original article

Poorer outcome of elderly patients treated with extended-field radiotherapy compared with involved-field radiotherapy after chemotherapy for Hodgkin's lymphoma: an analysis from the German Hodgkin Study Group

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Background: The optimal treatment of elderly patients with Hodgkin's lymphoma (HL) is still a matter of debate. Since many of these patients receive combined modality treatment, we evaluated the impact of different radiation field sizes, that is extended-field (EF) or involved-field (IF) technique when given after four cycles of chemotherapy.

Patients and methods: In the multicenter HD8 study of the German Hodgkin Study Group, 1204 patients with early-stage unfavorable HL were randomized to receive four cycles of chemotherapy followed by either radiotherapy (RT) of 30 Gy EF + 10 Gy to bulky disease (arm A) or 30 Gy IF + 10 Gy to bulky disease (arm B). A total of 1064 patients were assessable for the analysis. Of these, 89 patients (8.4%) were 60 years or older.

Results: Elderly patients had a poorer risk profile. Acute toxicity from RT was more pronounced in elderly patients receiving EF-RT compared with IF-RT [World Health Organization (WHO) grade 3/4: 26.5% versus 8.6%)]. Freedom from treatment failure (FFTF, 64% versus 87%) and overall survival (OS, 70% versus 94%) after 5 years was lower in elderly patients compared with younger patients. Importantly, elderly patients had poorer outcome when treated with EF-RT compared with IF-RT in terms of FFTF (58% versus 70%; $P = 0.034$) and OS (59% versus 81%; $P = 0.008$).

Conclusion: Elderly patients with early-stage unfavorable HL generally have a poorer risk profile and outcome when compared with younger patients. Treatment with EF-RT instead of IF-RT after chemotherapy has a negative impact on survival of elderly patients and should be avoided.

Key words: clinical trial, elderly patients, Hodgkin lymphoma, outcome, radiotherapy

introduction

The prognosis for patients with Hodgkin's lymphoma (HL) has substantially improved over the last decades. This success is mainly attributed to the introduction and optimization of effective chemotherapy regimens and progress in radiation techniques. With complete remission (CR) rates exceeding 95% and 5-year overall survival (OS) of >80%, aim of prospectively randomized trials has increasingly shifted towards potentially less toxic treatments. One example is the HD8 study of the German Hodgkin Study Group (GHSG) demonstrating that involved-field radiotherapy (IF-RT) is equally effective when compared

with extended-field radiotherapy (EF-RT) after four cycles of chemotherapy for patients with early-stage unfavorable HL [1].

In contrast to younger patients, in elderly patients with HL the prognosis is still unsatisfactory. Advanced age at presentation is one of the strongest negative risk factors. Different study groups showed significantly poorer outcome for elderly HL patients compared with younger patients when similar treatments were given [2–15]. Generally, factors such as more aggressive disease, shorter history of disease, more frequent diagnosis of advanced stage [2–4], comorbidity [5], poor tolerance of treatment [6], failure to maintain dose intensity [7–10], shorter survival after relapse [11, 12], and death due to other causes [13] contribute to the poorer outcome in elderly patients.

Thus, clinical interest increasingly focuses on this high-risk group of HL patients. A recent comprehensive analysis of GHSG

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trials' HD5–9 showed that elderly patients present with poorer risk factors, experience more treatment-associated toxicity, receive lower dose intensity, and suffer from higher mortality [14]. Furthermore, intensification of treatment that has been shown to improve outcome for younger HL patients cannot easily be applied to elderly patients. The only prospectively randomized trial in this age group, HD9$_{elderly}$ for patients with advanced-stage HL, reported better tumor control related to intensified chemotherapy which was offset by higher mortality [15].

Since RT is another key element in the treatment of HL, we revisited the HD8 data for possible differences with regard to the type of RT applied.

patients and methods

patients
From February 1993 to March 1998, newly diagnosed patients with biopsy-proven HL in clinical stages I and II with selected risk factors as well as patients in clinical stage IIIA without risk factors were enrolled into the GHSG HD8 multicenter trial. Risk factors included the following: (a) large mediastinal mass (≥1/3 of maximal thorax diameter, determined by posterior–anterior chest radiography); (b) extranodal disease; (c) massive spleen involvement (diffuse infiltrations or more than five focal lesions); (d) elevated erythrocyte sedimentation rate (≥50 mm/h in patients without B symptoms; ≥30 mm/h in patients with B symptoms); or (e) three or more nodal areas involved. All patients with clinical stage IIB with risk factors a, b, or c were allocated to the study for advanced stages.

