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ORIGINAL REPORT

Risk-Adapted Treatment in Clinical Stage I Testicular Seminoma: The Third Spanish Germ Cell Cancer Group Study

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ABSTRACT

Purpose
To confirm the efficacy of a risk-adapted treatment approach for patients with clinical stage I seminoma. The aim was to reduce both the risk of relapse and the proportion of patients receiving adjuvant chemotherapy while maintaining a high cure rate.

Patients and Methods
From 2004 to 2008, 227 patients were included after orchiectomy in a multicenter study. Eighty-four patients (37%) presented no local risk factors, 44 patients (19%) had tumors larger than 4 cm, 25 patients (11%) had rete testis involvement, and 74 patients (33%) had both criteria. Only the latter group received two courses of adjuvant carboplatin, whereas the rest were managed by surveillance.

Results
After a median follow-up time of 34 months, 16 relapses (7%) have been documented (15 [9.8%] among patients on surveillance and one [1.4%] among those treated with carboplatin). All relapses occurred in retroperitoneal lymph nodes, except for one case in pelvic nodes. Median node size was 25 mm, and median time to recurrence was 14 months. All patients were rendered disease-free with chemotherapy. The actuarial 3-year disease-free survival rate was 88.1% (95% CI, 82.3% to 93.9%) for patients on surveillance and 98.0% (95% CI, 94.0% to 100%) for those treated with adjuvant chemotherapy. Overall 3-year survival was 100%.

Conclusion
With the limitations of the short follow-up duration, we confirm that a risk-adapted approach is effective for stage I seminoma. Adjuvant carboplatin seems adequate treatment for patients with 2 risk criteria, as is active surveillance for those with 0 to one risk factors. More reliable predictive factors are needed to improve the applicability of this model.

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INTRODUCTION

More than a half of testicular germ cell tumors are seminomas, and approximately 75% of them are diagnosed in patients with clinical stage I disease, thus representing 40% of all testicular cancers. In this clinical scenario, the probability of long-term survival approaches 100% and this implies an additional life span of about 50 years. Current therapeutic trials in stage I seminoma are aiming to maintain these favorable results while reducing treatment-related toxicity.[1] Several management options are now available (ie, radiation therapy, active surveillance, and adjuvant carboplatin), but no international consensus exists among urologists and oncologists on the preferred treatment plan.[2] The only published randomized trial in this setting compared one course of single-agent carboplatin with paraortic radiotherapy (20 to 30 Gy). Five-year relapse-free survival rates were equivalent, but the toxicity data and the incidence of second neoplasms (both testicular and extratesticular) favored adjuvant chemotherapy.[3] However, both modalities may represent overtreatment, as more than 80% do not experience relapse after orchiectomy without additional therapy (active surveillance).[4]

In a previous Spanish Germ Cell Cancer Group (SGCCG) study, we demonstrated that adjuvant carboplatin may be safely restricted to patients with high risk of relapse (tumor size > 4 cm and/or rete

