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Original Paper

Prognostic Factors for Patients with Advanced Seminoma Treated with Platinum-based Chemotherapy

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Prognostic factors for 3-year progression-free survival (PFS) were defined in 286 patients with advanced seminoma treated with cisplatin-based chemotherapy at 10 European oncology units (no prior treatment: 236; prior radiotherapy: 50). Previously irradiated patients displayed a 69% PFS as compared to 87% in those presenting with advanced seminoma at the time of diagnosis ($P = 0.009$). In the univariate analysis, the extent and site of disease before chemotherapy and the level of serum LDH (<2.0 versus ≥2.0 × upper limit of normal) correlated with PFS in previously non-irradiated patients, but not in patients with prior radiotherapy. The multivariate analysis was, therefore, restricted to previously non-irradiated patients. The presence of non-pulmonary visceral metastases and a serum LDH level of ≥2 × normal (N) proved to be independent prognostic factors. Based on these variables, two prognostic models were constructed and validated in an external data set of 166 comparable patients. For clinical use, Model 2 is recommended. The good-prognosis group comprises non-irradiated patients with stage II seminoma and any LDH level at presentation, or stage III and IV patients (with lung metastases only) whose serum LDH level is <2 × N. These patients display a 94% 3-year PFS. The poor prognosis group includes all other patients with a 56% PFS. With this prognostic model, individualisation of the therapeutic approach may be considered in patients with advanced seminoma and a high risk of chemotherapy-related toxicity. © **1997 Elsevier Science Ltd.**

Key words: advanced seminoma, progression-free survival, prognostic factors

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INTRODUCTION

OF PATIENTS with seminoma 20–25% present with metastatic disease. The majority of these have disease confined to lymph nodes, presenting as stage II or stage III disease [1]. In addition, approximately 3% of the patients with initially stage I seminoma relapse after adjuvant abdominal radiotherapy, most frequently beyond the radiation field.

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Until the mid-1980s radiotherapy was widely accepted as the treatment of choice in such cases [2]. However, during the last decade, cisplatin-based chemotherapy has gained increasing popularity as the optimal treatment approach, and long-term survival after such chemotherapy has been reported in 70–90% of cases [2–10].

In order to establish a more individualised and risk-based treatment, it is necessary to define prognostic factors. These help the clinician to identify those patients most at risk of treatment failure with routine cisplatin-based chemotherapy and help to select those patients who may be cured by less

Table 1. Patient characteristics

	Prior radiotherapy	No prior radiotherapy	Total
Number of patients	50	236	286
Mean age (standard deviation) (Years)	39 (11.4)	41 (9.5)	40 (11.1)
Initial treatment/treatment policy			
Surveillance		13	13
XRT below diaphragm	45		45
XRT below and above diaphragm	5		5
No previous treatment		223	223
Clinical stage at start of chemotherapy*			
II	5	143	148
III	23	39	62
IV PVM	9	27	36
IV NPVM	12	21	33
Unknown	1	6	7
LDH			
$<2 \times N$	14	89	103
$2-3 \times N$	5	21	26
$>3 \times N$	4	23	27
Unknown	27	103	130

*Royal Marsden Classification System [1].
NPVM, non-pulmonary visceral metastases; PVM, pulmonary visceral metastases.

intensive therapy with reduced toxicity. With this background, clinical information on a large number of patients with advanced seminoma was collected and analysed with regard to prognostic factors, using the endpoint of progression-free survival.

PATIENTS AND METHODS

Members of the Medical Research Council Testicular Tumour Working Party (Medical Research Council, U.K.) were asked retrospectively to provide data on patients with advanced seminoma treated with chemotherapy, either as first-line treatment or following relapse after radiotherapy. Clinical data were collected on a form especially designed for the study, and included details of stage and treatment at initial diagnosis, sites and dimensions of disease at the start of chemotherapy, serum tumour marker levels (AFP [alpha fetoprotein], HCG [human chorionic gonadotrophin], LDH [lactate dehydrogenase]) and smoking history. The chemotherapy regimen and number of courses were recorded, together with details of treatment given to postchemotherapy residual masses. Outcome measures included response to chemotherapy, time to disease progression and overall survival. Data management and statistical analysis were carried out by the MRC Cancer Trial Office, Cambridge, U.K.

