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● *Clinical Original Contribution*

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Purpose: To evaluate whether or not a total dose (TD) of 30 Gy is sufficient for treatment of assumed subclinical Hodgkin's Disease compared to 40 Gy TD with early stage Hodgkin's Disease (ESHD).
Methods and Materials: In a prospective multicenter trial, 376 patients with laparotomy-proven ESHD stages PS IA to PS IIB without risk factors such as large mediastinum, massive splenic involvement, extranodal disease, elevated erythrocyte sedimentation rate (ESR), and/or three or more involved lymphnode areas were randomly allocated either to receive (ARM A) 40 Gy TD extended field-radiotherapy (EF-RT) or (ARM B) 30 Gy TD EF-RT plus 10 Gy TD involved field-radiotherapy (IF-RT), both arms without any chemotherapy. Three hundred sixty-six of these patients were evaluable for early and long-term response, such as remission status, freedom from treatment failure (FFTF), and overall survival (OAS). For quality control, all planning and verification films as well as dose charts were prospectively reviewed by a panel of four experts, all heads of a radiotherapy department, where protocol violations (PV) were seen either with regard to errors in treatment technique, treatment volume, in TD and/or in dose/time-relationship.
Results: Treatment resulted in a complete remission (CR) of 98%; in a 5-year FFTF of 76%, and a 5-year OAS of 97%. There was no difference between the two arms in favor of 40 Gy EF compared to 30 Gy EF regarding FFTF and OAS, without any in field relapse throughout the EF volumes. Expectedly, 5-years FFTF was significantly influenced by the quality of radiotherapeutical procedures: 70% with protocol violations (PV) vs. 82% without PV.
Conclusion: Subclinical involvement in ESHD without risk factors is sufficiently treated by a TD of 30 Gy without chemotherapy, leading to a 5-years FFTF of 82% and a 5-year OAS of 97% in a multicenter treatment setting, where quality assurance is mandatory. Copyright © 1996 Elsevier Science Inc.

Early-stage Hodgkin's disease, Radiotherapy, Randomized trial, Sufficient extended field treatment dose.

INTRODUCTION

To date, it has been an open question whether or not 30 Gy total fractionated dose (TD) is sufficient in extended field (EF) radiotherapy (RT) of early stage Hodgkin's disease (ESHD) without additional chemotherapy, where involved field (IF) volumes are treated with 40 Gy TD according to revised dose calculations [(5) vs. (4)].

Therefore, in 1988 the German Hodgkin's Study Group (GHSG) designed and activated a prospective randomized trial treating stages CPS IA to IIB with radiation therapy alone, to test 30 Gy vs. 40 Gy EF-RT (Fig. 1).

METHODS AND MATERIALS

The study population consisted of a total of 399 perviously untreated patients (Study Center Cologne, SCC) and 393 patients (Radiation Therapy Reference Center Munich, RTRCM) without risk factors, out of which identical 376 patients qualified for randomization to receive either 40 Gy EF-RT (ARM A) or 30 Gy (ARM B) with a TD of 40 Gy to all macroscopically involved regions in both arms.

Clinical and pathologic staging procedures followed the rules of Ann Arbor classification (1) and always in-