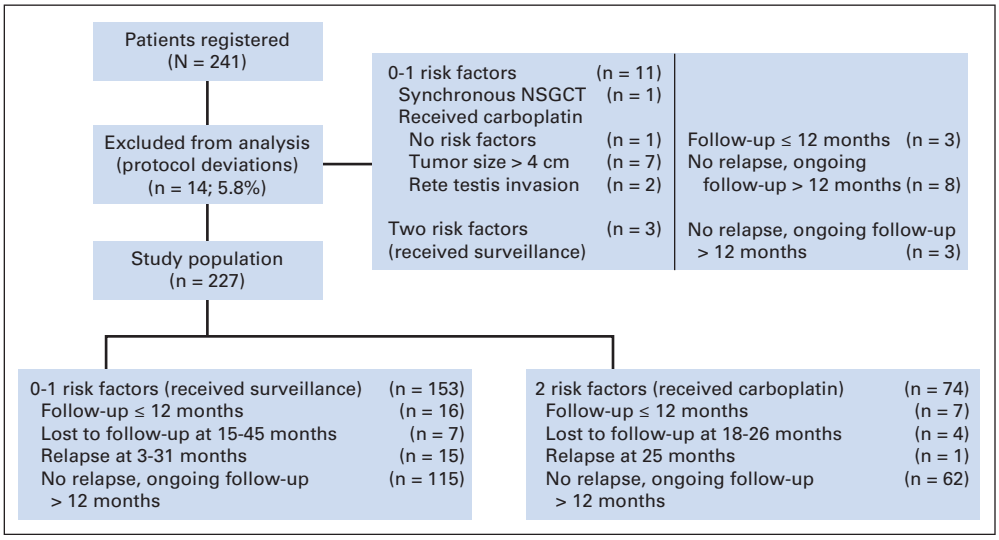

Fig 1. CONSORT diagram of patients in the study. NSGCT, nonseminomatous germ cell tumor.

testis invasion, the most widely accepted prognostic factors for recurrence[4]). Long-term results were excellent (4% relapse rate and 100% cause-specific survival), but as many as 68% of patients needed to be treated with postoperative chemotherapy.[5] The present study was designed as a prospective audit of practice with the following objectives: (1) to confirm the efficacy of a risk-adapted treatment policy by using widely accepted risk criteria in a multicenter setting and (2) to reduce the proportion of patients receiving adjuvant carboplatin while maintaining a high cure rate.

PATIENTS AND METHODS

After orchiectomy performed at any of the SGCCG participating centers, patients with histologically proven pure seminoma, clinical stage I disease, and resection margins free of tumor were included in this study. Routine staging procedures consisted of clinical history, physical examination, chest x-ray films, computed tomography (CT) of abdomen and pelvis, ultrasonography of the contralateral testicle, whole blood cell counts, and serum chemistries including lactate dehydrogenase, α-fetoprotein (AFP), and β-human chorionic gonadotropin (BHCG). Increased values of BHCG were acceptable preoperatively. However, the persistence of increased postoperative BHCG levels or any pre- or postoperative elevation of AFP were considered exclusion criteria. The American Joint Committee on Cancer (1997 edition) TNM classification was used.[6] Informed consent for this risk-adapted policy was attained before group allocation, and a central, prospective registration at the SGCCG data center was used. Patients with two local risk factors (tumors $>$ 4 cm and invasion of the rete testis[4]) received two courses of adjuvant single-agent carboplatin (area under the curve of 7, with 21-day interval). Treatment was given on an outpatient basis, within 2 hours. Systematic antiemetic prophylaxis with dexamethasone and 5-hydroxytryptamine-3 antagonists was used. Complete blood cell counts, serum biochemistry, and toxicity assessment (World Health Organization criteria) were performed on days 1, 22, and 43. Patients with 0 or one of the aforementioned risk factors were managed by clinical surveillance. In both groups (chemotherapy and surveillance), clinical history, physical examination, chest x-rays, AFP, and BHCG were scheduled at months 3, 6, 9, 12, 18, 24, 30, 36, 48, 60, and 72 months after orchiectomy, and abdominal CT scans were performed at 6, 12, 18, 24, 30, 36, 48, 60, and 72 months. Tumor recurrences were treated with etoposide and cisplatin chemotherapy,[7] independently of the initial management.

Potential predictive factors for relapse were prospectively recorded, including patient age ($\leq$ 30 *v* $>$ 30 years), tumor size ($\leq$ 40 *v* $>$ 40 mm), histologic variant (classical *v* anaplastic), pT stage (pT1-2 *v* pT3-4), presence of vascular invasion, rete testis invasion, and preoperative BHCG levels (negative *v* positive). Histologic features were reviewed locally. To compare proportions between groups, Pearson's χ^2 or Fisher's exact tests (when appropriate) were used. Overall survival (OS) and disease-free survival (DFS) were estimated from the date of orchiectomy with the Kaplan-Meier method. Comparison of resulting curves and univariate analysis of prognostic factors were performed with the log-rank test. Ninety-five percent CIs were given when appropriate.

