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EORTC Trial Non-Hodgkin Lymphomas

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Abstract—*Results of an EORTC trial* (20751) *in non-Hodgkin lymphomas are presented. Patients were treated in the same way independent of the histological type.*

There were 468 *patients in the study of whom* 124 *patients were in stage I* (85% 5 *year survival*), 57 *in stage II* (55%), 121 *in stage III* (55%) *and* 166 *in stage IV* (45%).

Using the Kiel classification the low grade lymphomas were subdivided into two categories: those with a follicular (80% 5 *year survival*) *and with a diffuse cell pattern* (50% 5 *year survival*) *with an intermediate prognosis compared with the high grade lymphomas* (35% 5 *year survival*).

Treatment was stratified according to stage. In stage I regional radiotherapy was given followed by randomization for maintenance chemotherapy with Vincristine, Cyclophosphamide and Prednisone. No influence in survival was seen (85% *at* 5 *years*), *although disease free survival was better in the maintenance chemotherapy group* (75% *vs* 55% *at* 5 *years*). *In stage II regional radiotherapy was followed, after randomization, by transdiaphragmatic irradiation, all patients received maintenance chemotherapy. The group was too small to draw conclusions about the effect of this treatment. Primary radiotherapy in stage II disease with diffuse histology gave bad results. Patients in stage III and IV were treated with* 8 *courses of chemotherapy with Adriamycin, VM*26, *Cyclophosphamide and Prednisone, given in two different time schedules. Iceberg radiation was then given to areas with initially large or slowly responding disease. All patients had maintenance chemotherapy. No difference was found for the* 2 *chemotherapy schedules in remission rate, disease free interval and survival. In stage III and IV patients with a follicular lymphoma have a longer relapse free interval and total survival* (39% *and* 68% *at* 5 *years*) *compared with those with a lymphoma diffuse histology* (19 *and* 30% *at* 5 *years*). *Patients with stage IV disease due to bone marrow involvement only had a better prognosis compared with stage IV disease for other reasons.*

INTRODUCTION

THE RADIOTHERAPY–CHEMOTHERAPY group of the EORTC conducted a multicentered clinical trial for all stages of non-Hodgkin lymphomas in which separate two armed comparisons were made for stages I, II and III and IV.

The trial started in 1975 and was closed in 1982.

Survival data are available for 468 patients who were eligible and evaluable. From 306 out of these 468 patient slides were evaluable for central pathology review.

MATERIALS AND METHODS

All patients included had histologically proven non-Hodgkin lymphoma localized in the lymph nodes or Waldeyer's ring. Primary extra nodal localizations were excluded. Age limits were 15–70 years. The diagnosis was made by the local pathologists and the slides were sent for review to the trial pathology committee, which reclassified them. For each stage treatment procedure and randomization were identical for all histologic categories in the Kiel classification.

Staging procedure consisted of clinical and laboratory investigations, lymphangiography and X-ray of the chest, liver and spleen scan. Yamshidi biopsy of the posterior iliac crest was done. If the patient was in stage IV after this procedure, he was randomized for treatment. If the disease remained in stage I, II or III, a laparoscopy with liver biopsy was done. Patients with disease in stage III and IV or over 60 years of age were randomized for treatment. If after laparoscopy the disease remained in stage I or II and the patient was below 60 years of age a laparatomy was done for final staging. The outline of the trial is given in Table 1.

Patients in stage I were treated with radiotherapy on the involved and adjacent lymph node

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Table 1. Trial design

Stage I	RT Regional nodes	R → No further treatment R → CVP × 12 R → VCP × 12	
Stage II	RT Regional nodes	Prophylactic RT R → Lymph nodes other side of diaphragm R → No further RT	R → CVP × 12 R → VCP × 12
Stage III, IV		R → CHVmP × 8 + RT R → CICS × 8 + RT	R → CVP × 12 R → VCP × 12

See text for details.

areas (mantlefield excluding the mediastinum, or inverted Y technique) to a dose of 40 Gy in 20 fractions in 4 weeks.

After reaching a complete remission patients were randomized to no further treatment or maintenance treatment, with 12 monthly courses with one of two combinations of Vincristine, Cytoxan, Prednisone.

In the CVP scheme Vincristine (1.4 mg/m^2) was given on day 1, Cyclophosphamide (300 mg/m^2 p.o.) on day 1–5; Prednisone 40 mg/m^2 on day 1–5.

In the VCP scheme Vincristine was given on day 1, Prednisone and Cytoxan started on day 2, at the same doses for the same number of days as the CVP scheme.

Patients in stage II were randomized between regional radiotherapy vs regional radiotherapy with prophylactic radiotherapy to the lymph node areas on the other side of the diaphragm.

In one arm in stage II (supra-diaphragmatic), radiotherapy was given as above by mantlefield technique, excluding the mediastinum unless it was involved. The other arm received, in addition to mantlefield irradition, radiotherapy also to the whole abdomen to a total dose of 25 Gy in fractions of 1.5 Gy/day five times a week. The liver and kidneys were shielded after 15 Gy.

In stage II (infra-diaphragmatic), in one arm the whole abdomen was first irradiated to a total dose of 25 Gy in daily fractions of 1.5 Gy, with liver and kidney shielding after 15 Gy. Thereafter a booster dose to a total of 40 Gy was given to para-aortic, iliac and inguinal nodes. After randomization half of the patients received prophylactic radiotherapy to areas above the diaphragm by limited mantle technique to a total dose of 40 Gy.

An interval of 3–4 weeks was allowed between supra- and infra-diaphragmatic irradiation. After radiotherapy, patients were given 12 courses of maintenance chemotherapy with CVP or VCP, at doses described for stage I.

Patients in stages III and IV were initially treated with chemotherapy. They were randomized to receive one of two chemotherapy induction schemes consisting of Adriamycin, VM 26, Cyclophosphamide and Prednisone (Table 2). After eight courses local adjuvant radiotherapy (Iceberg radiotherapy) in a total dose of 30 Gy in fractions of 1.5 Gy was given to areas with initial disease wider than 5 cm, or those areas where the nodes were still present after three courses of chemotherapy. After radiotherapy the patients were randomized to one of the two maintenance chemotherapy schedules as for stage I.

Out of the 468 eligible and evaluable patients, 124 patients (26%), were included in stage I, 57 (12%) in stage II, 121 (26%) in stage III and 166 (36%) in stage IV. Relapse-free interval and survival curves were calculated from the date of the first randomization by the method of Kaplan and Meier [2]. For statistical comparison the log-rank test [3] was used.

The disease status was evaluated at the end of radiotherapy in stages I and II or after the eight induction chemotherapy courses in stages III and IV. For a complete remission, disappearance of all palpable glands was necessary, with the nodes having a normal size and structure on the lymphangiogram.