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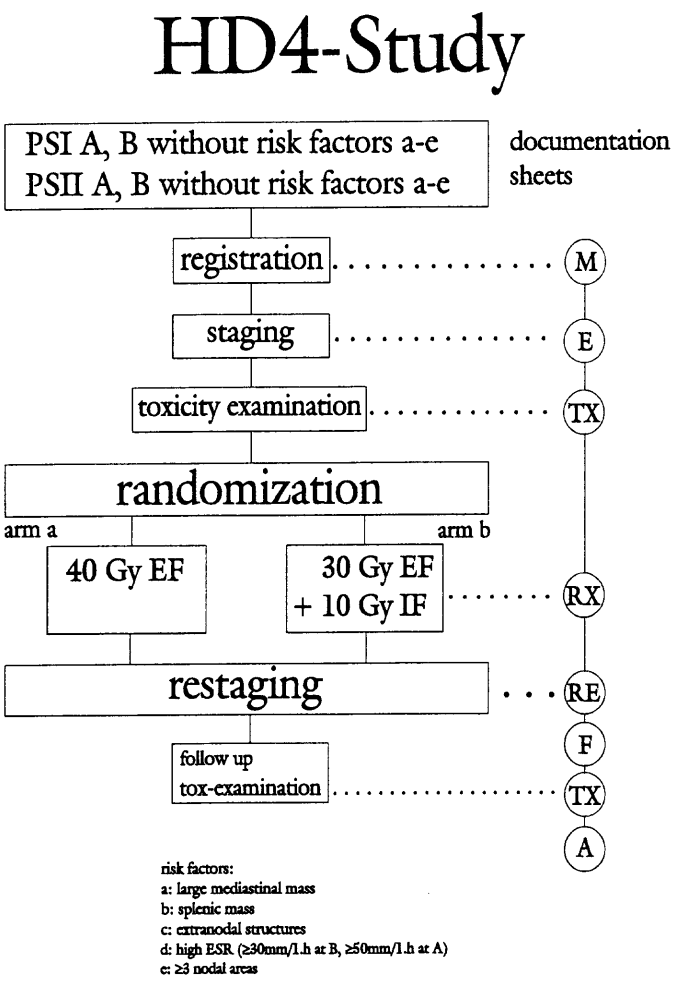


Fig. 1. Study design of HD4-trial of the German Hodgkin's Study Group (GHSG).

cluded staging laparotomy (6). Risk factors, such as large mediastinal mass measuring one-third or more of the maximal diameter of the thorax, a massive involvement of the spleen with five or more nodules or diffuse involvement, extranodal disease, an elevated erythrocyte sedimentation rate (ESR) of 30 mm or more at CS B or 50 mm or more at CS A after 1 h, and/or three or more involved lymph node areas, excluded from HD4 study (2, 7–8, 10–12, 15), shifting those patients to combined modality treatment (HD5).

After receiving a new patient's entrance data, SCC was responsible for randomization, and RTRCM worked out the appropriate radiation treatment plan according to EF strategy and treatment arm. Additionally, the planning and verification films as well as RT report charts of each newly randomized patient were seen prospectively by a panel of four experienced chairpersons of different radiation therapy departments to establish quality control. This procedure comprised 2D-RT geometry for complete inclusion of all macroscopic disease with an appropriate safety margin, irradiation technique with mandatory large field volumes and high-voltage beams, as well as a strict biological planning with a TD of 30 or 40 Gy ±10%, a single fraction size between 1.8 and 2.0 Gy, a weekly dose of 9.0 to 10.0 Gy, and a break of 2–4 weeks between supra- and infradiaphragmatic treatment or vice-versa. This prospective quality control could be achieved in 98% of all randomized HD4 patients and in about one-third resulted in a assignment of a protocol violation PV, if at least three out of four independent panelists voted for a PV, whatever the reason or the number was (Table 1).

The same panel analyzed all relapses in an analogous way to date, and reported results to all 141 individual radiation departments and free standing centers for quality assurance. After the study was closed for patient accrual in 1993, 345 out of 376 randomized patients were evaluable for early response and long-term results at a median follow-up of 3.5 years (1–7 years), to date. Early response was defined as clinically and radiologically complete remission (CR), partial remission (PR), and progression (P) (%). Long-term results were calculated in terms of freedom from treatment failure (FFTF) and overall survival (OAS) (probability of FFTF or OAS vs. time since end of RT) by the method of Kaplan-Meier, where differences were tested for significance by the log rank test (13).

RESULTS

Patients' characteristics are shown in Table 2; as expected, there was an equal distribution between ARMS A and B regarding gender, age, reviewed histology, definitive stages CPS, and therapy quality in terms of protocol violations PV (%). Thus, all remaining, possibly relevant prognostic factors were equally effective in both arms.

