Prognostic Factors for Relapse in Stage I Seminoma Managed by Surveillance: A Pooled Analysis

By Padraig Warde, Lena Specht, Alan Horwich, Tim Oliver, Tony Panzarella, Mary Gospodarowicz, and Hans von der Maase

Purpose: **Several management options are available to patients with stage I seminoma, including adjuvant radiotherapy, surveillance, and adjuvant chemotherapy. We performed a pooled analysis of patients from the four largest surveillance studies to better delineate prognostic factors associated with disease progression.**

Patients and Methods: **Individual patient data were obtained from each center (Princess Margaret Hospital, Danish Testicular Cancer Study Group, Royal Marsden Hospital, and Royal London Hospital) for 638 patients. Tumor characteristics (size, histologic subtype, invasion of rete testis, and tumor invasion into small vessels [SVI]) as well as age at diagnosis were analyzed for prognostic importance for relapse.**

Results: **With a median follow-up of 7.0 years (range, 0.02 to 17.5 years), 121 relapses were observed for an actuarial 5-year relapse-free rate (RFR) of 82.3%. On univariate analysis, tumor size (RFR: ≤ 4 cm, 87%; > 4 cm, 76%; *P* = .003), rete testis invasion (RFR: 86% [absent] *v* 77% [present], *P* = .003), and the presence of SVI (RFR: 86% [absent] *v* 77% [present], *P* = .038) were predictive of relapse. On multivariate analysis, tumor size (≤ 4 cm *v* > 4 cm, hazard ratio 2.0; 95% confidence interval [CI], 1.3 to 3.2) and invasion of the rete testis (hazard ratio 1.7; 95% CI, 1.1 to 2.6) remained as important predictors for relapse.**

Conclusion: **We have identified size of primary tumor and rete testis invasion as important prognostic factors for relapse in patients with stage I seminoma managed with surveillance. This information will allow patients and clinicians to choose management based on a more accurate assessment of an individual patient's risk of relapse. In addition, it will allow clinicians to tailor follow-up protocols based on risk of occult disease.**

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THE INCIDENCE RATE of testicular germ cell tumors has doubled in the past 30 years, and although the vast majority of patients present with early-stage curable disease, the continued rising incidence of these tumors presents a major challenge.[1-3] Approximately 45% of germ cell tumors are seminomas, and the majority of these patients (70% to 80%) present with clinical stage I disease.[4] Initial management involves a radical inguinal orchidectomy with high division of the spermatic cord. Orchidectomy is both diagnostic and therapeutic by providing adequate tissue to ascertain the diagnosis and offering cure in a high proportion of patients.

Failure to cure stage I seminoma with orchidectomy alone is due to the presence of occult nodal metastasis, most often present in the paraaortic lymph nodes. This observation led to adjuvant retroperitoneal radiation therapy (RT) being the standard treatment for stage I seminoma for the past 60 years. Such a policy resulted in a relapse-free rate of 95% and an overall cure rate of 99% to 100%. However, it has been recognized that, with the routine use of adjuvant RT, many patients receive unnecessary treatment. The success of a surveillance policy in stage I nonseminomatous germ cell testis tumors and the availability of curative chemotherapy for advanced disease together with improvements in diagnostic imaging led to the investigation of surveillance in stage I testicular seminoma. This approach was pioneered by investigators at the Royal Marsden Hospital. Over the past two decades, a number of other prospective nonrandomized studies of surveillance have been performed.[5-15] The interest in surveillance is due to concerns regarding the use of RT with a known risk of induction of second malignancies caused by RT.[16-18] However, the success of adjuvant RT, the lack of apparent serious late morbidity, and concerns regarding late relapse have dissuaded many clinicians from abandoning the traditional strategy of postoperative RT in favor of surveillance.