The principal endpoint for the present analysis of prognostic factors was progression-free survival (PFS). PFS curves were obtained by the Kaplan–Meier method, and compared using the logrank test, with tests for trend across ordered categories where appropriate. Multivariate analysis used Cox's proportional hazards regression model, with a forward stepwise variable selection procedure. The robustness of the prognostic models developed was tested by applying the model to an independent data set comprising 166 patients from two recent prospective clinical trials.

MRC trial TE12 is a randomised comparison of single-agent carboplatin with EP (etoposide + cisplatin) in advanced metastatic seminoma [11]. The trial recruited 130 patients between 1990 and 1994. 14 patients died; the median follow-up time of surviving patients being 28 months. Progression-free survival at 2 years is 80% (95% confidence interval [CI]: 72–88%).

EORTC trial 30874 is a non-randomised phase II study of HOP (ifosphamide, vincristine, cisplatin) in patients with advanced metastatic seminoma [12]. The trial recruited 42 eligible patients between 1988 and 1992. Six patients have been excluded from the validation set as they had already been included in the main database. Three patients died, and the median follow-up of surviving patients is 29 months. Progression-free survival at 2 years is 91% (95% CI: 82–99%).

RESULTS

A total of 303 patients were entered into the study, of whom the 286 patients receiving platinum-based chemotherapy have been included in this report. Patients were entered from nine Oncology units in the U.K. and from one Norwegian Cancer Centre. They were treated between 1978 and 1992, with 43% treated after 1985 and represent a subgroup of the patients with seminoma included in the meta-analysis performed by the International Germ Cell Cancer Collaborative Group, from whom more detailed clinical data were available [13].

Of the 286 patients, 223 (78%) first presented with advanced disease, 13 had developed metastases during surveillance for stage I disease, and 50 had relapsed after previous radiotherapy (Table 1). 148 patients had stage II disease [1] at the time of chemotherapy, 74% of whom had abdominal masses >5 cm in maximum transverse diameter. Of the 69 patients with visceral metastases (stage IV), 33 had metastases to non-pulmonary visceral organs such as liver or bone (with or without other sites of disease manifestations, IV NPVM), whereas the lungs were the only site of the visceral involvement in 36 patients (IV PVM). All patients had normal levels of serum AFP. Serum HCG

