tunical invasion; %SEM, percentage of seminoma; NA, not applicable.
[c] Multivariate analysis.

Table 3 *Probability of occult disease in clinical stage I NSGCT based on percentage of embryonal carcinoma and presence/absence of vascular invasion*

%EMB	VI	No VI
100	0.92	0.58
75	0.83	0.37
50	0.67	0.20
25	0.46	0.10
0	0.27	0.04

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