Patients had to be between 16 and 75 years of age, in good general condition (Karnofsky performance status ≥70%), not previously treated, and free of concurrent infection. Patients with impaired heart, lung, liver, or kidney function; previous malignant disease; or HIV-positive status were not included. Minimal hematological requirements included a WBC count >3000/μl and platelet count >100,000/μl. Patients were also excluded if they were pregnant or lactating. Biopsy material was judged by the local pathologist and then centrally reviewed by at least one member of a panel of six HL expert pathologists. Composite lymphomas were excluded. Routine staging procedures included medical history; physical examination; chest radiography; computed tomography of the chest, abdomen, and pelvis; bone marrow biopsy; skeletal scintigraphy; serum chemistry; lung function tests; and echocardiography. Each patient signed an informed consent form which was based on Institutional Review Board guidelines.

study design
Patients were registered in the HD8 trial and randomly assigned to the two treatment arms as previously described [1]. In arm A, patients received two cycles of COPP/ABVD (COPP alternating with ABVD in every cycle) followed by 30-Gy RT to the EF + 10 Gy to initial bulky disease (single lymph node involvement or conglomerate mass of ≥5 cm in any diameter). In arm B, the same chemotherapy was applied followed by 30-Gy RT to the IF + 10 Gy to initial bulky disease.

chemotherapy
Patients were scheduled to receive a total of two cycles of COPP alternating with two cycles of ABVD. COPP was given from days 1 to 14 [cyclophosphamide 650 mg/m^2 i.v. day 1 + 8; vincristine 1.4 mg/m^2 (max. 2 mg/m^2) i.v. day 1 + 8; procarbacine 100 mg/m^2 p.o. day 1–14; prednisone 40 mg/m^2 p.o. day 1–14], followed by ABVD on days 29 and 43 (doxorubicin 25 mg/m^2 i.v. day 29 + 43; bleomycin 10 mg/m^2 i.v. day 29 + 43; vinblastine 6 mg/m^2 i.v. day 29 + 43; dacarbazine 375 mg/m^2 i.v. day 29 + 43).

Treatment application, delay, dose reduction, and the use of hematopoietic growth factors were carried out as previously described [1].

radiotherapy
RT was planned centrally by an expert radiation oncology review panel. According to treatment arm, patients received 30 Gy in either the EF technique (arm A) or IF technique (arm B) for a period of 3–3.5 weeks. Additional RT of 10 Gy was given during the fourth week to areas of initial bulky disease. For patients presenting with HL on both sides of the diaphragm, EF-RT was applied in two separate series. Single fraction size was 1.8–2.0 Gy and was given five times a week.

EF-RT included the involved lymph node region as well as all anatomic and functionally adjacent but clinically uninvolved lymph node regions. Generally, EF-RT indicated treatment delivered to regions on both sides of the diaphragm. For a supradiaphragmatic involvement, such as the mediastinal nodes, the EF-RT volume included a mantle field and also the para-aortic area (inferior border L4–5 interspace), the splenic hilar region, and the spleen if necessary. The mantle field extended from the inferior portion of the mastoid to the level of the insertion of the diaphragm. Individually contoured lung blocks were designed to conform to the patient's anatomy and tumor extension. The first series of radiation adding up to 16 Gy total were delivered to the initial mediastinal–hilar lymph node enlargement. Subsequently, the mediastinal–hilar contour was modified and included only the extension after chemotherapy. A subdiaphragmatic radiation field was similar to an inverted Y, including the retroperitoneal and pelvic lymph nodes and the spleen. In addition, a mantle field without the upper cervical and axillary region was irradiated (T field). If there was an involvement in the upper cervical region or the Waldeyer's ring only, radiation therapy was administered to supradiaphragmatic regions only. The EF-RT consisted of a mantle field plus additional Waldeyer fields. If only the inguinal nodes were involved, the EF-RT was applied in the inverted-Y technique.

IF-RT was administered to all initially involved lymph node regions. All these regions were treated in one field, if possible, for example a T field for supraclavicular and mediastinal involvement. The procedure for the design of the field contour of bulky mediastinal disease was the same as for EF-RT.

statistical analysis
Response criteria (CR, partial remission, no change, and progressive disease) as well as selection criteria for analysis of acute toxic effects during RT were used as previously described [1]. The Mann–Whitney U test was applied for arm comparisons of acute toxicity (WHO grades 1 to 4); for categorical data, Fisher's exact test was used. Freedom from treatment failure (FFTF) and OS rates were analyzed according to the Kaplan–Meier method [16]. The main end point of the trial was FFTF after the start of RT. FFTF was defined from the start of RT to the first of the following events: progression during RT, lack of CR at the end of protocol treatment, relapse, or death from any cause. The arm comparison for OS was also based on the time calculated from the start of RT until death from any cause or date of last information, respectively. Kaplan–Meier estimates were compared using the log-rank test. A P value <0.05 was considered significant in this explorative retrospective analysis without adjustment for multiplicity. All statistical analyses were carried out with SAS 8.2 (SAS Institute Inc., Cary, NC).

results

patient characteristics
A total of 1204 patients were randomly assigned to the two treatment arms. The median observation time was 55 months for both treatment groups. The flow of patients through the various stages of the trial as well as reasons for exclusion and

discontinuation were presented in detail elsewhere [1]. The 1064 patients actually starting RT (informative patients) provide the basis for the current analysis. Of these, 89 patients (8.4%) were 60 years or older and 975 patients were younger than 60 years. Demographic data and the number of patients according to treatment arm are given in Table 1.