Table 2. Univariate analyses

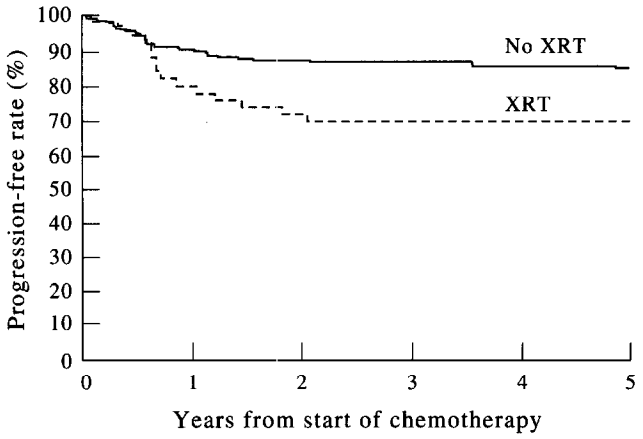
		Number of patients	3-year PFS	Logrank P*
Clinical stage at chemotherapy start	II	148	93%	
	III	62	75%	
	IV PVM†	36	71%	
	IV NPVM‡	33	67%	<0.0001
Number of lung metastases	none	243	97%	
	1–5	23	70%	
	>5	11	51%	<0.0001
LDH (× upper limit of normal)	<1.5	86	89%	
	1.5–1.9	17	87%	
	2.0–2.9	26	73%	
	>3.0	27	67%	0.003
Non-pulmonary visceral metastases	no	253	86%	
	yes	33	67%	0.009
Previous radiotherapy	no	236	87%	
	yes	50	69%	0.009
Supraclavicular nodes	none	242	86%	
	≤2 cm	6	83%	
	2.1–5 cm	17	65%	
	>5 cm	8	67%	0.02
Mediastinal nodes	none	232	86%	
	≤5 cm	20	67%	
	>5 cm	25	75%	0.03
Previous treatment	Newly diagnosed	223	87%	
	Relapse after surveillance	13	83%	
	Relapse after radiotherapy	50	69%	0.03
Age (years)	<35	78	91%	(d.f. = 2)
	35–45	119	81%	
	>45	89	81%	0.11
HCG	Normal	135	83%	
	<100	101	85%	
	100–1000	32	93%	
	>1000	18	67%	0.34
Year of chemotherapy	1978–1985	163	81%	
	1986–1992	123	86%	0.34
Abdominal nodes	none	64	76%	
	≤5 cm	52	88%	
	5.1–10.0 cm	100	87%	
	>10.0 cm	42	80%	0.56
Primary site	testis	254	84%	
	extragonadal	32	81%	0.70
Chemotherapy				
Carboplatin monotherapy		58	79%	
Cisplatin monotherapy		15	100%	0.22 (d.f. = 4)
BEP		69	88%	
PVB		70	81%	
Other cisplatin-based combinations		74	81%	
Smoking history				
Never smoked		76	90%	
Ex-smoker		27	81%	0.34 (d.f. = 2)
Smoker		92	84%	
Not known		90		

*One degree of freedom (d.f.) unless otherwise specified; †Visceral metastases to the lungs only; ‡Non-pulmonary visceral metastases. PVB, cisplatin, vinblastine, bleomycin; BEP, cisplatin, etoposide, bleomycin; LDH, lactate dehydrogenase.

levels were normal in 135 patients and elevated in 151. Serum LDH levels were not routinely measured in several centres and so were available for only 156 patients. Levels were normal in 57 (37%).

A variety of platinum-based chemotherapy regimens were employed depending on the individual institution's policy PVB (cisplatin, vinblastine, bleomycin [14]): 70 patients; BEP (cisplatin, etoposide, bleomycin [15]): 69 patients; carboplatin monotherapy [9]: 58 patients; cisplatin monotherapy: 15 patients; HOP (cisplatin, vincristine, ifosphamide [12]): 10 patients; POMB/ACE (cisplatin, vincristine, methotrexate, bleomycin, actinomycin D, cyclophosphamide and etoposide [16]): 9 patients; other cisplatin regimens: 55 patients. High-dose chemotherapy with stem cell support was not used as first-line treatment in any patient.

161 patients had a total of 194 residual masses following chemotherapy. 70 masses were observed without further treatment, 78 were irradiated, 30 resected (26 completely)



Numbers at risk

No XRT	236	202	185	174	155	131
XRT	50	38	33	31	30	25

Figure 1. Progression rates by prior use of radiotherapy (XRT) (all patients).

and a further 7 residual mass sites were irradiated after resection. Of the 37 masses which were resected, histology was available for 34: 4 masses contained viable seminoma, 2 contained viable non-seminomatous germ cell tumour, a further 2 contained teratoma differentiated and the remaining 26 contained only necrosis and/or fibrosis. For 9 residual masses, information on postchemotherapy treatment was not available (a more detailed analysis of the postchemotherapy residual masses and their treatment is under preparation).

