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Risk factors in germ cell tumour patients with relapse or progressive disease after first-line chemotherapy: Evaluation of a prognostic score for survival after high-dose chemotherapy

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ABSTRACT

Purpose: To retrospectively re-evaluate a published prognostic score for response to salvage treatment in patients with germ-cell tumours relapsing or progressing after cisplatin-based first-line chemotherapy.

Patients and methods: From a database of 257 germ cell tumour (GCT) patients treated with salvage high-dose chemotherapy (HDCT) we identified 176 patients (67%) with relapse or progression after first-line conventional-dose chemotherapy (CDCT). Patients were retrospectively grouped according to a published prognostic score defined by Fossa and colleagues [Fossa SD, Stenning SP, Gerl A, et al. Prognostic factors in patients progressing after cisplatin-based chemotherapy for malignant non-seminomatous germ cell tumors. *Br J Cancer* 1999; **80**:1392–9]. Overall survival (OS) and event free survival (EFS) after HDCT were retrospectively evaluated in each prognostic group.

Results: After a median follow-up of 9 years the OS probability for all 176 patients was 38% and the EFS probability was 35%. The respective survival probability at 5 years in 100/176 (57%) good prognosis patients and 76/176 (43%) poor prognosis patients were 47% versus 28% for OS ($p < 0.001$) and 41% versus 26% for EFS ($p < 0.005$). Whereas survival probabilities did not differ in good prognosis patients, OS and EFS in poor prognosis patients were substantially better in the current series of patients treated with HDCT compared to the ones reported by Fossa treated with CDCT.

Conclusion: This retrospective analysis confirms the impact of prognostic factors on the results of salvage treatment in patients with GCT and suggests a clinical benefit for patients with poor prognosis features receiving a single course of HDCT.

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1. Introduction

The concept of salvage chemotherapy in patients with germ cell tumour (GCT) relapsing or progressing after cisplatin-based first-line chemotherapy consists of either further conventional-dose chemotherapy (CDCT) or treatment with high-dose chemotherapy (HDCT).[1–5] Both treatments are being utilised successfully, but for the majority of patients it is unclear which of the two concepts is more promising.[6]

Knowledge of prognostic subgroups of patients may help to decide on the best salvage treatment option. Risk factors such as early relapse, high tumour-markers, cisplatin-refractory disease and primary mediastinal non-seminomas have been shown to be associated with a high risk of treatment failure.[7–13] Fossa and colleagues evaluated risk factors for patients relapsing or progressing after cisplatin-based first-line chemotherapy who received CDCT as salvage treatment. The following factors predicted poor prognosis to conventional-dose salvage treatment: high levels of serum tumour-marker, a short progression-free interval of less than 2 years and failure to achieve a complete remission (CR) to first-line chemotherapy. Patients with a maximum of two risk factors represented a good prognosis subgroup, whereas patients with all three risk factors were considered to be poor prognosis.[7] The aim of the present study was to re-evaluate the prognostic score described by Fossa and colleagues in an independent dataset of patients treated with HDCT as first salvage attempt.

2. Patients and methods

2.1. Patients

Among 257 patients who had received induction salvage chemotherapy followed by a single course of HDCT within prospective studies of the German Testicular Cancer Study Group (GTCSG), 176 patients (67%) presenting with relapse or progression after first-line chemotherapy were identified. All patients were treated in one of two subsequent phase II trials of the German Testicular Cancer Study Group between 1988 and 1999.[1,3]

2.2. Treatment

In both trials, salvage treatment consisted of one to three induction courses of CDCT followed by one single course of HDCT. In the first trial CDCT with PEI (cisplatin 100 mg/m^2, etoposide 500 mg/m^2, ifosfamide 6 g/m^2 in divided doses from day 1 to day 5) was followed by HDCT consisting of CEI (carboplatin 1500–2000 mg/m^2, from day −6 until day −4 or from day −6 until day −3 in doses above 1500 mg/m^2, etoposide 1200–2400 mg/m^2 from day −6 until day −3 and ifosfamide up to 10 g/m^2 from day −6 until day −3).[1] In the second trial, CDCT consisted of TIP (paclitaxel 175 mg/m^2 on day 1 followed by ifosfamide 6 g/m^2 and cisplatin 100 mg/m^2 in divided doses from day 2 to day 6) and HDCT consisted of CET (carboplatin 1500 mg/m^2/d in divided doses from day −6 until day −4, etoposide 2400 mg/m^2/d in divided doses from day −6 until day −3, and thiotepa 450 to 750 mg/m^2/d in divided doses from day −6 until day −4).[3] On day 0 all patients received stem cell rescue. Details of the trials have been reported previously.[1,3]