Generally, there were more negative risk factors, such as B symptoms, elevated erythrocyte sedimentation rate, and poorer Karnofsky performance status, in the elderly group. On the other hand, there were fewer large mediastinal masses, a smaller number of lymph node areas involved, and fewer bulky tumors in elderly patients. Younger patients more often presented with nodular sclerosis subtype, whereas the frequency of mixed-cellularity subtype was higher in elderly patients. Patient characteristics are shown in Table 2.

administration of treatment and toxicity

All patients were scheduled to the same initial chemotherapy consisting of two cycles of COPP alternating with two cycles of ABVD. The most commonly observed toxic effects during chemotherapy included WHO grade 3 or 4 leucopenia (71.6% for patients ≥60 years; 56.2% for patients <60 years), alopecia (36.4% for patients ≥60 years; 23.8% for patients <60 years), and nausea (6.8% for patients ≥60 years; 11.1% for patients <60 years) with no difference between study arms. Other acute grade 3 or 4 toxic effects during chemotherapy occurred in <2% of all patients.

Acute toxicity during RT was more pronounced in patients undergoing EF-RT (arm A), including nausea, hematological, pharyngeal, and gastrointestinal (GI) toxicity [1]. A total of 11.3% of all patients had WHO grade 3 or 4 toxicity during RT. Compared with the group of patients younger than 60 years, elderly patients more often suffered from severe toxicity especially those assigned to the EF-RT arm (26.5% in arm A and 8.6% in arm B, P < 0.05). As shown in Table 3, in elderly patients especially nausea and leucopenia grade 3 and 4 were more pronounced in the EF-RT arm with 3 of 34 (8.8%) versus 0 of 35 in the IF-RT arm.

treatment outcome, causes of death, and secondary malignancies

Response rates, causes of death, and secondary malignancies according to age and treatment are shown in Table 4. In all, 97.8% of all patients achieved CR or CR unconfirmed, without notable differences with respect to age and treatment modality. In contrast to younger patients, however, more elderly patients died during follow-up. Causes of death included HL, toxicity from primary or salvage treatment, secondary malignancies, and cardiovascular or pulmonary disease. The total number of secondary malignancies was 39 (3.7%), with 10 (11.2%) occurring in elderly patients and 29 (3.0%) in younger patients. So far, in elderly patients, there were six secondary malignancies after EF-RT (13.0%) as compared with four after IF-RT (9.3%).

survival

In the current analysis, FFTF and OS was remarkably lower for elderly compared with younger patients: after a median follow-up of 60 months, the 5-year FFTF was 64% [95% confidence

Table 1. Demographic characteristics

	Elderly patients ≥60 years		Younger patients <60 years	
	Arm A, n	Arm B, n	Arm A, n	Arm B, n
Total number of eligible patients	46	43	486	489
Age, years				
16–29	–	–	240	243
30–44	–	–	173	180
45–59	–	–	73	66
60–75	46	43	–	–
Median age	65.5	65	30	30
Sex				
Male	24	25	232	242
Female	22	18	254	247

Table 2. Patient characteristics

	% of elderly patients ≥60 years		% of younger patients <60 years	
	Arm A (n = 46)	Arm B (n = 43)	Arm A (n = 486)	Arm B (n = 489)
Stage				
IA	8.7	14.0	5.3	3.7
IB	2.2	7.0	3.5	2.2
IIA	50.0	44.2	68.1	69.5
IIB	37.0	30.2	20.6	22.5
IIIA	2.2	4.7	2.5	2.0
Risk factors				
Large mediastinal mass	8.7	7.0	18.1	20.4
Massive spleen involvement	2.2	2.3	0.2	0.2
Extranodal involvement	6.5	11.6	7.2	7.2
High ESR (n = 1061)	76.1	62.8	44.7	49.0
≥3 Lymph node areas	56.5	46.5	66.7	65.8
Bulky disease (n = 1057)	47.7	53.5	62.6	60.7
Laparotomy carried out (n = 1025)	9.1	7.1	4.3	3.0
Karnofsky performance status (n = 1040)				
80–100	86.7	95.3	99.8	98.7
<80	13.3	4.7	0.2	1.3
Review histology (n = 807)				
LP/LR	5.1	0	2.2	2.7
NS	43.6	42.4	74.0	77.0
MC	35.9	45.5	16.4	15.4
LD	0	0	0.8	0.3
Unclassifiable or other	15.4	12.1	6.6	4.6

ESR, erythrocyte sedimentation rate; LP, lymphocyte predominant; LR, lymphocyte rich; NS, nodular sclerosis; MC, mixed cellularity; LD, lymphocyte depleted.

interval (CI) 52% to 76%) in patients ≥60 years and 87% (85% to 90%) in patients <60 years (log-rank, P < 0.001)]. The 5-year OS was 70% (59% to 81%) and 94% (92% to 96%), respectively (log-rank, P < 0.001) as shown in Figure 1.