One of the reasons for reluctance in adopting a surveillance program is the lack of well-defined prognostic factors that would allow the selection of patients with a low risk of relapse. Prognostic factors for relapse have been studied in a number of the surveillance studies.[8,12,14] The Danish Testicular Carcinoma Study Group (DATECA) study was the first to point out the prognostic importance of tumor size. In this study, a multivariate analysis identified the size of the primary tumor as the only statistically significant predictive factor for relapse.[12] In the Princess Margaret Hospital (PMH) series, on multivariate analysis, age and tumor size were predictive of relapse, while small vessel invasion approached statistical significance.[14] In the Royal Marsden Hospital series of 103 patients managed with surveillance, the only statistically significant factor predicting for relapse was the presence of lymphatic and/or vascular invasion (9% *v* 17% relapse rate).[8]

The available data from surveillance and adjuvant RT series suggest that almost all patients with stage I testicular seminoma are cured, regardless of the management strategy adopted after orchidectomy. The purpose of this study was to more accurately define risk of relapse in patients with stage I seminoma by pooling individual patient data from the four major surveillance series.

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Submitted January 10, 2002; accepted July 25, 2002.

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0732-183X/02/2022-4448/$20.00

DOI: 10.1200/JCO.2002.01.038

Table 1. Candidate Prognostic Factors

Variable	No.	% Missing
Tumor size		
≤ 4 cm	317	6.3
> 4 cm	281	
Age		
≤ 36 years	344	0.3
> 36 years	292	
Small vessel invasion		
Absent	384	9.9
Present	191	
Histologic features		
Classical	548	6.3
Anaplastic	50	
Rete testis invasion		
Absent	299	25.5
Present	176	

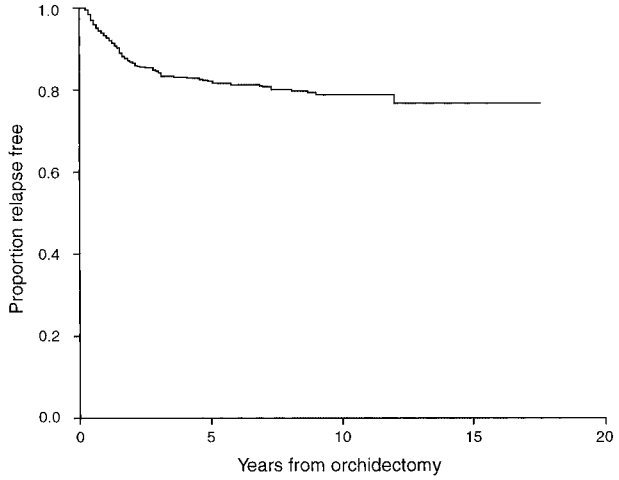

Fig 1. Relapse-free rate for all cases from date of orchidectomy.

PATIENTS AND METHODS

Data Collection

Individual patient data on 638 patients were obtained from four centers: Royal Marsden Hospital (110 cases; median follow-up, 10.7 years), Danish Testicular Cancer Study Group (258 cases; median follow-up, 5.2 years), PMH (226 cases; median follow-up, 7.7 years), and the Royal London Hospital (44 cases; median follow-up, 7.4 years). Using standardized extraction forms, data were collected on patient age, date of diagnosis, date of last follow-up, relapse, and survival status at last follow-up, as well as tumor size and histologic features of the primary tumor (Table 1). Central pathology review was not performed, but individual pathology material was reviewed by an expert pathologist at each center. Data on pathologic factors other than rete testis involvement was available in more than 90% of cases (Table 1). Rete testis invasion in this study meant extension of tumor into the testicular mediastinum without necessarily involving the tubular lumens. Vascular invasion was usually diagnosed by adherence of tumor to the wall of the blood vessel or to thrombus. Endothelial markers were rarely used. The patients were diagnosed between January 1981 and November 1997. At the time of analysis, the overall median follow-up was 7.0 years in this study.

Patient Population

All patients had an inguinal orchidectomy followed by staging investigations to exclude nodal or distant disease. These investigations included chest x-rays (97% of patients), computed tomography scans of the abdomen and pelvis (66% of patients), lymphograms (81% of patients), and serum tumor marker assessments (alpha-fetoprotein and the beta subunit of human chorionic gonadotrophin). The patients were not selected for surveillance by any specific criteria. The surveillance program consisted of regular physical examinations, chest x-rays, and imaging of the retroperitoneal nodes. The frequency of investigations was different in the four centers but largely consisted of repeat investigations every 2 to 6 months in the first 2 to 3 years and less frequently thereafter. At relapse, the standard management was with radiotherapy when disease was confined to the retroperitoneal nodes. In cases of relapse with bulky retroperitoneal disease or distant metastases, chemotherapy was used.