RESULTS

Between 2004 and 2008, 241 consecutive patients with testicular seminoma were prospectively registered for this study. All of them underwent an inguinal orchiectomy at any of the 33 SGCCG participating hospitals (Appendix, online only). Fourteen cases (5.8%) were excluded from per-protocol analyses because of major protocol deviations detected at the time of registration, leaving a study population of 227 patients. Figure 1 shows a flowchart diagram of the process. One patient (0.4%) presented with a synchronous bilateral seminoma, whereas 123 tumors (54%) were right-sided and 103 were (45%) left-sided. Median patient age was 33 years (range, 21 to 59 years). The median of maximum tumor diameter was 41 mm (range, 3 to 120 mm). Preoperative serum BHCG levels were increased (ie, $>$ 9 mU/mL) in 31 cases (15%; median 25 mU/mL; range, 11 to 21,955 mU/mL). Eighty-four patents (37%) presented no local risk factors for relapse, 44 (19%) had tumors larger than 4 cm, 25 (11%) had rete testis involvement, and 74 (33%) had both risk factors. Only the latter group received two courses of adjuvant carboplatin, whereas the rest were managed by active surveillance. Main patient characteristics and distribution of prognostic factors among treatment groups are depicted in Table 1. Median time from orchiectomy to start of chemotherapy was 40 days (range, 7 to 87 days). Median time interval between courses was 21 days (range, 21 to 35 days). No dose reductions were performed. Grade 3 to 4 adverse events consisted of uncomplicated

Table 1. Patient Characteristics

Characteristic	Surveillance (n = 153) No.	%	Carboplatin (n = 74) No.	%	All Patients (n = 227) No.	%
Age, years						
≤ 30	57	37.5	17	23.0	74	32.7
> 30	95	62.5	57	77.0	152	67.3
Tumor diameter, mm						
≤ 40	109	71.2	0	0	109	48.0
> 40	44	28.8	74	100	118	52.0
Preoperative serum BHCG positive*						
Yes	14	10.4	17	24.6	31	15.2
No	121	89.6	52	75.4	173	84.8
Histologic subtype						
Classical	149	98.7	69	94.5	218	97.3
Anaplastic	2	1.3	4	5.5	6	2.7
Staging, pT						
pT1	124	82.1	36	49.3	160	71.4
pT2	26	17.2	32	43.8	58	25.9
pT3	1	0.7	5	6.8	6	2.7
Vascular invasion†						
Yes	23	15.2	32	44.4	55	24.7
No	128	84.8	40	55.6	168	75.3
Rete testis invasion						
Yes	25	16.3	74	100	99	43.6
No	128	83.7	0	0	128	56.4
Local risk criteria				0		
None	84	54.9	0	0	84	37.0
Tumor > 40 mm	44	28.8	0	0	44	19.4
Rete testis invasion	25	16.3	0	0	25	11.0
Both criteria	0	0	74	100	74	32.6

Abbreviation: BHCG, β-human chorionic gonadotropin.
*Data available in 204 patients (89.9%).
†Data available in 223 patients (98.2%).

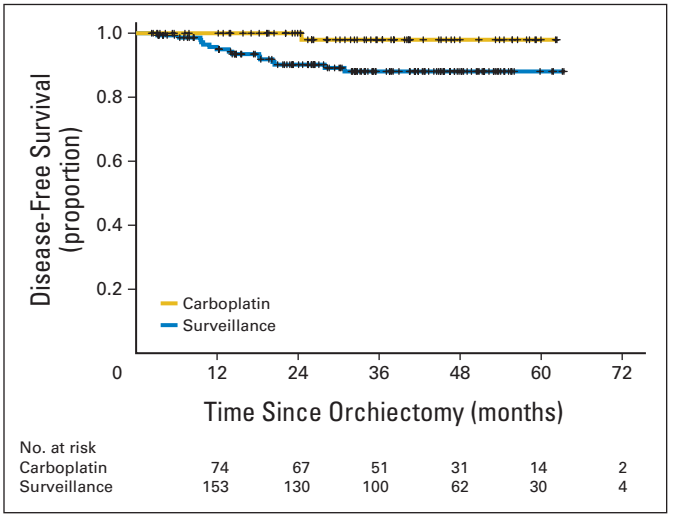

Fig 2. Actuarial disease-free survival for the entire study population according to treatment allocation: adjuvant carboplatin (upper curve, n = 74) versus surveillance (lower curve, n = 153).