Most importantly, elderly patients showed different outcomes according to the type of RT received: patients older than 60 had

Table 3. Radiotherapy-associated acute toxicity (WHO grade 1/2 and 3/4)

WHO grade	% of elderly patients ≥60 years		% of younger patients <60 years		% of all patients (n = 925)
	in Arm A (n = 35)	in Arm B (n = 35)	in Arm A (n = 441)	in Arm B (n = 414)	
Total					
1/2	67.6	80.0	82.3	88.8	84.6
3/4	26.5	8.6	14.4	6.8	11.3
Hematological toxicity					
Leucopenia					
1/2	47.1	25.7	44.5	31.5	38.1
3/4	8.8	0.0	4.1	2.4	3.4
Thrombopenia					
1/2	23.5	2.9	14.7	5.6	10.5
3/4	2.9	2.9	1.1	0.0	0.8
Anemia					
1/2	20.6	5.7	8.3	6.6	7.9
3/4	2.9	0.0	0.5	0.0	0.3
Other toxicity (≥1.0%)					
Nausea					
1/2	32.4	28.6	56.7	27.9	41.8
3/4	8.8	0.0	7.6	1.5	4.6
Skin					
1/2	55.9	37.1	46.3	49.4	47.7
3/4	2.9	2.9	1.8	2.0	2.0
Esophagus					
1/2	55.9	28.6	43.6	44.3	43.8
3/4	0.0	0.0	1.4	1.0	1.1
Pharynx					
1/2	50.0	22.9	47.5	41.1	43.8
3/4	2.9	2.9	1.1	0.5	1.0

WHO, World Health Organization.

Table 4. Treatment outcome and causes of death

	% of elderly patients ≥60 years		% of younger patients <60 years		% of all patients (n = 1064)
	Arm A (n = 46)	Arm B (n = 43)	Arm A (n = 486)	Arm B (n = 489)	
Response					
CR/CRu	93.5	100	99.0	96.9	97.8
PR	2.2	0.0	0.4	0.4	0.5
NC	0.0	0.0	0.0	0.2	0.1
PRO	2.2	0.0	0.6	2.0	1.3
Unknown	2.2	0.0	0.0	0.4	0.3
Death	41.3	16.3	4.9	5.5	7.2
Causes of death					
HL	4.3	2.3	2.1	2.2	2.3
Secondary malignancy	8.7	4.7	1.6	1.2	1.9
Toxicity (primary RT)	2.2	0.0	0.2	0.0	0.2
Toxicity (salvage therapy)	0.0	0.0	0.4	0.6	0.5
Cardiovascular	4.3	4.7	0.0	0.8	0.8
Lung	6.5	0.0	0.0	0.2	0.4
Other or unknown	15.2	4.7	0.6	0.4	1.3
Secondary malignancies	13.0	9.3	3.7	2.2	3.7
AML or MDS	8.7	2.3	0.6	0.2	0.8
NHL	0.0	0.0	1.0	0.8	0.8
Solid tumor	4.3	7.0	2.1	1.2	2.0

CR, complete remission; CRu, complete remission unconfirmed; PR, partial remission; HL, Hodgkin's lymphoma; NC, no change; PRO, early progression; RT, radiotherapy; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; NHL, non-Hodgkin's lymphoma; SM, secondary malignancy.

a significantly inferior outcome when treated with EF-RT as compared with IF-RT, in terms of both, FFTF (EF: 58%, 42% to 73%; IF: 70%, 52% to 88%; log-rank $P = 0.034$) and OS (EF: 59%, 44% to 75%; IF: 81%, 67% to 95%; log-rank $P = 0.008$) (Figure 2).

discussion

The objective of the current analysis was to compare toxicity and treatment outcome for elderly and younger HL patients depending on the technique of RT applied (EF or IF). The following results emerge from this study: first, acute toxicity from RT was more pronounced in the group of patients receiving EF-RT. Second, FFTF (64% versus 87%) and OS (70% versus 94%) at 5 years was lower in elderly patients when compared with younger patients receiving identical treatment. Third, elderly patients who were treated in the EF-RT arm had a significantly inferior outcome compared with elderly patients in the IF-RT arm with a difference of 12% for FFTF and 22% for OS after 5 years.

Elderly HL patients with early-stage disease and adequate organ function qualify for very similar curative approaches as younger patients. The treatment generally involves combined modality treatment including chemotherapy and RT. Even selected elderly patients, however, have a significantly poorer

outcome when compared with younger HL patients due to poorer tolerance of treatment resulting in less dose intensity. Other factors include shorter survival after relapse, more comorbidity, and others [2–13]. A recent GHSG analysis on 373 elderly HL patients (≥60 years) demonstrated that higher mortality during treatment as well as lower dose intensity were the major factors explaining the poorer overall outcome of elderly HL patients [14]. In an attempt to improve the poor prognosis for elderly HL patients, the GHSG conducted the HD9$_{elderly}$ trial in which patients with advanced disease aging 60 years and more were randomized between eight courses of COPP–ABVD or BEACOPP (combination therapy with bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone) baseline. The better tumor control achieved with BEACOPP baseline, however, was offset by more toxicity and did not translate into better outcome [15].