Statistical Analysis

The number of patients used in this prognostic factor pooled analysis was not based on prestudy considerations of statistical power but on the available number of patients from the four centers. The primary study end point was time to relapse. Secondary end points included time to death and cause-specific survival. Each end point was measured from the date of orchidectomy. The principal method of analysis used in this study was proportional hazards regression, which is a multiple regression technique for investigating the relationship between a time to failure outcome (relapse in our study) and possible explanatory (prognostic) variables.[19]

Prognostic factors were identified using a general model selection strategy.[20] First, candidate prognostic factors were individually assessed for their association with outcome. The variables with a $P < .10$ (using a likelihood ratio χ^2 statistic) were then collectively fit in a model. Each variable was then individually removed and the difference in the fit of the resulting two models was calculated. If this difference was statistically significant (ie, $P < .10$), the variable was retained in the model; if not, it was removed and the aforementioned step was repeated. At the conclusion of this iterative process, the set of variables in the model was such that the removal of any one of them would significantly worsen the model fit. As a final step, variables that did not reach statistical significance on their own were introduced into the model to see if the model fit improved significantly. Assumptions of the model were checked and were not found to be in violation.

Plots summarizing time to relapse and relapse-free rate comparisons were produced using the Kaplan-Meier estimate. We performed two sets of analyses. First, we pooled all the data assuming homogeneity across the four series. Then we repeated the analysis, stratifying by series to allow for possible heterogeneity. The results were very similar, and thus we report only the nonstratified analysis. Analyses were performed using SAS software (SAS Institute Inc, Cary, NC) while plots were produced in Splus (Insightful Corporation, Seattle, WA).

RESULTS

With a median follow-up of 7.0 years (range, 0.02 to 17.5 years), relapse occurred in 121 of 638 patients and the 5- and 10-year relapse-free rates were 82.3% and 78.7%, respectively (Fig 1). Most relapses (68.6%) occurred within 2 years of surgery. However, eight relapses (6.6%) occurred more than 6 years after diagnosis. Twenty-seven patients (4.2%) had died at the time of last follow-up, giving a 5-year overall survival rate of 97.7%. In the whole series, six patients (0.9%) died of disease or complications of treatment for relapse, giving a 5-year cause-specific survival rate of 99.3%.

Prognostic Factors for Relapse

The candidate prognostic factors included age, tumor size, rete testis invasion, small vessel invasion, and histologic subtype (classical *v* anaplastic). On univariate analysis, tumor size, rete testis invasion, and the presence of small vessel invasion were statistically significantly associated with relapse (Table 2). Larger tumors had a greater risk of relapse when tumor size was analyzed as a continuous variable or as a dichotomous variable based on the median value of 4 cm. No other factor reached conventional levels of statistical significance. Multivariate analysis was confined to cases with complete information (453 cases with 86 events), and the relapse-free rate in this subgroup was similar to that of the cases excluded from the analysis (185 cases

Table 2. Candidate Prognostic Factors: Univariate Analysis

Variable	No.	5-Year Relapse-Free Rate (% ± SE)	*P* (likelihood χ^2)
Tumor size			
≤ 4 cm	317	86.6 ± 2.0	.003
> 4 cm	281	75.9 ± 2.6	
Age			
≤ 36 years	344	83.2 ± 2.1	.68
> 36 years	292	81.2 ± 2.3	
Small vessel invasion			
Absent	384	85.6 ± 1.8	.038
Present	191	77.3 ± 3.1	
Histologic features			
Classical	548	83.2 ± 1.6	.056
Anaplastic	50	71.4 ± 6.5	
Rete testis invasion			
Absent	299	86.3 ± 2.0	.003
Present	176	76.7 ± 3.3	