Treatment was considered a failure if after initial regression of the tumour there was progression, or if new lesions appeared before the eighth course of chemotherapy. Partial remission was defined as a decrease of more than 50% in size of the nodes, after eight courses.

RESULTS

Results according to histology

Data on the relapse-free interval and survival of the patients in this study in relation to the histological classification have been published [1]. Only two points will be raised here, taking into account patients of all stages for whom adequate histological material was available.

Table 2. Induction regimens for stages III and IV

CHVmP		day 1	2	3	4	5	6	
Adriamycin	50 mg/m²	+						
VM 26	60 mg/m²	+						
Cyclophosphamide	600 mg/m²	+						
Prednisone	40 mg/m²	+	+	+	+	+	+	
CICS		**day 1**	**2**	**3**	**4**	**5**	**6**	**7**
Adriamycin	50mg/m²	+						
VM 26	60mg/m²	+						
Cyclophosphamide	300 mg/m²			+	+			
Prednisone	40mg/m²			+	+	+	+	+

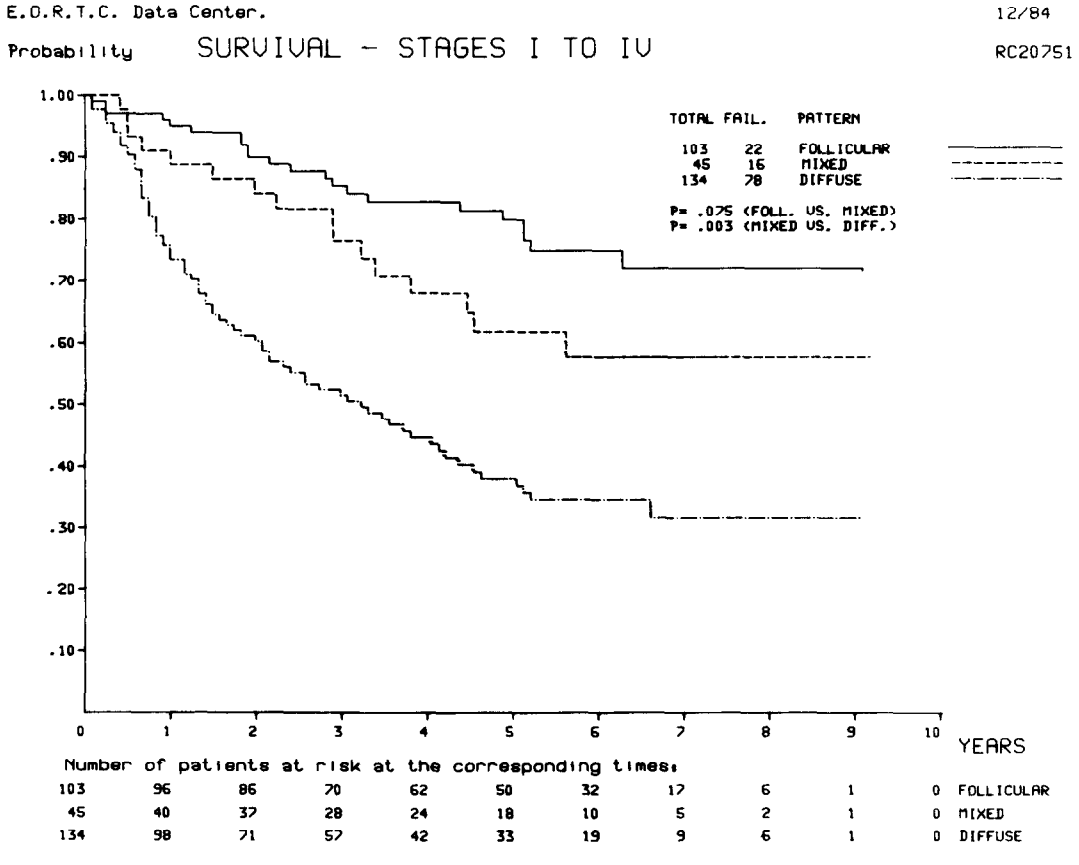


Fig. 1.

The histological pattern influenced the relapse-free interval and survival. The percentage of patients with a 5-year survival was 82% for the follicular lymphomas compared to 39% for the diffuse cases. Patients with a lymphoma with a mixed follicular and diffuse cell pattern behave more like patients with a follicular lymphoma: 62% survived 5 years in this group (Fig. 1).

When using the Kiel classification, the lymphomas of the low grade category could be subdivided according to the cell pattern in follicular and diffuse low grade lymphomas.

Three prognostic groups could then be delineated, with significant differences in 5-year survival: low grade lymphoma with a follicular cell pattern (80% 5-year survival) with a diffuse cell pattern (50% 5-year survival) and the high grade lymphomas (35% 5-year survival) (Fig. 2).

Results according to treatment

Survival per stage is shown in Fig. 3. Survival at 5 years in stage I was 85%, in stage II: 55%, for stage III: 55% and for stage IV: 45%. Results of treatment will be discussed per stage.