Older age at presentation was also described as negative risk factor in patients undergoing treatment of other malignancies: in a population-based study including 381 patients with aggressive non-Hodgkin's lymphoma (NHL), the proportion of patients who received chemotherapy decreased with older age. There were more patients requiring dose reduction due to comorbidity, poor performance status, or chemotherapy-related
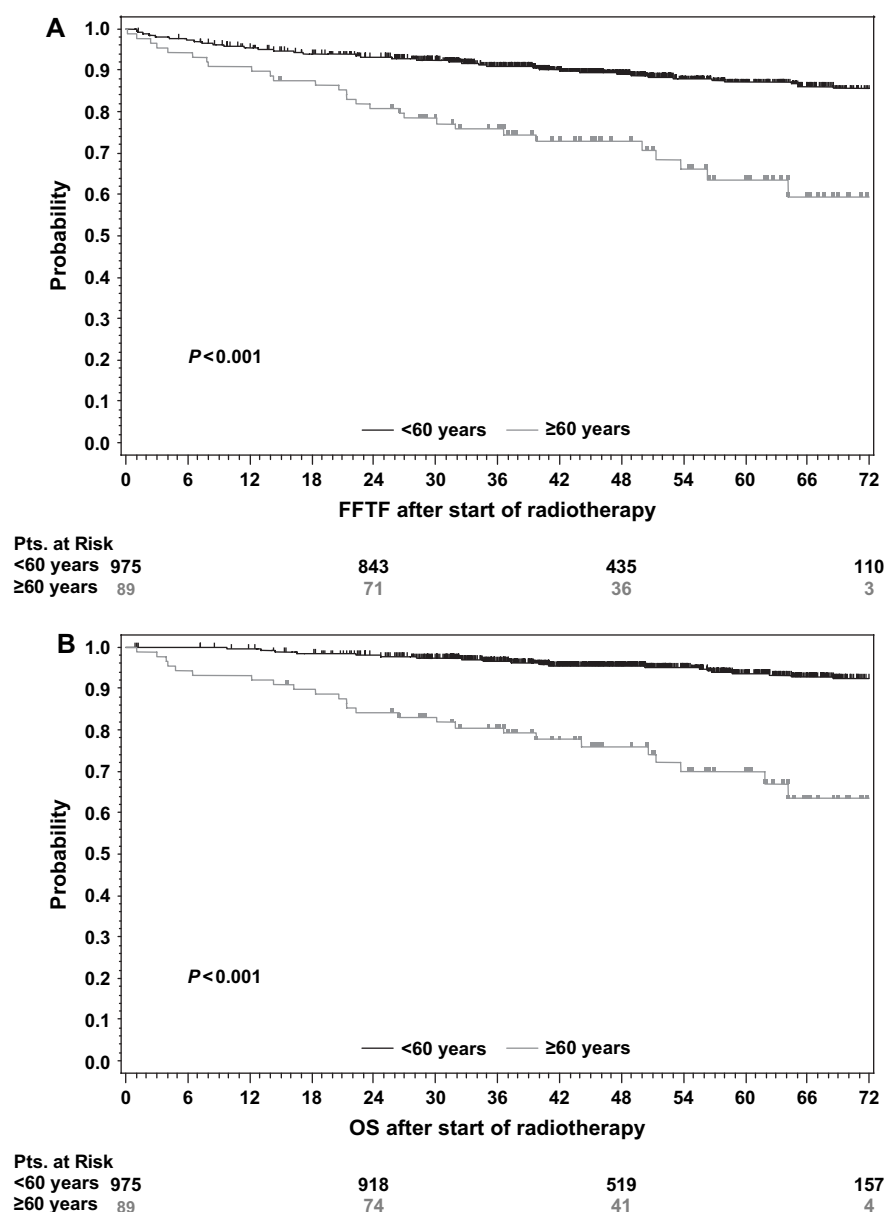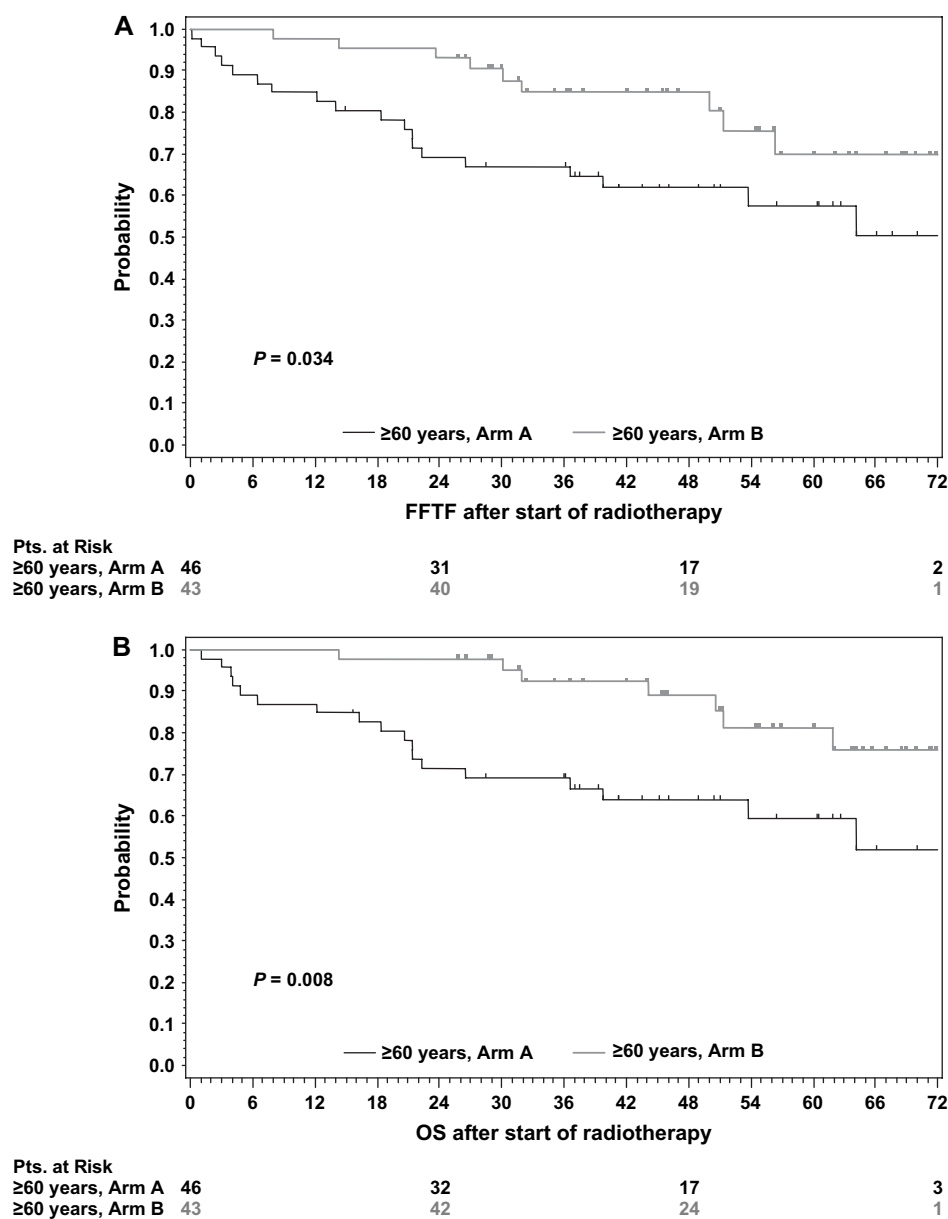
Figure 1. Kaplan–Meier analysis of (**A**) freedom from treatment failure (FFTF) and (**B**) overall survival (OS) after start of radiotherapy according to age (<60 years and ≥60 years).