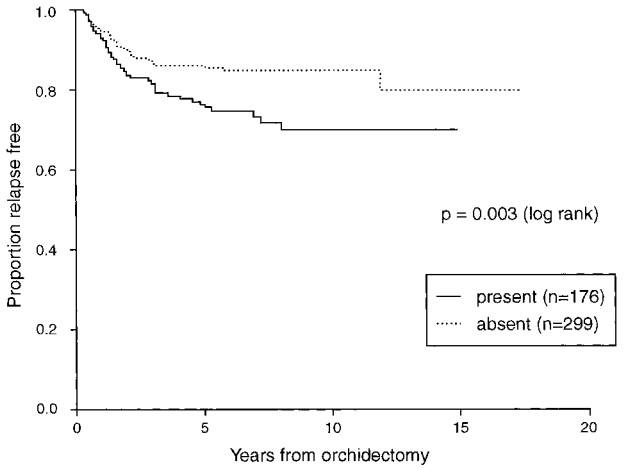

Fig 3. Relapse-free rate based on rete testis invasion from date of orchidectomy.

with 35 events, $P = .98$). In this analysis, only two variables, (tumor size and rete testis invasion, remained independently statistically significant. Patients with tumors greater than 4 cm in greatest diameter were twice (95% confidence interval [CI], 1.3 to 3.2) as likely to relapse as those with smaller cancers, while those with rete testis invasion had a 1.7 (95% CI, 1.1 to 2.6) greater risk of relapse than those without this feature on histologic examination. The effect of tumor size on relapse rate is shown in Fig 2; the effect of rete testis invasion is shown in Fig 3. Only 21 of 176 patients (5-year relapse rate, 12.2%) with no adverse prognostic factor (tumor size ≤ 4 cm, no rete testis involvement) relapsed. In 182 patients with one adverse factor, the 5-year relapse rate was 15.9%, and in the 95 patients with two adverse factors present, the 5-year relapse rate was 31.5% ($P < .0001$, Fig 4). Patients with two adverse prognostic factors were 3.4 times more likely to relapse than patients with no adverse factors (Table 3).

Patient age was not found to be predictive for relapse in the overall population when all factors were included in the pooled analysis. However, a report from PMH showed that younger patients were more likely to relapse; therefore, we investigated the influence of age (≤ 30 years old, lowest quartile) in patients with tumors ≤ 4 cm in greatest diameter. In this subgroup, age was an important prognostic variable, with a 5-year relapse-free rate of 89% in those older than 30 years old (227 patients) as compared with 80.5% in those patients aged ≤ 30 years (90 patients, $P = .038$, Fig 5).

DISCUSSION

This study confirms tumor size as an important factor predicting relapse in patients with stage I seminoma managed with surveillance, as previously noted in the DATECA and PMH reports.[12,14] Patients with tumor size greater than 4 cm (median size of tumors in study) were twice as likely to relapse as those with tumors less than 4 cm in diameter. Tumor size was also highly predictive of relapse when analyzed as a continuous variable.

In the DATECA study, tumor size was the only independent statistically significant predictive factor predictive for relapse.[12] The cumulative risk of relapse after 4 years was 6% in those with tumors less than 3 cm in diameter, 18% for those with tumors 3 to 6 cm in diameter, and 36% for those with tumors 6 cm or larger. In the PMH series, tumor size and age were predictive for relapse, with a 5-year relapse-free rate of 88% in patients with tumors up to 6 cm in greatest diameter, as compared with 67% in those with tumors more than 6 cm in diameter ($P = .004$).[14]

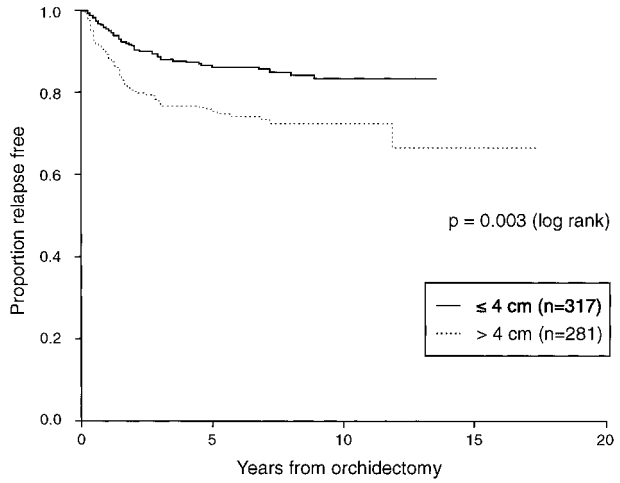

Fig 2. Relapse-free rate based on primary tumor size from date of orchidectomy.