45 patients died, 7 of other causes when disease-free and 38 of or with seminoma (for 6 of the latter patients, the event and the time to progression were not stated in the case record forms). The surviving patients have been followed for a median of 6.5 years (range 1–14 years) with 92% followed for more than 3 years from the start of chemotherapy. Of the 241 surviving patients, 20 have residual seminoma. The overall survival rate (death from any causes) at 3 years is 85% (95% CI: 81%–89%). In 48 patients, the time to progression was reported, of whom 14 were rendered tumour free by salvage treatment and are alive and disease-free with a median follow-up time from progression of 5 years (range 1–9 years). One of the progressing patients died from pulmonary embolism with unknown tumour status, one is alive with residual seminoma and 32 died from seminoma. Progression-free survival at 3 years is 84% (95% CI: 80–88%) for all patients.

Univariate analysis

Table 2 summarises the results of the logrank analyses. Individually, the most significant variables were clinical stage at the start of chemotherapy, the presence or absence of non-pulmonary visceral metastases and the level of serum LDH, despite the latter being available in only 156 patients. The prognosis was not significantly worse in patients with extragonadal primary tumours, nor in those with elevated HCG. Patients with prior radiotherapy had a significantly poorer prognosis (Figure 1; $P = 0.009$). Although the adverse prognosis of irradiated patients is partly explained by the extent of their disease at the start of chemotherapy, there was evidence that the prognostic factors in patients with previous radiotherapy were different to those of previously non-irradiated patients with respect to further subdivision of disease stage and also serum LDH level (Table 3). Formal tests for interaction between prior radiotherapy and both clinical stage and LDH level yielded P-values of 0.06 and 0.02, respectively. Further evaluation of PFS (Figures 2 and 3) and the multivariate analysis was, therefore, restricted to those patients who had not previously received radiotherapy.

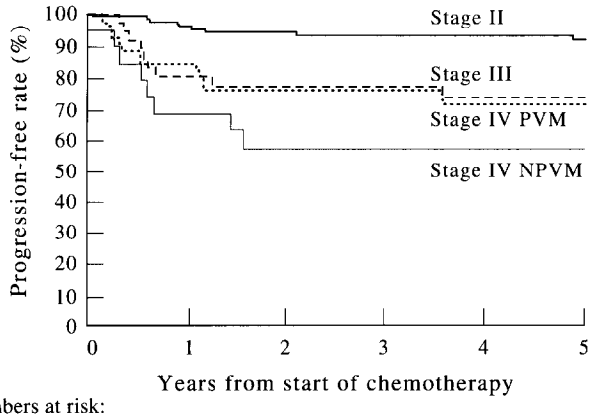
Multivariate analyses

All variables described in Table 2 were entered into the multivariate analysis. In addition, LDH and HCG were considered both as log-continuous variables and as binary variables (raised versus not raised for both LDH and HCG, $2 \times N$ versus $\geq 2 \times N$ for LDH). Clinical stage was considered as an ordered categorical variable with three groups: 1: stage II, 2: stage III + stage IV PVM, 3: stage IV NPVM. This latter variable was the single most important variable (hazard ratio: 2.73; 95% CI 1.55, 4.82), to which only LDH as a binary variable ($<2 \times N \geq 2 \times N$, hazard ratio 3.58, 95% CI 1.44, 9.08) added independent significance ($P < 0.01$). The final model thus included only the 140 patients for whom an LDH level was reported in addition to clinical stage.

Table 3. Progression-free survival (PFS), clinical stage and LDH in patients with or without prior radiotherapy

	Prior radiotherapy				
	No. pts	3 yr PFS	No. pts	3 yr PFS	Test for interaction
Clinical stage					
II	143	94%	5	60%	
III	39	78%	23	70%	$P = 0.06$
IV PVM	27	77%	9	56%	
IV NPVM	21	58%	12	83%	
LDH					
$<2 \times N$	89	93%	14	64%	
$2–3 \times N$	21	71%	5	80%	$P = 0.02$
$>3 \times N$	23	65%	4	75%	

Abbreviations as in Tables 1 and 2.