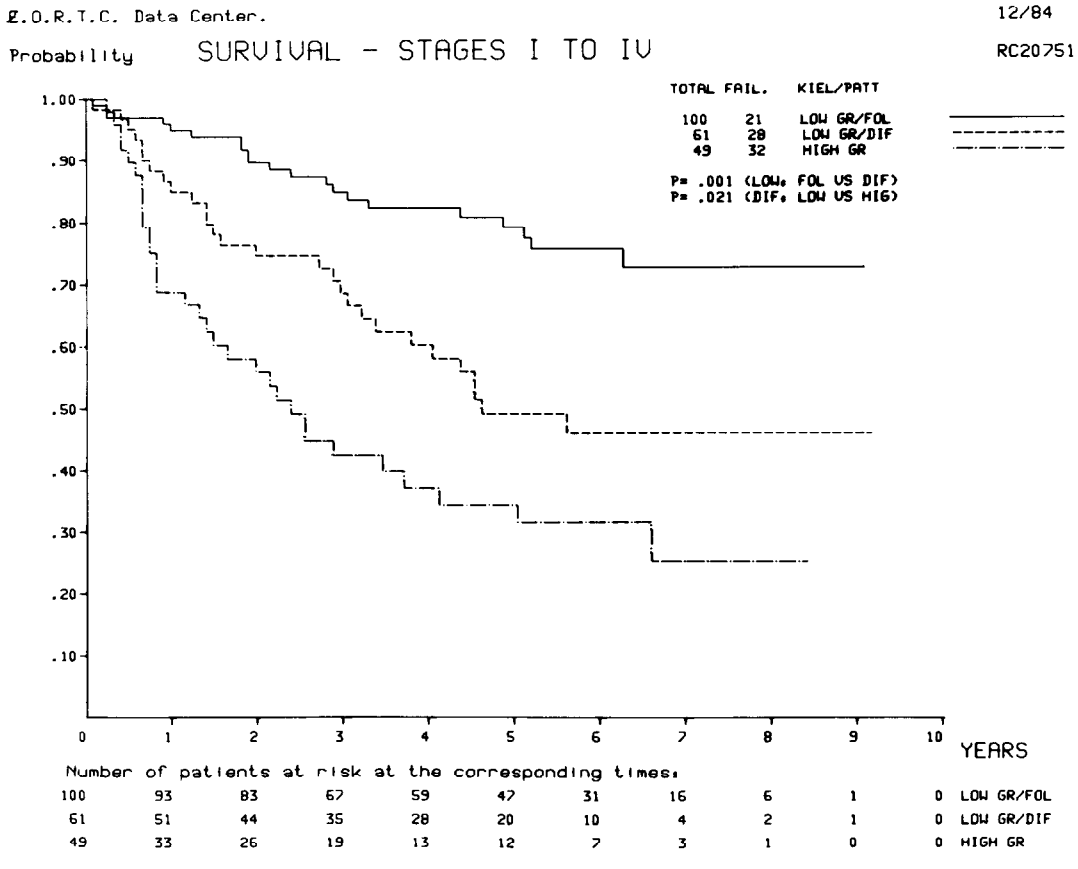
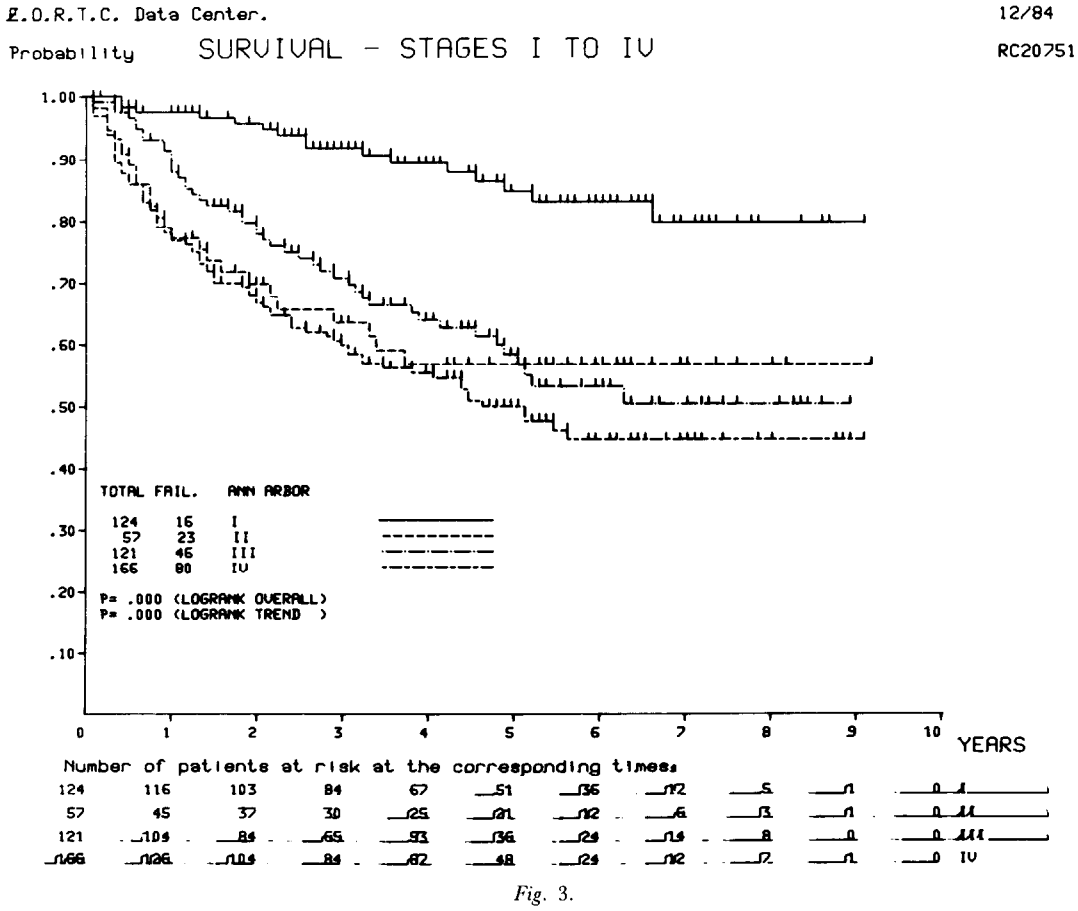

E.O.R.T.C. Data Center.
12/84
Probability
SURVIVAL - STAGES I TO IV
RC20751
TOTAL FAIL. KIEL/PATT
100 21 LOW GR/FOL
61 28 LOW GR/DIF
49 32 HIGH GR
P= .001 (LOW, FOL VS DIF)
P= .021 (DIF, LOW VS HIG)
1.00
.90
.80
.70
.60
.50
.40
.30
.20
.10
0 1 2 3 4 5 6 7 8 9 10
YEARS
Number of patients at risk at the corresponding times:
100 93 83 67 59 47 31 16 6 1 0 LOW GR/FOL
61 51 44 35 28 20 10 4 2 1 0 LOW GR/DIF
49 33 26 19 13 12 7 3 1 0 0 HIGH GR

Fig. 2.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12/84
Probability
SURVIVAL - STAGES I TO IV
RC20751
TOTAL FAIL. ANN ARBOR
124 16 I
57 23 II
121 46 III
166 80 IV
P= .000 (LOGRANK OVERALL)
P= .000 (LOGRANK TREND)
1.00
.90
.80
.70
.60
.50
.40
.30
.20
.10
0 1 2 3 4 5 6 7 8 9 10
YEARS
Number of patients at risk at the corresponding times:
124 116 103 84 67 51 36 12 5 1 0 I
57 45 37 30 25 21 12 6 3 1 0 II
121 109 84 65 53 36 24 14 8 0 0 III
166 126 103 84 62 48 24 12 7 1 0 IV

Fig. 3.