Early response and long-term results of primary radiation treatment without chemotherapy are presented in Table 3:

Complete remission (CR) was achieved in 98% of all evaluable patients with a very small number of PR and progressive disease (P). There was no significant difference between both arms in early response.

Table 1. Protocol violations–definitions for the HD4 study (Radiation Therapy Reference Center Munich)

Technique
Orthovoltage device
Single-field technique
Volume
Incompletely covered tumor
Field junction within tumor mass
Inadequate safety margins (<0.5 cm)
Extended field–volumes larger or smaller than defined
Treatment dose
Total dose >10% higher or lower than prescribed
Fraction size higher than 2.0 Gy or lower than 1.8 Gy
Dose/time–relationship
A weekly dose below 9 Gy and beyond 10 Gy
More than 2 weeks/4 weeks break within supradiaphragmatic or/and infradiaphragmatic treatment period

Table 2. HD4 patients' characteristics

	40 Gy EF (ARM A)	30 Gy EF (ARM B)	All
Pts. in study	187	189	399
Pts. evaluable for response	170	175	366
Gender	117	116	248
(male)	(63%)	(61%)	(62%)
Age			
Range	16–63	16–70	16–70
Median	32	31	32
Reviewed histology			
LP	15	17	35
NS1	39	42	85
NS2	4	8	13
MC	21	23	47
LD	—	—	—
EP	6	4	10
Pending	90	83	182
Definitive stages (CS/PS)			
IA	87	83	177
IB	6	2	10
IIA	91	99	203
IIB	3	5	9
Therapeutic Quality			
(% protocol violations)	36	35	35.5

Long-term results are characterized by eight deaths and 58 treatment failures including 46 relapses of disease with a border-line difference in favor of ARM B. This is also recognizable from the FFTF course with a median value of 76% probability at five years (Fig. 2) and the OAS course with a median value of 97% after the same follow-up (Fig. 3) for both arms. Relapse analysis might give a hint to the cause of this effect, as discussed below.

Results and role of Prospective Quality Control (PQC) of radiation therapy are illustrated by Figs. 4 and 5. The cumulative pattern of different types of protocol violations PV revealed that prospectively assigned PVs mainly consisted of too small or narrow treatment volumes, often without appropriate safety margins (n = 112), followed by too long treatment periods per total dose TD (n = 25), too low TD (n = 18), and interdicted single-field irradiation techniques instead of large field volumes (n = 14). The impact of PQC on prognosis is significant ($p \leq 0.0418$) where patients without PV are living better with a FFTF probability of 82% at 5 years than the PV assigned group with only 70%.

Prognosis in terms of FFTF and OAS is determined by negative events like treatment failures (TF), especially relapses of disease and death numbers, where TF numbers most sensitively indicate effectiveness of treatment strategies and techniques including total dose in EF-volumes.

Table 3. HD4 results of radiotherapy

	ARM A (40 Gy EF) n = 170	ARM B (30 Gy EF) n = 175	Total n = 366
Short term			
(at the end of RT)			
CR	167 (98.2%)	171 (97.7%)	359 (98%)
PR	1	1	2
Progression	2	3	5
Deaths before end of RT	—	—	—
Long-term			
(after end of RT)			
Death after end of RT	6	1	8
Relapses	30	15	46
Treatment failures	36	20	58

RT = Radiotherapy.
CR = complete remission.
PR = partial remission.