Numbers at risk:

Stage II	143	133	125	115	104	90
Stage III	39	29	27	26	25	19
Stage IV PVM	27	22	20	20	14	12
Stage IV NPVM	21	13	9	9	9	7

Figure 2. Progression rates by clinical stage (patients with no prior radiotherapy): PVM, pulmonary visceral metastases; NPVM, non-pulmonary visceral metastases.

These two factors were combined into the following prognostic models:

Model 1

Group 1: Stage II with LDH $< 2 \times N$

Group 2: Stage II with LDH $\geq 2 \times N$ or

Stage III with LDH $< 2 \times N$ or

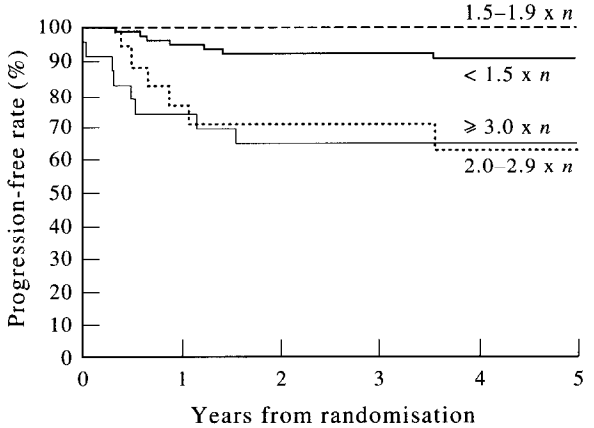
Stage IV PVM with LDH $< 2 \times N$

Group 3: Stage III with LDH $\geq 2 \times N$ or

Stage IV PVM with LDH $\geq 2 \times N$ or

Stage IV NPVM with any LDH.

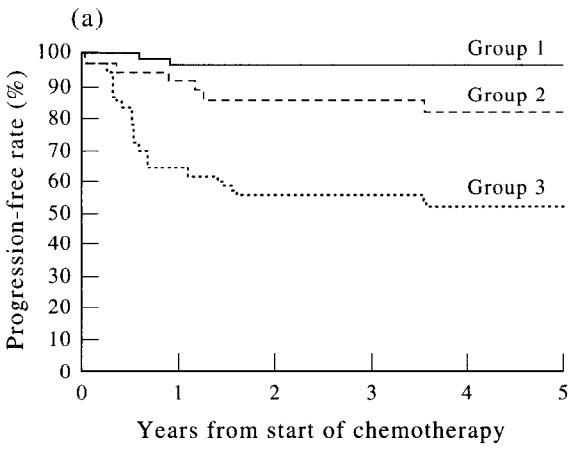
There were 64 patients in group 1, with 3 year PFS of 97% (95% CI 93%, 99%). Group 2 comprised 38 patients with 3 year PFS of 86% (95% CI: 74%, 98%), while group 3 included 38 patients with 56% PFS at 3 years (95% CI: 40%, 72%). Figure 4(a) shows the curves for the three prognostic groups according to Model 1.



Numbers at risk

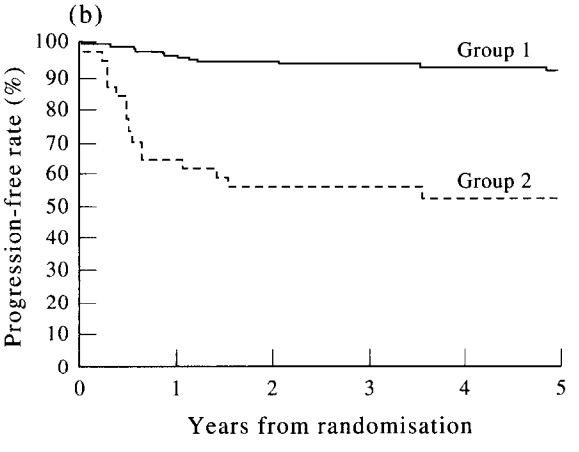
< 1.5 x *n*	76	71	66	62	52	41
1.5–1.9 x *n*	13	10	10	9	9	9
2.0–2.9 x *n*	21	13	12	11	8	8
≥ 3.0 x *n*	23	17	13	12	12	10

Figure 3. Progression rates by LDH (patients with no prior radiotherapy).