2.3. Clinical monitoring and follow-up

All 176 patients were evaluable for response to CDCT and HDCT. Follow-up evaluations were performed at 6 and 12 weeks post-HDCT. For long-term follow up tumour status was re-evaluated every 3 months during the first 2 years every 6 months during the subsequent 3 years and once yearly thereafter. The last survival status was obtained between November 2003 and May 2004. The data included in the present follow-up was based on written documentation from the local physicians as well as on telephone interviews. Individual patients received follow-up examinations at our institutions.

2.4. Definitions

A complete remission (CR) was defined by absence of all radiologic manifestations and normalisation of tumour-markers by chemotherapy alone or after complete resection of residual tumor. Patients with normalisation of tumour-markers but radiologic evidence of disease were considered PRm+. Patients with a reduction of radiologic manifestations of 50% or more or with normalised tumour-markers were considered as having a PRm–. Any patient with an increase of radiologic manifestations of more than 25% or an increase in tumour-markers of more than 10% was considered as having progressive disease (PD). Patients with disease that did not classify for any of the above mentioned response criteria were classified as having stable disease (SD). Sensitivity to cisplatin was assessed after the preceding first-line chemotherapy. Disease was considered sensitive to cisplatin when more than SD was achieved for more than 4 weeks. Disease was defined as being refractory to cisplatin when initially SD or better was achieved but there was evidence of tumour progression within 4 weeks of the last cisplatin-based treatment. Disease was considered absolutely refractory to cisplatin when not even SD was achieved despite cisplatin-based chemotherapy.[8]

2.5. Prognostic models

Patients were retrospectively grouped according to the score published by Fossa et al. predicting outcome after CDCT as first salvage treatment.[7] Criteria identified as risk factors by multivariate analysis according to this report are as follows: high tumour-marker levels [human chorionic gonadotropin (HCG) >100 IU/l and/or alpha fetoprotein (AFP) >100 KU/l] at the time of relapse or progression, a progression free interval of less than 2 years and a tumour-response to first-line chemotherapy of less than a CR. Patients presenting with all three risk parameters were considered to be poor prognosis whereas patients with less than three risk factors were assigned to a good prognosis group. Outcomes in these two different subgroups of patients were re-evaluated in the present patient population treated with HDCT as first salvage attempt.

2.6. Statistical analysis

Survival probabilities were calculated according to the method of Kaplan and Meier.[14] Overall survival (OS) started with study entry and ended with the death of the patient from any causes

or the date of last follow-up. Event-free survival (EFS) was calculated from study entry to disease progression, death from any cause, or the date of last follow-up. The Log rank test was used to compare the survival curves of the various prognostic subgroups. Differences in probability for survival were considered to be significant if the p-value was <0.05.

Table 1 – Patient characteristics at study entry

	Patients (n = 176)	Percent (100 %)
Primary tumour		
Testis	138	78
Retroperitoneum	26	15
Mediastinum or other	12	7
Histology present at time of initial diagnosis		
Pure Seminoma	14	8
Other	162	92
Sensitivity to cisplatin		
Sensitive	139	79
Refractory	32	18
Absolute refractory	5	3
Best response to first line therapy		
CR	60	34
PRm–	53	30
PRm+	60	34
SD	1	1
PD	2	1
Duration of best response to initial chemotherapy		
Less than 6 months	85	48
6 to 12 months	56	32
More than 12 and less than 24 months	22	13
More than 24 months	13	7
Level of HCG (in U/L)		
Less or equal 100	102	58
More than >100	74	42
Level of AFP (in ng/mL)		
Less or equal 100	140	80
More than 100	36	21
Cytostatic agents used in induction regimen		
Cisplatin	174	99
Etoposide	169	96
Bleomycin	135	77
Ifosfamide	78	44
Other	17	10
Number of previous cisplatin containing CDCT courses		
Two to three	27	15
Three to five	114	65
More than five	33	19
Tumour manifestations at time of first relapse		
CNS	26	15
Retrop./abdominal	119	68
Mediastinal	48	27
Liver	37	21
Pulmonal	106	60
Bone	8	5
Cervical LN	18	10
Other	7	4

Abbreviations: HDCT = high-dose chemotherapy; HCG = human chorionic gonadotropin; AFP = alpha-fetoprotein; CR = complete remission; PR = partial remission; m+ = marker positive; m– = marker negative; SD = stable disease; PD = progressive disease; NE = not evaluable; CNS = central nervous system; Retrop. = retroperitoneal and LN = lymph nodes.