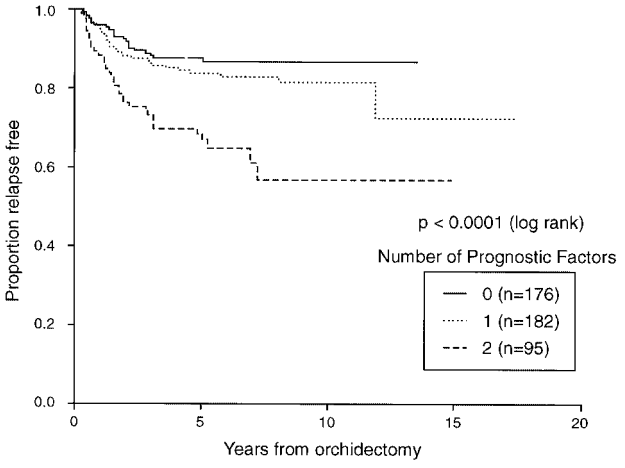

Fig 4. Relapse-free rate based on number of adverse prognostic factors.

Table 3. Five-Year Relapse-Free Rates Based on Tumor Size and Rete Testis Invasion

Tumor Size	Rete Testis Involvement	
	No	Yes
≤ 4 cm	n = 176	n = 75
	87.8% ± 2.5%*	85.6% ± 4.3%*
	HR = 1.0†	HR = 1.7†
		95% CI, 1.1-2.6‡
> 4 cm	n = 107	n = 95
	83.0% ± 3.7%*	68.5% ± 4.9%*
	HR = 2.0†	HR = 3.4†
	95% CI, 1.3-3.2	95% CI, 2.0-6.1

Abbreviation: HR, hazard rate.

*Mean ± SE.

†Hazard ratio relative to baseline (tumor size ≤ 4 cm and no rete testis involvement).

‡Relapse-free rate ± SE.

The rete testis is a communicating network of seminal channels traversing the mediastinum (or hilum) of the testis. Invasion of the rete testis by tumor was seen in 37% of (nonmissing) cases in this study. This rate is similar that of other series in the literature. The prognostic importance of rete testis invasion in predicting for relapse in patients managed by surveillance was noted on univariate analysis in the DATECA study but was not statistically significant on multivariate analysis.[12] Microscopic rete testis invasion has also been reported with greater frequency in patients with stage II seminoma as compared with patients with stage I.[21] In this study, patients with rete testis invasion were 1.7 times more likely to relapse than patients in whom the tumor was confined within the testicular parenchyma. The biologic basis for this increased risk for relapse is unclear. However, the blood and lymph vessels of the testis are in close contact with the rete testis in the testicular hilum, which may explain this observation. In addition, extratesticular extension of germ cell tumors, which has been shown to predict for nodal and distant metastatic disease, has been demonstrated to occur most frequently at the hilum of the testis.[22]

In the PMH series, younger patients were shown to be at greater risk of relapse on surveillance. Age was not a prognostic factor in the DATECA study and was not examined in the Royal Marsden study. In this pooled series of all major surveillance studies, age was not predictive of relapse when all patients were considered. However, in patients with smaller tumors (≤ 4 cm), younger patients (< 30 years) were more likely to develop recurrence.

A number of other histopathologic factors have been studied for prognostic importance, including DNA ploidy status, mitotic rate, DNA S phase percentage, the presence of syncytiotrophoblasts, the degree of lymphocytic infiltration of the primary tumor, and expression of beta–human chorionic gonadotrophin and low-molecular-weight keratin on immunohistochemical analyses.[14] While none of these factors has been shown to be associated with a higher risk of relapse, given the small number of events in the studies, these results must be interpreted with caution.