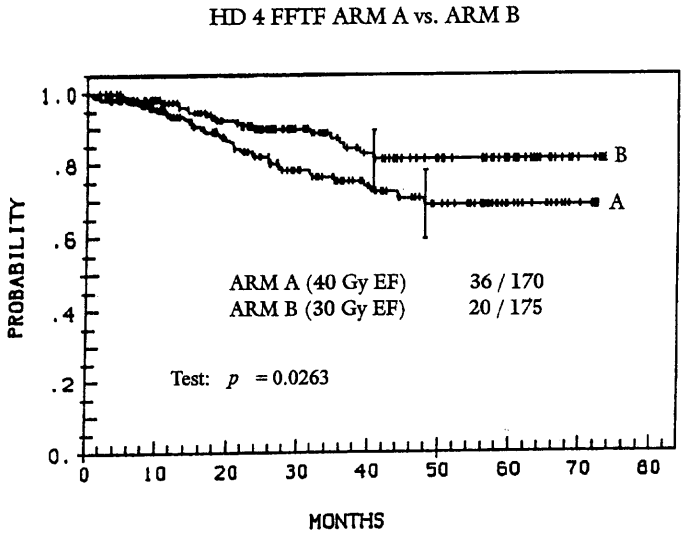


Fig. 2. Freedom from treatment failure (FFTF) probability courses, starting from the end of radiotherapy (RT) with a significantly ($p \leq 0.0263$) better FFTF of 81% at 5 years for ARM B than ARM A (70%).

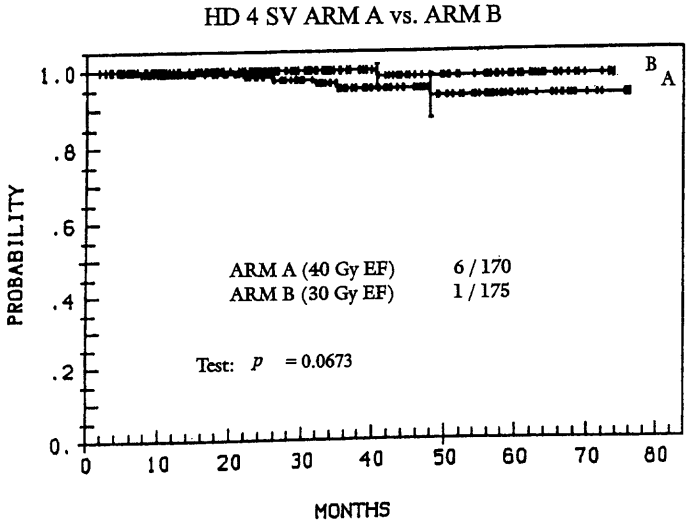


Fig. 3. Overall survival (OAS) probability courses starting from end of radiotherapy (RT), slightly in favor of ARM B, with 98% at 5 years compared to 93% in ARM A, but without a significant difference ($p \leq 0.0673$).

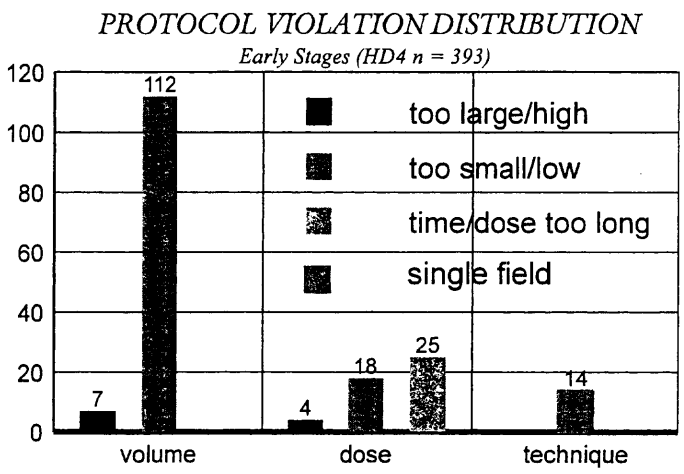


Fig. 4. Types of protocol violations (PV), assigned prospectively by a panel of experts, where volume-PVs with too small volumes or too narrow margins were most common. Cumulative display to count multiple PVs in single patients, too (for PV-criteria; see Table 1).

Retrospective Quality Control (RQC) of all reported relapses ($n = 45$) interestingly revealed an indentical pattern of PV types compared to PQC, with the highest level for PVs by too small treatment volumes or too narrow saftey margins ($n = 17$). The ratio of PV number to all relapsed patients in RQC with about one-half, expectedly, was higher then in PQC with about one-third PVs. There were slightly more PVs by RQC in ARM A than in ARM B (55% vs. 50%), but without any statistical significance. Analyzing only volume-related PVs; however, there was a recognizable difference in favor of ARM B with only five PVs, but 13 PVs in ARM A. This finding might indicate that the radiotherapist feels free be more generous in volume planning with lower prescribed treatment doses, if such a difference should be confirmed by final evaluation after three more years.