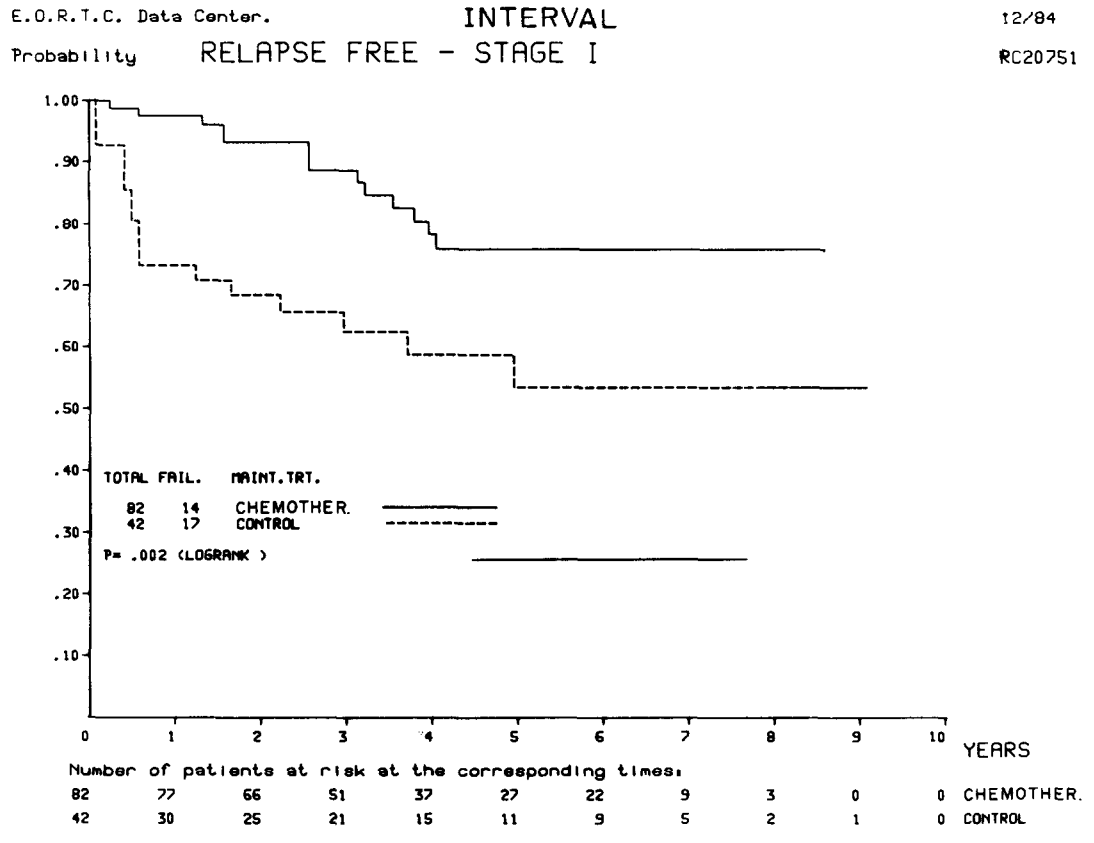


Fig. 4.

Stage I

Of the 124 patients in stage I, 42 were randomized to the control arm, 38 to the CVP chemotherapy arm and 44 to the VCP arm. As there were no significant differences between the two adjuvant chemotherapy arms they were combined to form the chemotherapy arm which consisted of 82 patients.

The relapse free interval was superior in the group receiving adjuvant chemotherapy (75% vs 55% at 5 years, Fig. 4, $P < 002$). Survival was excellent, 85% of the patients were alive at 5 years, without any significant difference between both groups (Fig. 5).

The value of adjuvant therapy was not significantly different in the follicular or the diffuse lymphomas. A more detailed study about prognostic influences in stage I and II has been published [4].

Stage II

In stage II, 26 patients received regional radiotherapy, and 31 patients were prophylactically irradiated on the other side of the diaphragm. Survival in stage II is the same as in stages III and IV, only 55% were alive at 5 years (Fig. 3). This part of the study was abandoned because of the disappointing results.

No significant difference was observed in the relapse-free interval and in survival (Fig. 6) between the group receiving local radiotherapy and the group receiving prophylactic radiotherapy on the other side of the diaphragm. But the groups were too small for statistical analysis. To analyse survival by cell type slides from 36 patients out of these 57 were available. Primary radiotherapy followed by adjuvant chemotherapy was very disappointing for patients with a lymphoma of diffuse histology in stage II. They nearly all relapsed and died within 3 years (Fig. 7).

For stage II cases with lymphoma of a follicular or partly follicular cell pattern primary radiotherapy followed by adjuvant chemotherapy gave a good survival of 75% with a plateau at 4 years.

Stage III, IV

In stages III and IV considered together no significant difference in the percentage of remission was found between the two induction regimens. A complete remission was reached in 42% (111 out of 265 patients), a partial response in 29% (78 out of 265). Another 9% of patients who had a partial response became complete responders at the end of Iceberg radiotherapy. In 20% (52 out of 265) progression occurred before the end of induction chemotherapy. There were two toxic deaths and two deaths due to intercurrent disease.