Numbers at risk

Group 1	64	62	59	54	47	39
Group 2	38	31	28	26	22	19
Group 3	38	23	17	17	14	12



Numbers at risk

Group 1	160	147	138	128	115	98
Group 2	38	23	17	17	14	12

Figure 4. Progression rates by (a) Model 1 or (b) Model 2 (patients with no prior radiotherapy, developmental data).

An alternative, simpler model was also considered which combined groups 1 and 2 of Model 1, thus giving two groups as defined as below (Figure 4(b)):

Model 2

Group 1: Stage II any LDH or

Stage III with LDH $< 2 \times N$ or

Stage IV PVM with LDH $< 2 \times N$

Group 2: Stage III with LDH $\geq 2 \times N$ or

Stage IV PVM with LDH $\geq 2 \times N$ or

Stage IV NPVM with any LDH

With this model, it was possible to include an additional 58 patients with stage II disease in whom LDH levels were not known. Group 1 included 160 patients, with 3 year PFS of 94% (95% CI: 90%, 98%), while group 2 remained as above, 38 patients (3 year PFS: 56% 95% CI 40–72%).

Validation

Table 4 shows the distribution of the main prognostic factors for all patients in the two validation databases. The

Table 4. Distribution of prognostic factors in the two validation data sets

	EORTC 30874 Prior radiotherapy				MRC TE12 Prior radiotherapy				
	No		Yes		No		Yes		Total
RMH stage									
II	11	44.0%	1	9.1%	70	65.4%			82
III	12	48.0%	4	36.4%	28	26.2%	13	76.5%	57
IV PVM	1	4.0%	3	27.3%	5	4.7%	2	11.8%	11
IV NPVM	1	4.0%	3	27.3%	4	3.7%	2	11.8%	10
Unknown					5		1		6
Total	25	100%	11	100%	112	100%	18	100%	166
LDH level									
$<2 \times N$	12	48.0%	6	54.5%	41	61.2%	10	71.4%	69
$\geqslant 2 \times N$	13	52.0%	5	45.5%	26	38.8%	4	28.6%	48
Unknown					45		4		49
Total	25	100%	11	100%	112	100%	18	100%	166

adverse impact of prior radiotherapy was not evident in either of the data sets. For consistency, the prognostic models were applied only to those patients without prior radiotherapy. Table 5 shows the number and outcome of patients falling into the prognostic groups defined by the two models.

The distribution of prognostic factors in the two validation data sets was such that one would expect particularly poor overall results in the EORTC data, in which there were few patients with stage II disease, the majority of patients with high serum LDH levels. However, the outcome for all patients from the EORTC phase II study was surprisingly good. The outcome in the prognostic groups defined by the two models in data from MRC TE12 was consistent with that seen in the developmental data set. The same could not be said of the EORTC data, which included very few patients in groups 1 and 3.

The hypothesis that this may be due to the more intensive HOP chemotherapy masking the effect of prognostic factors was not supported by the data in the developmental database. In this, the outcomes in the prognostic groups were consistent across the regimens detailed in Table 2. Furthermore, the developmental database included 11 patients treated with HOP, of whom 2 progressed, a rate entirely consistent with the developmental database as a whole. We therefore considered it justified to apply the two prognostic models to the *combined validation data*. The corresponding PFS curves are shown in Figure 5(a) and Figure 5(b). Taking into account the limited number of patients in some of the groups, there was acceptable agreement between curves derived from the developmental database and the combined data set.