There is no consensus regarding the optimal follow-up protocol for seminoma surveillance. The existing protocols have evolved over time. Currently, patients at PMH are followed up at 4-month intervals for the first 3 years, 6-month intervals in years 4 to 7, and at yearly intervals in years 8 to 10. At each visit, a computed tomography scan of the abdomen and pelvis is performed, chest x-rays are obtained at alternate visits, and serum tumor marker levels are estimated at each visit for the first 3 years of surveillance. The prognostic factors defined in this series could be used to tailor follow-up strategy based on individual patients' risk of relapse. The use of this information has the potential to lower the cost of surveillance, as the cost of any surveillance protocol is determined primarily by the frequency of follow-up.[23]

As stated earlier, the available data from surveillance and adjuvant RT series indicate that almost 100% of patients with stage I testicular seminoma are cured regardless of the management strategy adopted after orchidectomy. Individual patient preferences must be taken into account in decision making regarding postorchidectomy management. These preferences should be based on many factors, including patients' availability for follow-up, the side effects associated with both approaches, and patients' personal circumstances. Some patients may view the risk of second malignancy 20 to 25 years in the future as of little importance and may prefer adjuvant RT to minimize the more immediate risk of relapse. On the other hand, one of the most attractive features of surveillance is the prospect of avoiding unnecessary treatment in many patients who do not need it. However, surveillance must not compromise survival, and it is reassuring to find that there were only six disease-related deaths in the 638 patients in this series. While isolated occurrences of second nontesticular tumor following treatment of seminoma with RT have been reported in the past, there is now convincing data from large, population-based studies that patients with seminoma treated with RT have an increased risk of developing a second malignancy. The largest study of second cancers in long-term survivors of testicular cancer was conducted by Travis et al[17] at the National Cancer Institute, Cancer Epidemiology Division. More than 28,000 patients with testis cancer, including more than 15,000 with seminoma from 16 population-based registries worldwide, were evaluated. Overall, 1,406 second cancers, excluding contralateral testis cancers, occurred against 981 expected (observed-to-expected ratio, 1.43). An excess of rectal and small intestine cancers were seen in seminoma patients. The actuarial risk of developing a second malignancy, excluding contralateral testis cancers, increased over time from diagnosis and was 18.2% at 25 years. Secondary leukemia was

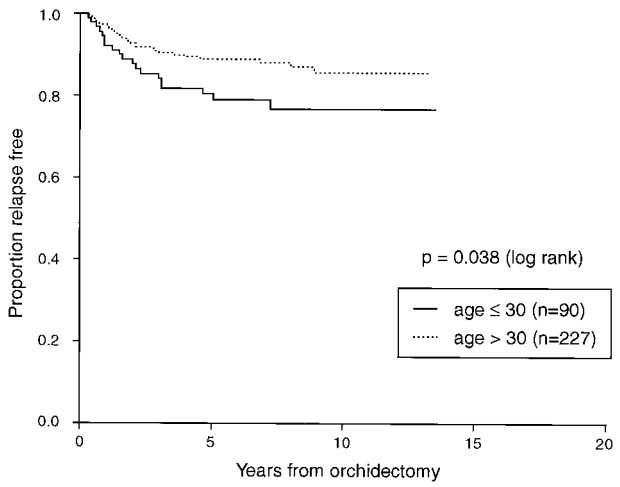

Fig 5. Relapse-free rate based on age comparison for tumor size subgroup ≤ 4 cm.

linked with RT and chemotherapy, whereas an excess of the stomach, bladder, and possibly pancreatic tumors was associated with prior RT. This factor is one of the major reasons to consider surveillance as an alternative to RT.

Both surveillance and adjuvant RT are choices for patients with stage I seminoma. The identification of prognostic factors for occult disease in this study will allow patients and clinicians to choose management based on a more accurate assessment of an individual patient's risk of relapse.

ACKNOWLEDGMENT

We thank Laura Nash for her assistance in preparation of the manuscript.

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Journal of Clinical Oncology

The Official Journal of the American Society of Clinical Oncology

Vol 20, No 22 **CONTENTS** **November 15, 2002**

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Journal of Clinical Oncology (ISSN 0732-183X) is published 24 times a year, twice monthly, by Lippincott Williams & Wilkins, 351 West Camden Street, Baltimore, MD 21201-2436. Periodicals postage paid at Hagerstown, MD, and at additional mailing offices. The GST number for Canadian Subscribers is 895524239.

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