thrombocytopenia (8% patients), afebrile neutropenia (4%), anemia (2%), and emesis (2%).

At the time of this analysis, median follow-up time was 34 months (range, 4 to 64 months), and 168 patients (74%) have been observed for more than 2 years. Relapses were observed in 15 patients (9.8%) on surveillance (4.8% of cases with no risk criteria, 13.6% of tumors larger than 4 cm, and 20% of those involving the rete testis) and in one patient (1.4%) treated with carboplatin (with both risk criteria). No patient experienced relapse with symptoms of disease, whereas recurrences were detected by means of routine CT scans (12 cases, 75%) or increase in serum BHCG levels (four cases, 25%). All relapses were located in retroperitoneal lymph nodes, except for one case (90 mm diameter) in pelvic nodes. Median tumor size at recurrence was 25 mm (range, 5 to 90 nm), and median time to relapse was 14 months (range, 3 to 31 months). All these patients were rendered disease-free, 14 of them with chemotherapy (etoposide and cisplatin chemotherapy), one with radiotherapy, and one with surgery plus chemotherapy. The actuarial 3-year DFS was 88.1% (95% CI, 82.3% to 93.9%) for patients on surveillance (93.5% for cases with no risk factors, 83.7% for patients with tumor size > 4 cm, and 78.3% for those with rete testis involvement) and 98.0% (95% CI, 94.0% to 100%) for those treated with adjuvant chemotherapy (Fig 2). Three-year OS was 100%.

A univariate analysis of predictive factors for DFS was performed with patients under surveillance. Although numbers are small, the presence of any local risk criteria was related with higher recurrence rate ($P = .048$, Pearson χ^2 test), whereas the presence of rete testis invasion showed a nonsignificant ($P = .061$) trend association. No other parameter was found to be correlated with patient outcome. Table 2 depicts the proportion of relapses among prognostic categories. Figure 3 shows the actuarial DFS curves according to the presence of tumor size over 4 cm, rete testis invasion, or no risk criteria among patients under surveillance.

DISCUSSION

Testicular cancer is an infrequent disease accounting for 1% to 2% of all malignant neoplasms in men. However, it represents the commonest malignancy in young males 15 to 34 years of age. It is the most curable solid tumor, with an overall 10-year relative survival rate of more than 95%.[8] Stage I seminoma is the most frequently diagnosed germ cell tumor, and almost all patients are cured, regardless of management approach. Three postorchiectomy treatment options have been developed for this group: adjuvant radiation therapy, active surveillance, and adjuvant chemotherapy with carboplatin, which offer similar results.[1,2] Randomized clinical trials have demonstrated that prophylactic radiotherapy can be safely limited to the paraortic field, the radiation doses can be reduced to 20 Gy, and one single course of adjuvant carboplatin is as effective as radiation therapy.[9] Although surveillance has not been evaluated in randomized trials, observational studies showed that 15% to 20% of patients experience relapse on follow-up, the majority in the para-aortic lymph nodes, but almost all recurrences could be successfully treated with chemotherapy or radiotherapy.[4]

Because cure is almost universally possible for all patients with stage I seminoma, management decisions should therefore rest predominantly on the likely morbidity and convenience of different treatment approaches. Particular concern has been expressed about the treatment of this young patient population with adjuvant