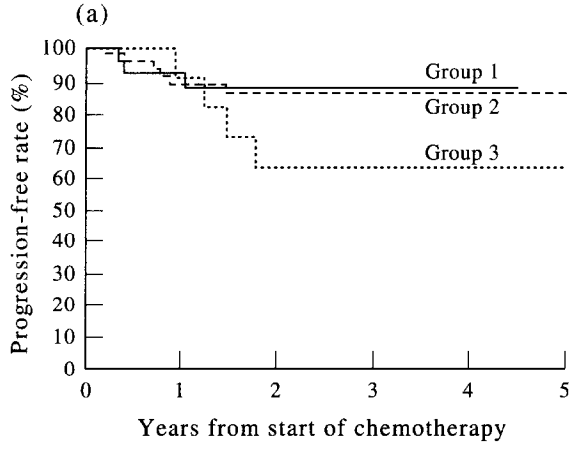
DISCUSSION

The overall prognosis of metastatic seminoma seems slightly superior to that of patients with metastatic non-seminoma [13]. One explanation may be the different stage distribution. At the start of chemotherapy, 78% of our non-irradiated patients presented with non-visceral disease which in both models was associated with a more favourable prognosis. The comparable figure for patients with metastatic non-seminoma is 45%. Furthermore, clinical experience suggests that seminoma is probably more sensitive to cisplatin-based chemotherapy than non-seminoma, especially if the combination regimen contains alkylating agents. This different biological behaviour suggests that curative treatment strategies for advanced seminoma can, if medically indicated, be less intensive than for those with non-seminoma in individual patients belonging to the good prognosis group. In elderly patients, for example, with advanced seminoma, the clinician may frequently prefer to select chemotherapy with a low risk of side-effects (omit bleomycin, use carboplatin instead of cisplatin, reduce number of cycles). This is not a rare clinical problem: patients with advanced seminoma are generally 8–10 years older than patients with advanced non-seminoma, 17% of our patients being above the age of 50 years. Patients with germ cell cancer in this age group are at a particular high risk of severe treatment-induced toxicity, favouring the concept of a more individualised risk-based chemotherapy. This idea is also

Table 5. Distribution of prognostic groups in the two validation data sets

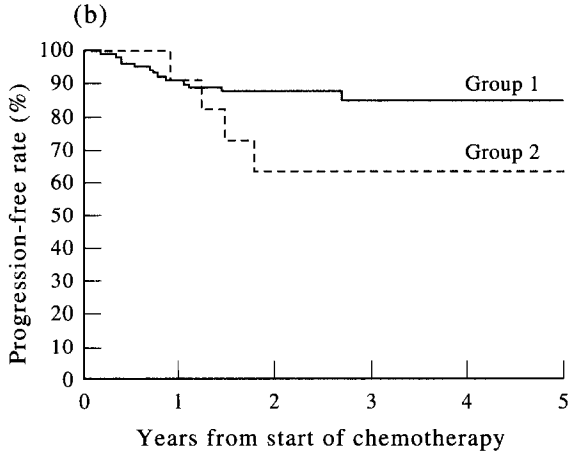
	EORTC 30874		MRC TE12		Total		
	N	2 year PFS	*N*	2 year PFS	*N*	2 year PFS	(95% CI)
Model 1							
Group 1	3	100%	24	87%	27	88%	(75, 99)
Group 2	17	88%	33	85%	50	87%	(77, 97)
Group 3	5	100%	9	33%	14	64%	(35, 92)
n.a.			46		46		
Model 2							
Group 1	20	90%	84	87%	104	87%	(81, 94)
Group 2	5	100%	9	33%	14	64%	(35, 92)
n.a.			19		19		
Total	25	92%	112	79%	137	82%	(75, 89)

Due to shorter follow-up, only 2 years PFS is considered.



Numbers at risk

Group 1	27	22	15	6	3	0
Group 2	50	39	27	11	3	1
Group 3	14	10	6	3	1	1



Numbers at risk

Group 1	104	84	58	24	8	1
Group 2	41	10	6	3	1	1

Figure 5. Progression rates by (a) Model 1 or (b) Model 2 (patients with no prior radiotherapy, validation data).

relevant in younger patients with a low risk of relapse where oncologists and patients would prefer to reduce chemotherapy to avoid long-term sequelae, such as fertility disturbances, nephrotoxicity and peripheral neuropathy. Our data indicate that such individualisation, if attempted, may be safe, in particular, as the type of chemotherapy was without significant influence on PFS.