3. Results

3.1. *Patient characteristics and comparison of the two study populations*

Detailed characteristics of patients from the current series including those considered to have prognostic relevance are listed in Table 1. All 176 patients were male and presented with treatment failure after first-line chemotherapy. This compares to 164 patients in the analysis by Fossa.

Gonadal GCT or a retroperitoneal primary manifestation was present in 164/176 (93%) patients (Table 1). Only 7% of the patients presented with a primary mediastinal tumour, comparable to 3% of such patients in the analysis by Fossa (Table 2). Nonseminomatous tumour-histology was present

Table 2 – Clinical data of the current patient series (n = 176) in comparison with the population by Fossa and colleagues (n = 164) at salvage treatment[7]

	Current series (n = 176)		Fossa patients (n = 164)	
	n	%	n	%
Primary extragonadal mediastinal GCT	12	7	5	3
Pure seminoma	14	8	0	0
Absolute cisplatin refractory disease	5	3	11	7
TTP (<2 years)	163	93	126	77
HCG > 100 U/L	74	42	30	18
AFP > 100 ng/mL	36	21	22	13
Best response less than CR	116	66	111	68
Extrapulmonary visceral metastasis	65	37	29	18
Time of first-line chemotherapy	1988 to 1998		1982 to 1986	
Time of salvage chemotherapy	1988 to 1999		1982 to 1991	
Detailed information on salvage therapy available	176	100	110	67
Type of salvage chemotherapy	176	100	103	62
Platin-based	176	100	89/103	86
Ifosfamide-based	176	100	15/103	15
Median time for follow-up	9 years (2 to 14 years)		8 years (1 to 12 years)	
Patients classified for prognostic score	176	100	124	76
Fossa score				
Good	100	57	94/124	76
Poor	76	43	30/124	24

Abbreviations: GCT = germ cell tumour; TTP = time to progression; HCG = human chorionic gonadotropin; AFP = alpha-fetoprotein.

in 162/176 (92%), whereas only 8% of patients in the present analysis presented with pure seminoma (Table 1). Seminoma patients did not have a better outcome compared to the remaining patients (OS of 42% for seminoma versus 40% for nonseminoma at 5 years). In 21% of all patients cisplatin-refractory disease was revealed after conventional salvage therapy (Table 1) including 3% showing absolute cisplatin refractory disease, whereas 7% of the patients in Fossa's analysis were considered to be absolute cisplatin refractory (Table 2). In our study 93% of the patients had suffered from either relapse or progression within the first 2 years after first-line chemotherapy. In contrast only 77% of patients had relapsed earlier than 2 years to the analysis by Fossa (Table 2). Furthermore, high tumour-marker levels were found in our analysis in 42% and 21% of the patients for HCG and AFP, respectively. In comparison the number of patients presenting with high tumour-markers at the time of relapse in Fossa's analysis was only 18% for HCG and 13% for AFP (Table 2). Similar numbers of patients not achieving CR to first-line treatment were included in the analysis by Fossa as well as in ours (68% versus 66%, Table 2). Extrapulmonal visceral metastasis as sites of relapse were observed in 37% of patients in our dataset compared to 18% of patients included in the analysis by Fossa (Table 2).

3.2. *Time of treatment and regimens used compared to Fossa's patient group*

HDCT as first salvage approach was given between 1988 and 1999 in our analysis, whereas conventional salvage treatment was given almost 10 years earlier between 1982 and 1991 in Fossa's analysis. First-line platinum based CDCT took place between 1988 and 1998 in our analysis as compared to 1982 and 1986 in Fossa's study (Table 2).