toxicity [17]. Similar factors contributing to a poorer OS in elderly patients were found in patients with acute myeloid leukemia (AML) and chronic myeloid leukemia [18, 19]. Thus, new approaches for elderly patients are warranted. New regimens specifically targeted at elderly HL patients, such as vinblastine, cyclophosphamide, procarbazine, etoposide, mitoxantrone and bleomycin (VEPEMB) [20], vincristine, doxorubicin, bleomycin, etoposide and prednisone (OBDEP) [21], bleomycin, doxorubicin, cyclophosphamide, vincristine, procarbacine and prednisone (BACOPP) [22], and prednisone, vinblastine, doxorubicin and gemcitabine (PVAG) [23], are currently being evaluated by different study groups.

To our knowledge, this is the first report derived from a prospective controlled study identifying significantly more mortality and toxicity in elderly patients when receiving larger field RT. Although combined modality treatment including

EF-RT resulted in similar responses as compared with IF-RT, there was significantly poorer OS associated with more toxicity in elderly patients. Radiation-induced effects, including nausea, hematological toxicity, pharyngeal, and GI toxicity, were clearly more often seen in elderly patients undergoing EF-RT. More GI toxicity from EF-RT is due to the larger radiation volume including abdominal regions in patients with supradiaphragmatic involvement only [24].

The reduction of RT field size seems to be essential in order to reduce long-term sequelae of treatment. Patients undergoing mantle field RT have a higher risk of late cardiac and pulmonary disease [25–27]. Furthermore, patients who receive large radiation fields, either alone or in combination with chemotherapy more often encounter secondary malignancies, such as AML [28], NHL [29], and solid tumors [30–34]. The relative risk of secondary cancers increases with radiation dose

Figure 2. Kaplan–Meier analysis of (**A**) freedom from treatment failure (FFTF) and (**B**) overall survival (OS) after start of radiotherapy (RT) of elderly patients (≥60 years) according to treatment arm; arm A: chemotherapy and extended-field RT and arm B: chemotherapy and involved-field RT.

and field size [30–34]. In the current analysis, 11.2% secondary malignancies occurred in elderly patients and 3.0% in younger patients. Though the numbers were small and the follow-up is still relatively short, there were more secondary malignancies in the EF-RT arm; 13.0% versus 9.3% in elderly and 3.7% versus 2.2% in younger patients.