Table 2. Distribution of Seminoma Relapses Among Prognostic Categories

Characteristic	Surveillance			Carboplatin			All Patients		
	No.	Total	%	No.	Total	%	No.	Total	%
Relapses	15	153	9.8	1	74	1.4	16	227	7.0
Age, years									
≤ 30	5	57	8.8	0	17	0	5	74	6.8
> 30	10	95	10.5	1	57	1.7	11	152	7.2
Tumor diameter, mm									
≤ 40	9*	109	8.3	—	—		9	109	8.3
> 40	6	44	13.6	1	74	1.4	7	118	5.9
Preoperative serum BHCG positive†									
Yes	3‡	14	21.4	0	17	0	3	31	9.7
No	11	121	9.1	0	52	0	11	173	6.4
Histologic subtype									
Classical	14§	149	9.4	1	69	1.5	15	218	6.9
Anaplastic	1	2	50.0	0	4	0	1	6	16.7
Staging, pT									
pT1	12	124	9.7	0	36	0	12	160	7.5
pT2	2	26	7.7	1	32	3.1	3	58	5.2
pT3	1	1	100	0	5	0	1	6	16.7
Vascular invasion‖									
Yes	2	23	8.7	1	32	3.1	3	55	5.5
No	13	128	10.2	0	40	0	13	168	7.7
Rete testis invasion									
Yes	5¶	25	20.0	1	74	1.4	6	99	6.1
No	10	128	7.8	—	—		10	128	7.8
Local risk criteria									
None	4#	84	4.8	—	—		4	84	4.8
Tumor > 40 mm	6	44	13.6	—	—		6	44	13.6
Rete testis invasion	5	25	20.0	—	—		5	25	20.0
Both criteria	—	—		1	74	1.4	1	74	1.4

Abbreviation: BHCG, β-human chorionic gonadotropin.
*$P = .270$ (Pearson's χ^2 test).
†Data available in 204 patients (89.9%).
‡$P = .162$ (Fisher's exact test).
§$P = .189$ (Fisher's exact test).
‖Data available in 223 patients (98.2%).
¶$P = .061$ (Pearson's χ^2 test).
#$P = .048$ (Pearson's χ^2 test).

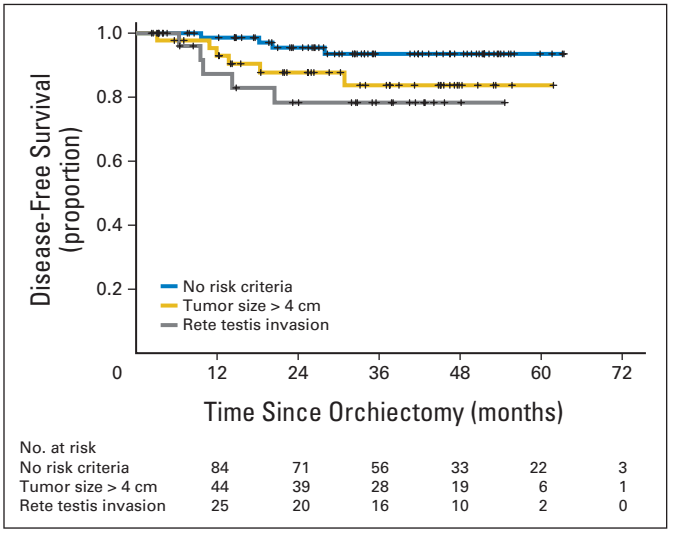

Fig 3. Actuarial disease-free survival for 153 patients undergoing active surveillance according to the presence of each risk criteria ($P = .067$, log-rank test with 2 *df*).

radiation therapy, which is associated with a marked increase in second malignancies after prolonged follow-up[10,11] and is thereby in rapid decline in the United States and Europe.[12] The problems with surveillance are the absence of a widely accepted, standardized follow-up schedule and the recent concern about the potential carcinogenic effect of radiation exposure from multiple CT scans, particularly among younger patients.[13] Adjuvant carboplatin is almost completely devoid of long-term toxicity[14] (although long-term data are spare), but it implies overtreatment, as some 80% patients would have never experienced relapse without any postorchiectomy treatment.