The majority of all patients in both studies received at least four courses of cisplatin and etoposide-containing regimens as first-line chemotherapy. However, relevant differences must be suspected in the number of patients who received ifosfamide as part of their first-line treatment. A total of 78/176 (44%) patients in the present analysis had been pretreated with ifosfamide (Table 1). This figure is not given in the report by Fossa and colleagues, but was probably much lower. Data from salvage chemotherapy were available in only 103/164 (62%) patients by Fossa and in all patients of our series (Table 2). Furthermore, cisplatin-based treatment combinations were used in only 89/103 (86%) of Fossa's patients and only 15% (15/103) of their patients received ifosfamide-containing regimens (Table 2). The number of etoposide containing salvage regimens in her patients is unknown. In the present analysis all 176 patients received all three drugs: cisplatin, etoposide and ifosfamide as well as HDCT as part of their salvage treatment.

3.3. *Responses to HDCT*

After HDCT 26 of all patients (15%) reached a CR and did not require any additional treatment. A PR was obtained by 40/176 (23%) patients. After additional residual tumour resection of necrosis/mature teratoma in 26 patients or undifferentiated viable tumour in 14 patients, they could be rendered disease-free. In 54/176 (31%) patients with PR and in 5/176 (3%) patients with SD surgical treatment could not be realised. Furthermore, 47/176 (27%) patients had progressive disease directly after HDCT and 4/176 (2%) patients died on multiorgan failure within the first 4 weeks after administration of HDCT. For these patients evaluation of remission status could therefore not be obtained.

3.4. *Long-term survival*

As shown in Table 2 the median time of follow up in our patients was 9 years (range 2 to 14 years) and was 8 years (range

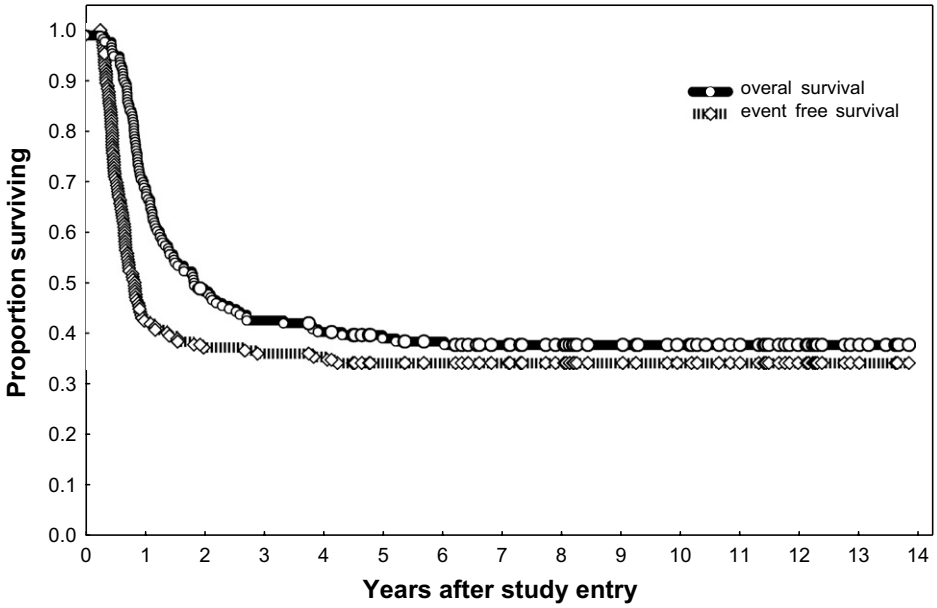

Fig. 1 – Overall and event free survival after HDCT (n = 176).

1 to 12 years) in the analysis by Fossa and colleagues. The OS and EFS probability after 5 years were 39% and 34%, respectively in our population, versus 30% by Fossa (Fig. 1).

3.5. *Fossa's prognostic score applied in the high-dose setting*

The risk score defined by Fossa and colleagues discriminated two prognostic subgroups with statistically significant different survival rates.[7] In the current series 57% of the patients presenting with ⩽2 risk parameters could be assigned to the good prognosis subgroup. The remaining 43% of the patients presented with all three adverse prognostic factors as defined by Fossa and colleagues, representing a poor prognosis group (Table 2). In terms of OS and EFS the differences between the two prognostic groups were statistically significant (Fig. 2). The OS after 5 years among patients assigned to the good prognostic subgroup were comparable in both analyses (47%). However, in the population reported by Fossa and colleagues no long-term survivors were found among poor prognosis patients. In contrast, 28% of the patients presenting with all three adverse prognostic factors in the current series eventually became long-term survivors (Fig. 2).