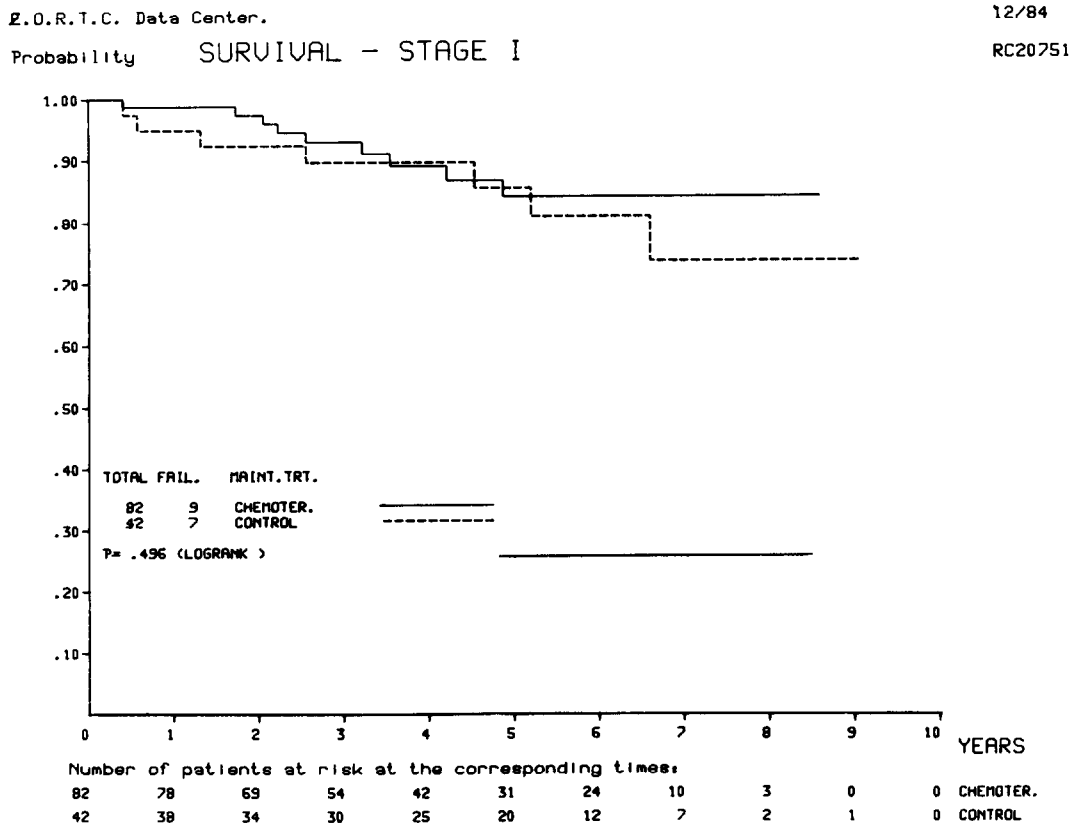

E.O.R.T.C. Data Center.
12/84
Probability SURVIVAL - STAGE I
RC20751
1.00
.90
.80
.70
.60
.50
.40
.30
.20
.10
TOTAL FAIL. MAINT.TRT.
82 9 CHEMOTER.
42 7 CONTROL
P= .496 (LOGRANK)
0 1 2 3 4 5 6 7 8 9 10 YEARS
Number of patients at risk at the corresponding times:
82 78 69 54 42 31 24 10 3 0 0 CHEMOTER.
42 38 34 30 25 20 12 7 2 1 0 CONTROL

Fig. 5.

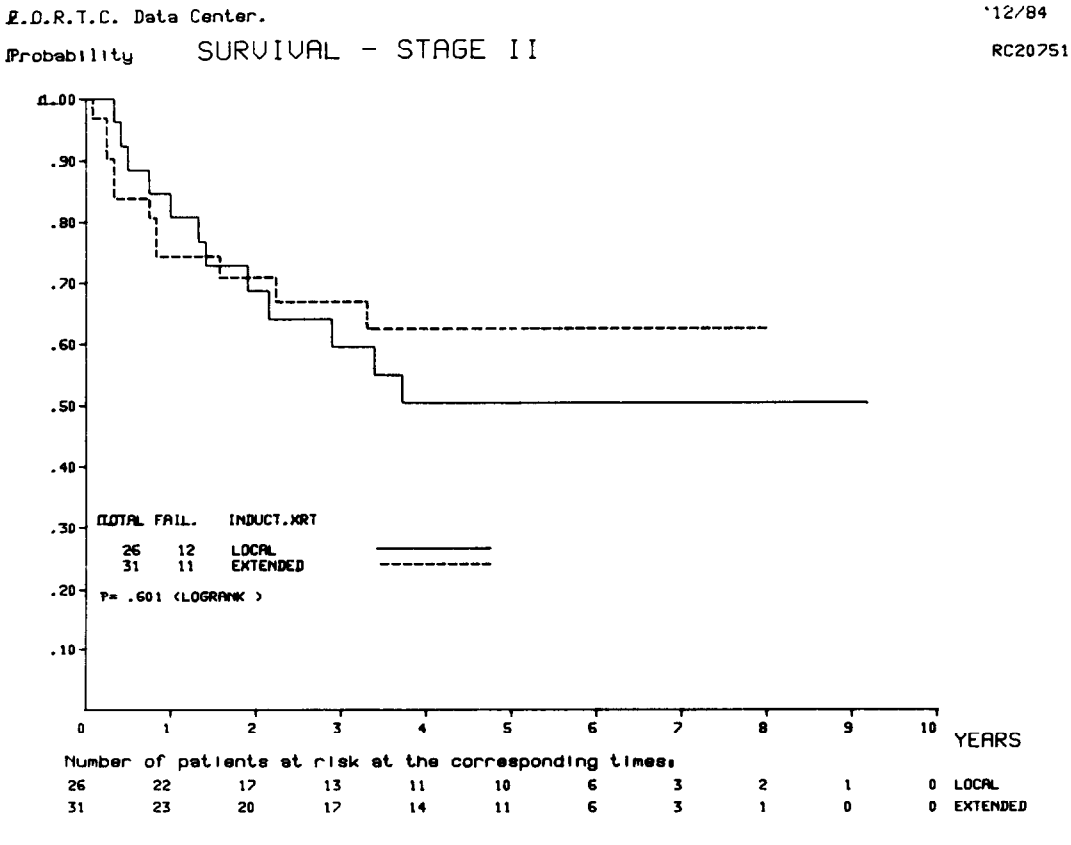

E.O.R.T.C. Data Center.
12/84
Probability SURVIVAL - STAGE II
RC20751
1.00
.90
.80
.70
.60
.50
.40
.30
.20
.10
TOTAL FAIL. INDUCT.XRT
26 12 LOCAL
31 11 EXTENDED
P= .601 (LOGRANK)
0 1 2 3 4 5 6 7 8 9 10 YEARS
Number of patients at risk at the corresponding times:
26 22 17 13 11 10 6 3 2 1 0 LOCAL
31 23 20 17 14 11 6 3 1 0 0 EXTENDED

Fig. 6.