A risk-adapted management is an entirely rational approach because it avoids treatment-related morbidity for patients whose disease was cured by orchiectomy and restricts adjuvant therapy for those at a higher risk of relapse. However, reliable prognostic factors have not been established. Tumor size greater than 4 cm and invasion of the rete testis are the most widely accepted ones,[4] although the model requires more refinement to increase its predictive value. In fact, results from validation studies have been discordant, mainly due to elevated percentages of missing data on rete testis invasion.[15-17] To our knowledge, the only published studies evaluating a risk-adapted approach in patients with stage I seminoma have been performed by the SGCCG. In the first study, 59% of 203 patients were safely preserved from any form of adjuvant therapy, with 100% 5-year cause-specific survival. However, the risk criteria used for administration of adjuvant chemotherapy were not standard.[18] In the second study, we treated patients with one or two of the aforementioned risk factors with carboplatin, which represented 68% of 314 cases. Relapses were observed in 6% of low-risk patients on surveillance and in 3.3% of high-risk patients after chemotherapy. No deaths owing to seminoma were observed.[5]

To minimize potential overtreatment, in this third study we restricted carboplatin to subjects with both risk criteria. Then 67% of 227 patients with stage I seminoma have not received adjuvant treatment. Relapse rates observed seem reasonable in all groups (9.8% on surveillance and 1.4% after carboplatin). Probably the 20% rate of recurrences among patients with rete testis invasion may require further study with larger numbers. Patient characteristics in the second and third SGCCG studies were quite similar, and their overall relapse rates were 4.1% and 7.0%, respectively. However, the relative frequency of cases within each prognostic category varied among both studies (particularly, the proportion of patients with two risk criteria increasing from 15% to 33%). This is perhaps a reflection of a referral bias: in Spain, the nonprotocol standard for these cases is adjuvant carboplatin, and some centers would have not included patients with one risk factor in the present study. Oliver et al[3] used one course of carboplatin in their randomized trial, which is now considered standard. However, there had been prior concerns that two courses could be more effective,[19] and thus we seemed justified in its administration for high-risk patients. In addition, acute toxicity is very manageable, and late adverse effects of carboplatin have not been described.[5,14] The present study did not specifically address these issues. Other limitations of this study are the lack of central review of histopathology,the

aforementioned overrepresentation of patients with two risk criteria, and the relatively short follow-up period.

In conclusion, our results confirm our previous suggestion that a risk-adapted treatment policy is feasible in a multicenter setting, as relapse rates are acceptable and no seminoma-related mortality was seen. Adjuvant carboplatin seems adequate treatment for patients with two risk criteria, as is active surveillance for those with 0 to one risk factor. Longer follow-up is needed to rule out the occurrence of late relapses and delayed toxicity of chemotherapy in this series. This management option spares 67% of cases from adjuvant treatment without compromising results and represents an alternative to systematic approaches such as irradiation, surveillance, and carboplatin. In fact, the second European consensus conference on diagnosis and treatment of germ cell cancer has recently accepted this recommendation.[20] Much work is to be done to better define more accurate predictive factors for relapse. We are now planning a multivariate analysis of clinical and pathologic risk features among 744 patients included in all three SGCCG studies. Future studies of molecular tumor characteristics, gene signatures, and improved imaging techniques may further refine the approach to the management of stage I seminoma.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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Collection and assembly of data: Jorge Aparicio, Andrés Meana, Purificación Martínez del Prado, Javier Sastre, Juan J. Satrústegui, Regina Gironés, Lidia Robert
Data analysis and interpretation: Jorge Aparicio, Pablo Maroto, Xavier García del Muro, Josep Gumà, Alfonso Sánchez-Muñoz, Mireia Margelí, Montserrat Doménech, Romá Bastús, Antonio Fernández, Marta López-Brea, Josefa Terrassa, José R. Germà
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Final approval of manuscript: All authors

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