As a consequence from the results of the GHSG HD8 trial and similar data by the European Organisation for Research and Treatment of Cancer (EORTC), IF-RT has become the new standard in combined modality treatment which should reduce acute and long-term toxicity [1, 35]. For elderly patients, current approaches include RT applied to residual lesions only or no RT at all [23]. Whether a further reduction of RT dose is possible while maintaining the excellent results in the whole HL population is subject to recently conducted and ongoing clinical trials. In the GHSG HD11 trial, patients with early unfavourable

HL were allocated to four cycles of chemotherapy followed by either 30- or 20-Gy IF-RT. Interim results at 2 years indicate no significant difference in treatment outcome [36]. Similar interim results were observed for early favorable stages in the GHSG HD10 trial [37]. In addition, the H9F trial of the EORTC and Groupe d'Etude des Lymphomes de L'Adulte (GELA) evaluated a possible dose reduction of RT (36 or 20 Gy or no RT) after six cycles of epirubicin, bleomycin, vinblastine and prednisone (EBVP) chemotherapy [38]. Here, the arm without RT had to be closed prematurely due to an unexpected high relapse rate. Thus, the use of chemotherapy only in early-stage HL is still experimental. Furthermore, development of new therapeutic approaches such as immunotherapy with monoclonal antibodies associated with less toxicity is urgently needed [39].

Taken together, our data demonstrate that outcome of patients aged 60 years or older clearly depends on the modality

of RT applied after chemotherapy for early-stage unfavorable HL. In this group of high-risk HL patients, application of EF-RT instead of IF-RT resulted in significantly lower FFTF and survival and should be avoided in future studies in the elderly.

acknowledgements

references

1. Engert A, Schiller P, Josting A et al. Involved-field radiotherapy is equally effective and less toxic compared with extended-field radiotherapy after four cycles of chemotherapy in patients with early-stage unfavorable Hodgkin's lymphoma: results of the HD8 trial of the German Hodgkin's Lymphoma Study Group. J Clin Oncol 2003; 21: 3601–3608.

2. Bosi A, Ponticelli P, Casini C et al. Clinical data and therapeutic approach in elderly patients with Hodgkin's disease. Haematologica 1989; 74: 463–473.

3. Austin-Seymour MM, Hoppe RT, Cox RS et al. Hodgkin's disease in patients over sixty years old. Ann Intern Med 1984; 100: 13–18.

4. Peterson BA, Pajak TF, Cooper MR et al. Effect of age on therapeutic response and survival in advanced Hodgkin's disease. Cancer Treat Rep 1982; 66: 889–898.

5. van Spronsen DJ, Janssen-Heijnen MLG, Breed WPM et al. Prevalence of co-morbidity and its relationship to treatment among unselected patients with Hodgkin's disease and non-Hodgkin's lymphoma, 1993–1996. Ann Hematol 1999; 78: 315–319.

6. Weekes CD, Vose JM, Lynch JC et al. Hodgkin's disease in the elderly: improved treatment outcome with a doxorubicin-containing regimen. J Clin Oncol 2002; 20: 1087–1093.

7. Landgren O, Algernon C, Axdorph U et al. Hodgkin's lymphoma in the elderly with special reference to type and intensity of chemotherapy in relation to prognosis. Haematologica 2003; 88: 438–444.

8. Levis A, Depaoli L, Urgesi A et al. Probability of cure in elderly Hodgkin's disease patients. Haematologica 1994; 79: 46–54.

9. Erdkamp FL, Breed WP, Bosch LJ et al. Hodgkin's disease in the elderly. A registry-based analysis. Cancer 1992; 70: 830–834.

10. Enblad G, Glimelius B, Sundstrom C. Treatment outcome in Hodgkin's disease in patients above the age of 60: a population-based study. Ann Oncol 1991; 2: 297–302.

11. Kim HK, Silver B, Li S et al. Hodgkin's disease in elderly patients (≥60): clinical outcome and treatment strategies. Int J Radiat Oncol Biol Phys 2003; 56: 556–560.

12. Specht L, Nissen NI. Hodgkin's disease and age. Eur J Haematol 1989; 43: 127–135.

13. Guinee VF, Geoffrey GC, Durand M et al. The prognosis of Hodgkin's disease in older adults. J Clin Oncol 1991; 9: 947–953.

14. Engert A, Ballova V, Haverkamp H et al. Hodgkin's lymphoma in elderly patients: a comprehensive retrospective analysis from the German Hodgkin's Study Group. J Clin Oncol 2005; 23: 5052–5060.

15. Ballova V, Ruffer JU, Haverkamp H et al. A prospectively randomized trial carried out by the German Hodgkin Study Group (GHSG) for elderly patients with advanced Hodgkin's disease comparing BEACOPP baseline and COPP-ABVD (study HD9$_{elderly}$). Ann Oncol 2005; 16: 124–131.

16. Kaplan EL, Meier P. Non parametric estimation from incomplete observations. J Am Stat Assoc 1958; 53: 457–481.

17. Janssen-Heijnen ML, van Spronsen DJ, Lemmens VE et al. Population-based study of severity of comorbidity among patients with non-Hodgkin's lymphoma: prognostic impact independent of International Prognostic Index. Br J Haematol 2005; 129: 597–606.

18. Buchner T, Berdel WE, Wormann B et al. Treatment of older patients with AML. Crit Rev Oncol Hematol 2005; 56: 247–259.