Compared to the non-irradiated patients, the outcome of patients relapsing after prior radiotherapy was significantly reduced. Further prognostic subdivision of this group was difficult. Heterogeneity of the initial clinical stage (before radiotherapy) may be one explanation for the inconsistency of prognostic factors in irradiated patients, and may, in particular, explain the surprisingly favourable outcome of patients in the EORTC trial 30874, who had relapsed after prior radiotherapy. Before 1980, radiotherapy was used in advanced cases of seminoma, whereas more recently this approach has been used only in patients with limited disease manifestations. In fact, of 14 evaluable patients with relapse after radiotherapy before 1980, only 5 had stage I at initial presentation (stage IIa/b: 3; stage IIc: 6). The comparable figures for 32 relapsing patients with radiotherapy after 1980 were 13 patients with stage I, 17 patients with stage IIa/b and only 2 patients with stage IIc. Only 4 of the 18 patients with initial stage I and relapse after radiotherapy have progressed after chemotherapy, 2 of 6 patients with radiotherapy before 1984 versus 2 of 12 patients with radiotherapy after 1984. The time-related shift in initial stage distribution indicates that patients relapsing after radiotherapy applied late in the 1980s probably had less advanced disease at the start of chemotherapy than patients with irradiation before this time. Furthermore, large-field radiotherapy was frequently applied in metastatic seminoma prior to 1985 and necessitated frequent reduction of salvage chemotherapy doses. Similar dose reductions are not required after modern infradiaphragmatic radiotherapy for stage I seminoma [6]. The use of ifosphamide as an alkylating agent may additionally have contributed to the favourable results after radiotherapy relapse in the data set from the EORTC 30874 trial. Currently, there is no evidence for decreased success of salvage chemotherapy in the 2–3% of patients who relapse after modern infradiaphragmatic radiotherapy of seminoma stage I. Some of the patients relapsing after radiotherapy may, however, display "atypical seminoma", which has been described after chemotherapy failure [17, 18] and may be more resistant to cisplatin-based chemotherapy than classical seminoma.

Mencel and associates [3] studied prognostic factors in 142 patients with advanced seminoma initially treated with chemotherapy. In this analysis, normal HCG and normal LDH were correlated with a favourable prognosis. The number of metastasic sites and the presence of an extragonadal primary were without prognostic significance. Prior radiotherapy had no significant impact on the success of salvage chemotherapy. The IGCCCG recognised the presence of non-pulmonal visceral metastases and elevated serum LDH as the most important adverse factors [13]. The present more detailed analysis confirms these prognostic parameters in previously non-irradiated patients, whereas the heterogeneity and the limited number of patients relapsing after radiotherapy prevents prognostic division of this subgroup.

The usefulness of both described prognostic models was successfully validated by the combined external data set. Though both models contain clinically valuable information, most oncologists will probably prefer Model 2, for the sake of simplicity. The overwhelming majority of patients seen in clinical practice belong to the good-prognosis group of Model 2, and 94% of these will be cured by cisplatin-based chemotherapy. In general, as many of these cancer patients as possible should be included in clinical trials in order to expand our knowledge on the management of advanced seminoma. At present the EORTC GU Group and MRC Testicular Cancer Working Party are coordinating a phase III trial which includes both patients with advanced seminoma and good-prognosis non-seminoma [13]. 3 cycles of BEP are compared to 4 cycles, with additional randomisation between chemotherapy given over 3 or 5 days. We recommend inclusion of patients with advanced seminoma into this protocol. However, in clinical practice, individualisation is sometimes necessary. Using one of the models,

clinicians will be able to identify patients with a favourable prognosis in whom less intensive chemotherapy may be considered.

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