In order to explain these findings, the individual influences of each of these three risk factors on survival in the current series were separately tested using a univariate analysis model. Only tumour marker status proved to be statistically significant and discriminated patients for OS and EFS. The sample size of patients with CR to first-line chemotherapy and time to relapse of more than 2 years did not allow a meaningful test and therefore, did not have a significant impact on survival after HDCT (Table 3).

3.6. *Comparison of prognostic scores*

The available prognostic scores have some similarities and also some differences. Table 4 shows that the scores of Beyer and colleagues[8] and Einhorn and colleagues[13] are suitable for patients with first and subsequent relapsed patients and for patients with platinum refractory disease. In contrast, the Fossa score[7] and the current analysis are suitable only for patients after first- line chemotherapy.

Table 3 – Univariate survival analysis (*n* = 176)

Variable	Patients		5-year OS (%)	*p*-value
	(*n*)	%		
Best response to first line therapy				
CR	60	34	38	
no CR	116	66	38	.6
Duration of best response to initial chemotherapy				
⩾2-years	13	7	54	
<2-years	163	93	37	.1
Level of HCG (in U/L)				
⩽100	102	57	42	
>100	74	43	34	<.05
Level of AFP (in ng/mL)				
⩽100	140	80	43	
>100	36	20	19	<.05

Abbreviations: OS = overall survival; HCG = human chorionic gonadotropin; AFP = alpha-fetoprotein, CR = complete remission.

4. Discussion

The 5-year OS probability of 40% and the EFS probability of 33% achieved after HDCT in patients of the present analysis were comparable to the rates observed in previous HDCT trials.[15,16] In the current analysis the OS of patients after first-salvage HDCT was similiar to the overall survival of patients treated by CDCT who were analysed by Fossa and colleagues.[7] These authors described an OS of 30% after 5 years in their patient cohort treated about 10 years earlier than the patients in the present analysis.

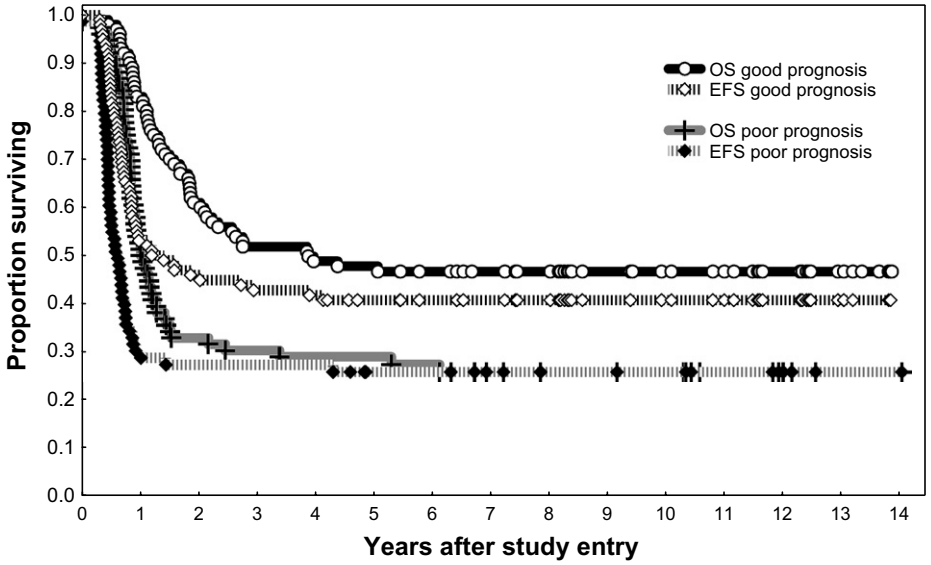

Fig. 2 – OS and EFS of patients after HDCT according to the prognostic score published by Fossa and colleagues[7] (*n* = 176). All comparison between good and poor prognostic groups were statistically significant in terms of OS and EFS (*p* < 0.001).