19. Berger U, Engelich G, Maywald O et al. Chronic myeloid leukemia in the elderly: long-term results from randomized trials with interferon alpha. Leukemia 2003; 17: 1820–1826.

20. Levis A, Anselmo AP, Ambrosetti A et al. VEPEMB in elderly Hodgkin's lymphoma patients. Results from an Intergruppo Italiano Linfomi (IIL) study. Ann Oncol 2004; 15: 123–128.

21. Macpherson N, Klasa RJ, Gascoyne R et al. Treatment of elderly Hodgkin's lymphoma patients with a novel 5-drug regimen (ODBEP): a phase II study. Leuk Lymphoma 2002; 43: 1395–1402.

22. Nogova L, Sieniawski M, Nisters-Backes H et al. New BACOPP schedule is feasible and effective in elderly Hodgkin's lymphoma patients—interim results of a multicenter phase-II trial of the German Hodgkin Study Group (GHSG). Blood 2005; 106: 4735 (Abstr).

23. Klimm B, Diehl V, Pfistner B et al. Current treatment strategies of the German Hodgkin Study Group (GHSG). Eur J Haematol 2005; (Suppl 66): 125–134.

24. Eich HT, Haverkamp U, Engert A et al. Biophysical analysis of the acute toxicity of radiotherapy in Hodgkin's lymphoma—a comparison between extended field and involved field radiotherapy based on the data of the German Hodgkin Study Group. Int J Radiat Oncol Biol Phys 2005; 63: 860–865.

25. Hancock SL, Tucker MA, Hoppe RT. Factors affecting late mortality from heart disease after treatment of Hodgkin's disease. JAMA 1993; 270: 1949–1955.

26. Hull MC, Morris CG, Pepine CJ et al. Valvular dysfunction and carotid, subclavian, and coronary artery disease in survivors of Hodgkin lymphoma treated with radiation therapy. JAMA 2003; 290: 2831–2837.

27. Horning SJ, Adhikari A, Rizk et al. Effect of treatment for Hodgkin's disease on pulmonary function: results of a prospective study. J Clin Oncol 1994; 12: 297–305.

28. Josting A, Wiedenmann S, Franklin J et al. Secondary myeloid leukemia and myelodysplastic syndromes in patients treated for Hodgkin's disease: a report from the German Hodgkin's Lymphoma Study Group. J Clin Oncol 2003; 21: 3440–3446.

29. Rueffer U, Josting A, Franklin J et al. Non-Hodgkin's lymphoma after primary Hodgkin's disease in the German Hodgkin's Lymphoma Study Group: incidence, treatment, and prognosis. J Clin Oncol 2001; 19: 2026–2032.

30. Behringer K, Josting A, Schiller P et al. Solid tumors in patients treated for Hodgkin's disease: a report from the German Hodgkin Lymphoma Study Group. Ann Oncol 2004; 15: 1079–1085.

31. van Leeuwen FE, Klokman WJ, Stovall M et al. Roles of radiation dose, chemotherapy, and hormonal factors in breast cancer following Hodgkin's disease. J Natl Cancer Inst 2003; 95: 971–980.

32. Aisenberg AC, Finkelstein DM, Doppke KP et al. High risk of breast carcinoma after irradiation of young women with Hodgkin's disease. Cancer 1997; 79: 1203–1210.

33. Travis LB, Gospodarowicz M, Curtis RE et al. Lung cancer following chemotherapy and radiotherapy for Hodgkin's disease. J Natl Cancer Inst 2002; 94: 182–192.

34. Ng AK, Bernardo MV, Weller E et al. Second malignancy after Hodgkin disease treated with radiation therapy with or without chemotherapy: long-term risks and risk factors. Blood 2002; 100: 1989–1996.

35. Raemaekers J, Kluin-Nelemans H, Teodorovic I et al. The achievements of the EORTC Lymphoma Group. European Organisation for Research and Treatment of Cancer. Eur J Cancer 2002; 38 (Suppl 4): 107–113.

36. Diehl V, Brillant C, Engert A et al. Recent interim analysis of the HD11 trial of the GHSG: intensification of chemotherapy and reduction of radiation dose in early unfavorable stage Hodgkin's lymphoma. Blood 2005; 106: 816 (Abstr).

37. Engert A, Pluetschow A, Eich HT et al. Combined modality treatment of two or four cycles of ABVD followed by involved field radiotherapy in the treatment of patients with early stage Hodgkin's lymphoma: update interim analysis of the randomised HD10 study of the German Hodgkin Study Group (GHSG). Blood 2005; 106: 2673 (Abstr).

38. Eghbali H, Brice P, Creemers GY et al. Comparison of three radiation dose levels after EBVP regimen in favorable supradiaphragmatic clinical stages (CS) I-II Hodgkin's Lymphoma (HL): preliminary results of the EORTC-GELA H9-F Trial. Blood 2005; 106: 814 (Abstr).

39. Klimm B, Schnell R, Diehl V, Engert A. Current treatment and immunotherapy of Hodgkin's lymphoma. Haematologica 2005; 90: 1680–1692.