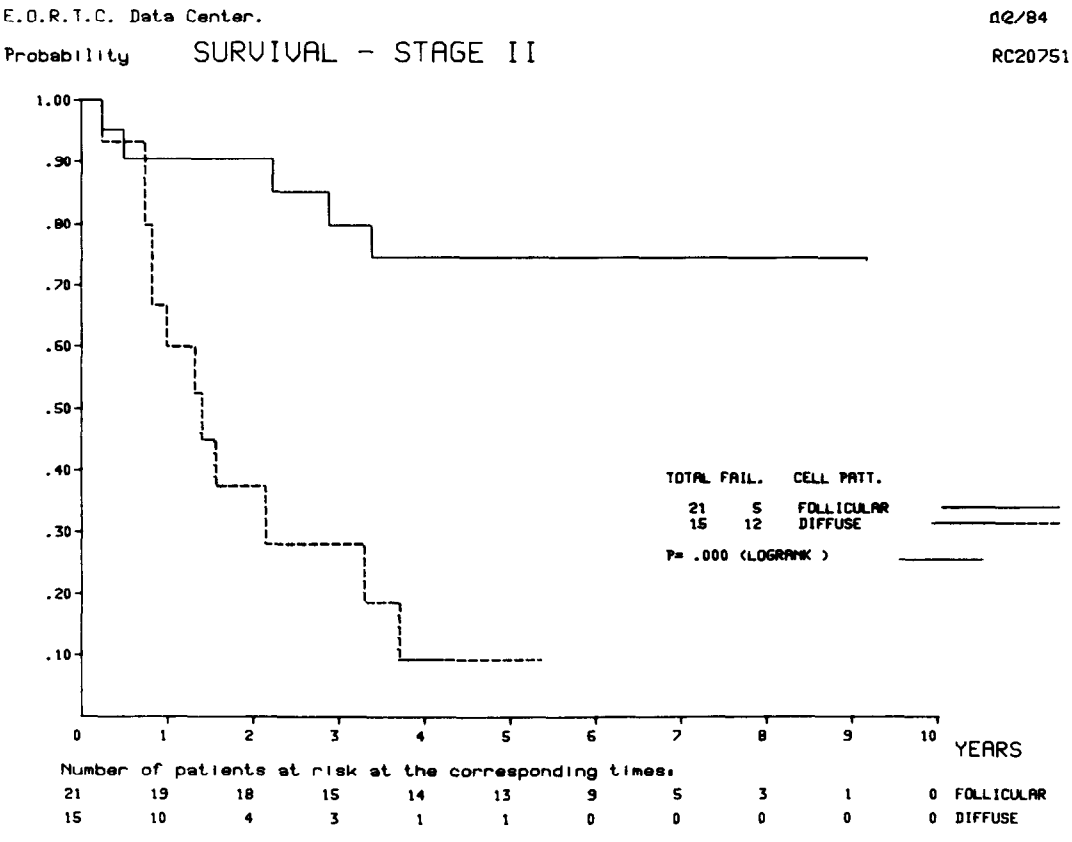


Fig. 7.

In patients with a high grade lymphoma in the Kiel classification, a complete remission was reached in 30%, a partial remission in 24% and chemotherapy failed in 46%. In the low grade lymphomas the complete response rate was 45%, partial response 40%, 15% showed progression during chemotherapy.

No statistical differences were found comparing the two induction regimens regarding the relapse-free interval ($P = 0.582$) or survival ($P = 0.546$, Fig. 8), nor when CVP was compared to VCP maintenance chemotherapy.

As shown in Figs 9 and 10 the relapse-free interval and survival are significantly better for patients with a follicular cell lymphoma (39% and 68% at 5 years) in comparison to patients with a diffuse lymphoma (19 and 30% at 5 years).

As described above for the whole group of patients, patients in stages III and IV with a low grade lymphoma with a follicular pattern had a better survival compared to those with a low grade lymphoma with a diffuse cell pattern (72 vs 45% at 5 years, $P = 0.016$), the relapse-free survival not being significantly different ($P = 0.362$).

Patients who were in stage IV because of bone marrow involvement only had a longer survival (70% at 5 years) as compared to those who were in stage IV due to involvement of other sites (Fig. 11) ($P = 0.006$).

DISCUSSION

Our study shows that the Kiel classification which divides lymphomas in low and high grade malignancy can be subdivided into three categories in accordance with the Working Formulation. The group classified as "low grade" can be divided in two categories when cell pattern is taken into account: low grade lymphoma with follicular and low grade lymphoma with diffuse cell pattern, with a different prognosis. The third category consisting of the high grade lymphomas.

For stage I the question asked in our study was whether adjuvant chemotherapy could improve survival and cure rate. Although we found a significant difference in the relapse-free interval this was not reflected in survival.

The data of Landberg *et al.* [5] are in accordance with our finding in that they also found a better disease free but not an improved overall survival. Monfardini *et al.* [6] found a significant difference in disease free survival in stages I and II together when treated with six courses of CVP after radiotherapy. When subdivided according to the histology, the patients with diffuse histology did better with adjuvant treatment than without, in contrast to the follicular types in which the difference was not significant.

For stage II patients the question was whether prophylactic radiotherapy on the other side of the

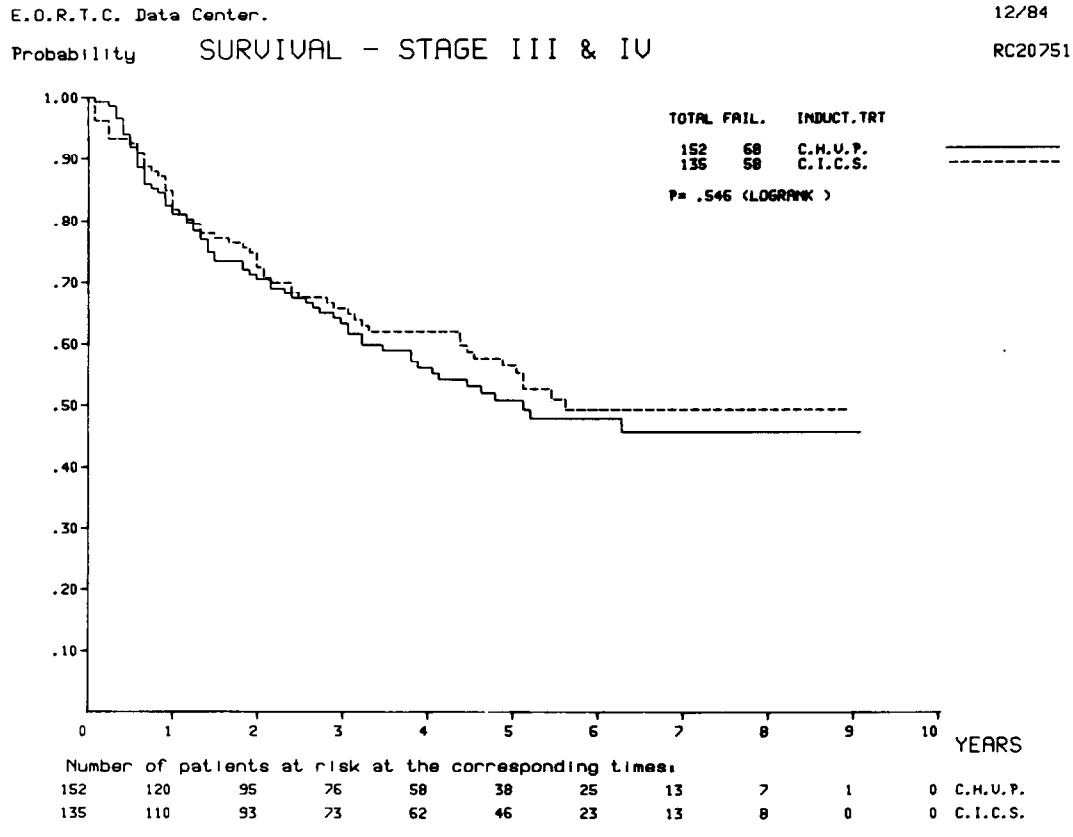
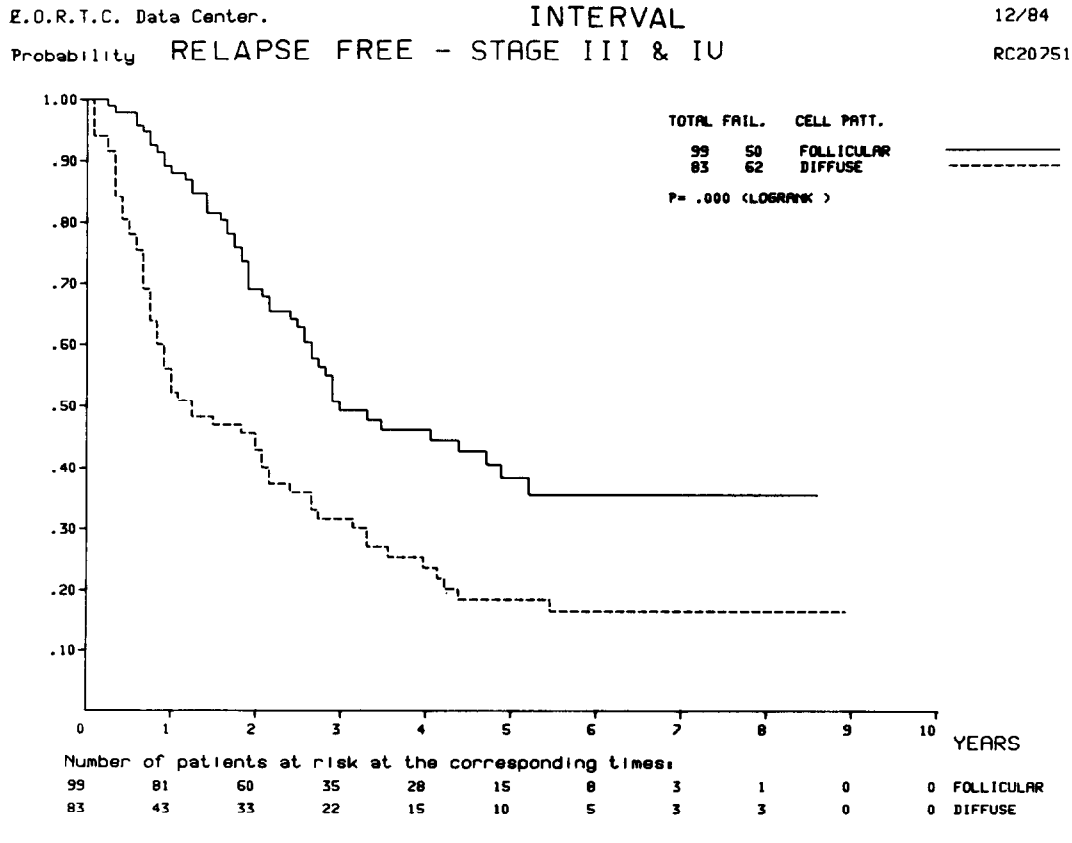