Table 4 – Comparison of the available prognostic scores

Adverse prognostic factor	Beyer score[8] $n = 283$	Einhorn score[13] $n = 184$	Fossa score[7] $n = 110$	Current series $n = 176$
No CR to first-line chemotherapy	–	–	X	–
Progression-free interval <2-years	–	–	X	–
HCG before HDCT >1000 U/L	X	–	n.i.	–
HCG before salvage treatment >100 U/L	–	–	X	X
AFP before salvage treatment >100 ng/ml	–	–	X	X
HDCT subsequent first-salvage chemotherapy	–	X	n.i.	n.i.
Platinum refractory disease	X	X	–	–
IGCCCG high-risk	–	X	–	–
PD before HDCT	X	–	n.i.	n.i.
Mediastinal primary tumour	X	n.i.	–	–

Abbreviations: CR = complete remission, HCG = human chorionic gonadotropin; AFP = alpha-fetoprotein, HDCT = high-dose chemotherapy; IGCCCG = International Germ Cell Cancer Collaborative Group; PD = progressive disease; n.i. = patients not included X = statistically significant adverse prognostic factor; – = factor is not statistically significant.

Using the score published by Fossa and colleagues we were able to separate a group of patients with good prognosis from a group of patients with poor prognosis by means of clinical prognostic factors. However, while three statistically significant prognostic factors were determined in the multivariate analysis by Fossa and colleagues, we were only able to determine the presence of elevated tumour markers as prognostically significant in our cohort. As more patients with a short progression-free interval of less than 2 years were included in the present analysis as compared to the one by Fossa and colleagues the limited number of patients relapsing later than 2 years did not allow to meaningfully test this variable.

According to the analysis by Fossa and colleagues, for patients with poor prognosis features prior to conventional-dose salvage treatment, no long-term survival was achievable. This contrasts to an OS probability of 28% that was determined by means of HDCT in the poor prognosis subset of patients in the current analysis. We believe that the improvement of the prognosis for this unfavourable patient subgroup must be attributed to the effect of HDCT, because no other clinically relevant factors or patient characteristics were identified which might explain such a large difference. This view is further supported by a most recent analysis by the Indiana group who have also found a significant long-term survival even in patients with cisplatin-refractory disease and those with multiple relapses.[13]

However, significant differences between the patient cohorts of Fossa and those patients included in the current analysis exist, indicating that we analysed a group of patients that had a poorer overall outlook than the patient cohort analysed by Fossa and colleagues. The number of patients suffering a relapse within the first 2 years after first-line therapy was much smaller in their cohort compared to those in our dataset (77% versus 93%). Only 18% of patients in the cohort of Fossa had significantly elevated HCG and only 13% elevated AFP levels, compared to 42% and 21% in our dataset. This may be explained by the fact that the poor prognostic group in the analysis by Fossa and colleagues comprised only 24% of patients compared to 43% of patients in our analysis.

Whereas the score devised by Fossa and colleagues is simple and can easily be applied in clinical practice, their analysis possesses a number of problems and differs from our own analysis in further aspects. While all patients in our dataset were uniformly treated with cisplatin-based therapy, detailed information concerning salvage therapy was only available for 67% of patients in the cohort analysed by Fossa. Only 86% of the patients analysed by Fossa and colleagues received cisplatin-based and only 15% of patients received ifosfamide-based chemotherapy. At least seven patients received no salvage chemotherapy at all, but were exclusively treated by salvage surgery. In the remaining patients, no details in respect to the type of salvage chemotherapy were given. As a result of the lack of detailed clinical information, only three-quarters of the patients analysed by Fossa could be included in the compilation of the prognosis score.

In summary, we tested the prognostic score published by Fossa and colleagues in a large and independent dataset of well-documented patients who failed first-line chemotherapy. Using the score devised by Fossa and colleagues we were able to separate two prognostically different groups for first-salvage treatment. Yet, whereas all patients in the poor prognosis subgroup of Fossa died after CDCT, we found an overall survival probability of 28% in such patients treated with HDCT. More recent data show that these results might even be further improved by sequential HDCT.[13] While the role of prognostic factors for first-salvage treatment is currently being evaluated in a large international cooperative effort, we believe that the present analysis supports the superiority of HDCT over CDCT in patients with poor prognostic features at the time of first relapse or progression. The ultimate proof of such an assumption, however, can only be derived from a prospective randomised study.

Conflict of interest statement

None declared.

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