E.O.R.T.C. Data Center.
12/84
Probability SURVIVAL - STAGE III & IV
RC20751
TOTAL FAIL. INDUCT.TRT
152 68 C.H.V.P.
135 58 C.I.C.S.
P= .546 (LOGRANK)
1.00
.90
.80
.70
.60
.50
.40
.30
.20
.10
0 1 2 3 4 5 6 7 8 9 10
YEARS
Number of patients at risk at the corresponding times:
152 120 95 76 58 38 25 13 7 1 0 C.H.V.P.
135 110 93 73 62 46 23 13 8 0 0 C.I.C.S.

Fig. 8.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INTERVAL
12/84
Probability RELAPSE FREE - STAGE III & IV
RC20751
TOTAL FAIL. CELL PATT.
99 50 FOLLICULAR
83 62 DIFFUSE
P= .000 (LOGRANK)
1.00
.90
.80
.70
.60
.50
.40
.30
.20
.10
0 1 2 3 4 5 6 7 8 9 10
YEARS
Number of patients at risk at the corresponding times:
99 81 60 35 28 15 8 3 1 0 0 FOLLICULAR
83 43 33 22 15 10 5 3 3 0 0 DIFFUSE

Fig. 9.

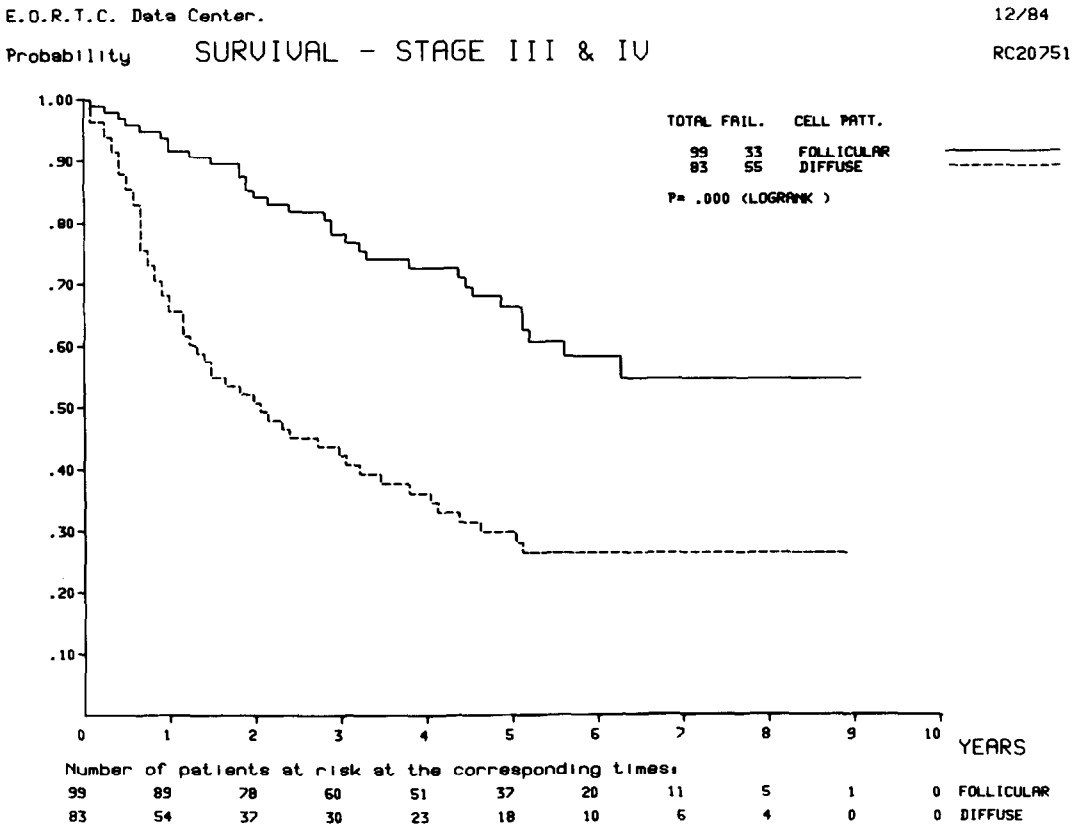
E.O.R.T.C. Data Center.
12/84
Probability SURVIVAL - STAGE III & IV
RC20751
TOTAL FAIL. CELL PATT.
99 33 FOLLICULAR
83 55 DIFFUSE
P= .000 (LOGRANK)
1.00
.90
.80
.70
.60
.50
.40
.30
.20
.10
0 1 2 3 4 5 6 7 8 9 10
YEARS
Number of patients at risk at the corresponding times:
99 89 78 60 51 37 20 11 5 1 0 FOLLICULAR
83 54 37 30 23 18 10 6 4 0 0 DIFFUSE

Fig. 10.

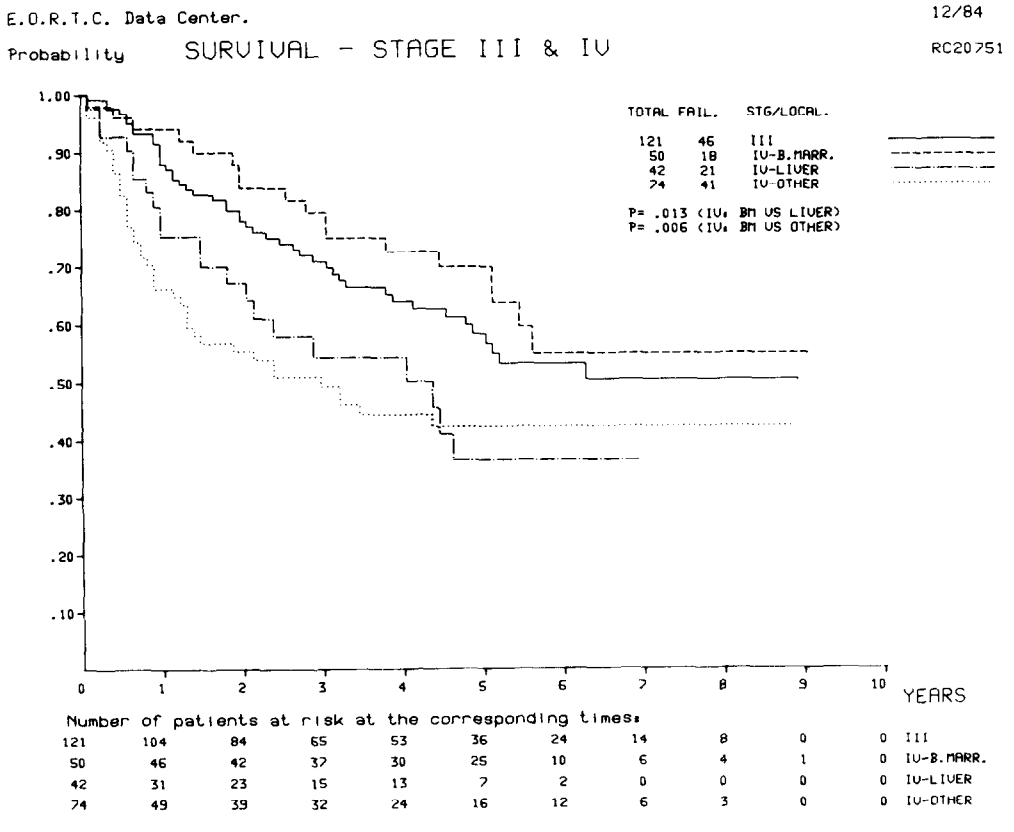
E.O.R.T.C. Data Center.
12/84
Probability SURVIVAL - STAGE III & IV
RC20751
TOTAL FAIL. STG/LOCAL.
121 46 III
50 18 IV-B.MARR.
42 21 IV-LIVER
74 41 IV-OTHER
P= .013 (IV: BM VS LIVER)
P= .006 (IV: BM VS OTHER)
1.00
.90
.80
.70
.60
.50
.40
.30
.20
.10
0 1 2 3 4 5 6 7 8 9 10
YEARS
Number of patients at risk at the corresponding times:
121 104 84 65 53 36 24 14 8 0 0 III
50 46 42 37 30 25 10 6 4 1 0 IV-B.MARR.
42 31 23 15 13 7 2 0 0 0 0 IV-LIVER
74 49 39 32 24 16 12 6 3 0 0 IV-OTHER

Fig. 11.

diaphragm influenced prognosis; too few cases were entered into the trial to give an answer to the question. Patients with disease in stage II with a follicular pattern had a good prognosis when treated with primary radiotherapy and adjuvant CVP chemotherapy as shown in this study. The results of primary radiotherapy for patients with a lymphoma of diffuse cell pattern are very disappointing. In later studies these patients are always treated with chemotherapy at the outset [7].

For stages III and IV we examined different time sequences in induction chemotherapy treatment. No influence on percentage of remission, relapse free interval and survival was found. Our chemotherapy regimen was designed in 1975, at a time when new combination regimens had proved their value in Hodgkin's disease. It was thought that intensive combination therapy might cure a considerable number of patients with low grade lymphomas. When the multicenter trial was designed it was thought that it would be difficult to select treatment on the basis of histological classification, because of the outset of the cooperation between the centers, especially between the individual pathologists who might use different criteria. Therefore the same treatment was given independent of the histology.

In patients with stages III and IV low grade or follicular lymphomas there are different opinions about the optimal treatment. Our results in stages III and IV follicular lymphoma (38% relapse free survival, 68% survival at 5 years) are not superior to other series published in which a less intensive treatment was given. Hoppe *et al.* [8] found 38% freedom relapse at 5 years in patients treated with single agents or with CVP with or without irradiation, and survival from 70 to 85%. "Wait and see" is a new approach possibly justified for some categories of patients [9]. The International Working Formulation [10] delineating three prognostic categories may give a more precise judgement about patients for whom this policy is acceptable.

The optimal treatment for low grade lymphomas is still uncertain. It must be kept in mind that 45% of the patients die of their disease in about 7 years after diagnosis. It remains mandatory that new approaches remain under investigation especially for the younger patients with this kind of lymphoma. An attitude of just "wait and see", or using single agent chemotherapy outside a clinical study, because it is a low grade lymphoma, may delay the finding of optimal treatment.

The results presented in the diffuse lymphomas in this study are in accordance with other studies using CHOP or CHOP-like regimens: 30% long-term survival, with a plateau after 5 years; the median survival of 26 months is equal to that of the CHOP regimen (23 months) [11]. The percentage of patients not reaching a complete remission is high. In more recent publications a higher complete remission rate (60–80%) is reported with a longer disease free survival period using more intensive regimens [12, 13]. These studies however are non-randomized single institute studies using comparisons with historical control; they also include patients with lower stages of the disease. It remains to be proven in prospective randomized studies whether these intensive regimens, with their higher morbidity, are necessary for all categories of intermediate and high grade lymphomas.

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