Relapse analysis in correlation with irradiated volumes at last is the most important procedure to determine whether or not 30 Gy TD is sufficient for durable eradication of subclinical Hodgkin's disease. In other words, did true recurrences occur within EF volumes in ARM B, i.e., after a TD of 30 Gy?

Figures 6a–b demonstrate the majority of recurrences happening outside the irradiated volumes, probably due to natural limits of diagnostic radiology, then along the margins of treated volumes, after that some very few recurrences formally within primarily involved regions (IF) and primarily noninvolved, but adjacently located and prophylactically irradiated regions (EF). Again, ARM B had less (half to one-third) relapses compared to ARM A. Only two formal EF-recurrences occurred in ARM B vs. six such events in ARM A.

One of those two events in ARM B was identified to have had an insufficient diagnostic procedure, where a mediastinal mass was not recognized and, therefore, was assigned to receive 30 Gy EF-RT only beside an involvement of the left lower cervical region. The second recurrence was due to underdosage near the margin of a mid-cervical mass by shielding the cervical spinal cord p.a. as well as the larynx a.p., resulting in tumor progression into EF regions, irradiated with only 30 Gy. Thus, both events were no true recurrences.

DISCUSSION

Early stages CPS IA to IIB without risk factors, i.e., less than 20% of all patients, seemed to be an unevitable condition in trying to avoid reseeding while observing the patterns of recurrences in EF volumes, to learn whether a total fractionated dose of 30 Gy can durably eliminate subclinical Hodgkin's disease or whether a TD of 40 Gy is also necessary, as in macroscopically involved lymph node regions. In Germany, only a nationwide multicenter trial could accrue enough patients within a reasonable time of 6 years; however, was accompanied by of a large variation of quality in diagnostic radiology and treatment procedures. For compensation of the latter uncertainty, a Radiation Therapy Reference Center (RTRC) was established in Goettingen, and later transferred to Munich, with a panel of four experienced head radiotherapists for PQC of treatment procedures and relapse analysis.

Prospective Quality Control was identified to be of prognostic value insofar as patients treated without protocol violations revealed a probability of about 80% and an OAS of 97% at 5 years after the end of EF-RT, comparable to a similar nationwide study in Denmark (9) and the Patterns of Care Study in the USA (3). In contrast, the PV group reached a FFTF of 70% only.

Relapse analysis to date expectedly confirmed that there were no true recurrences within EF volumes treated with 30 Gy only.

Retrospective quality control showed an identical pattern of PV types with a majority in volume PVs as in PQC,

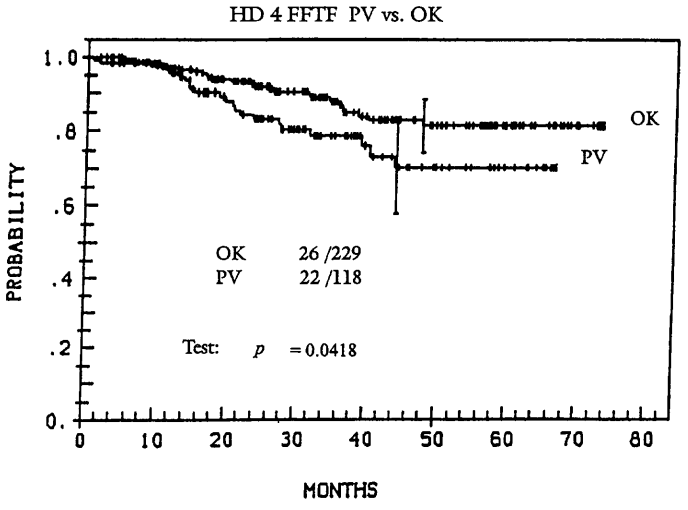
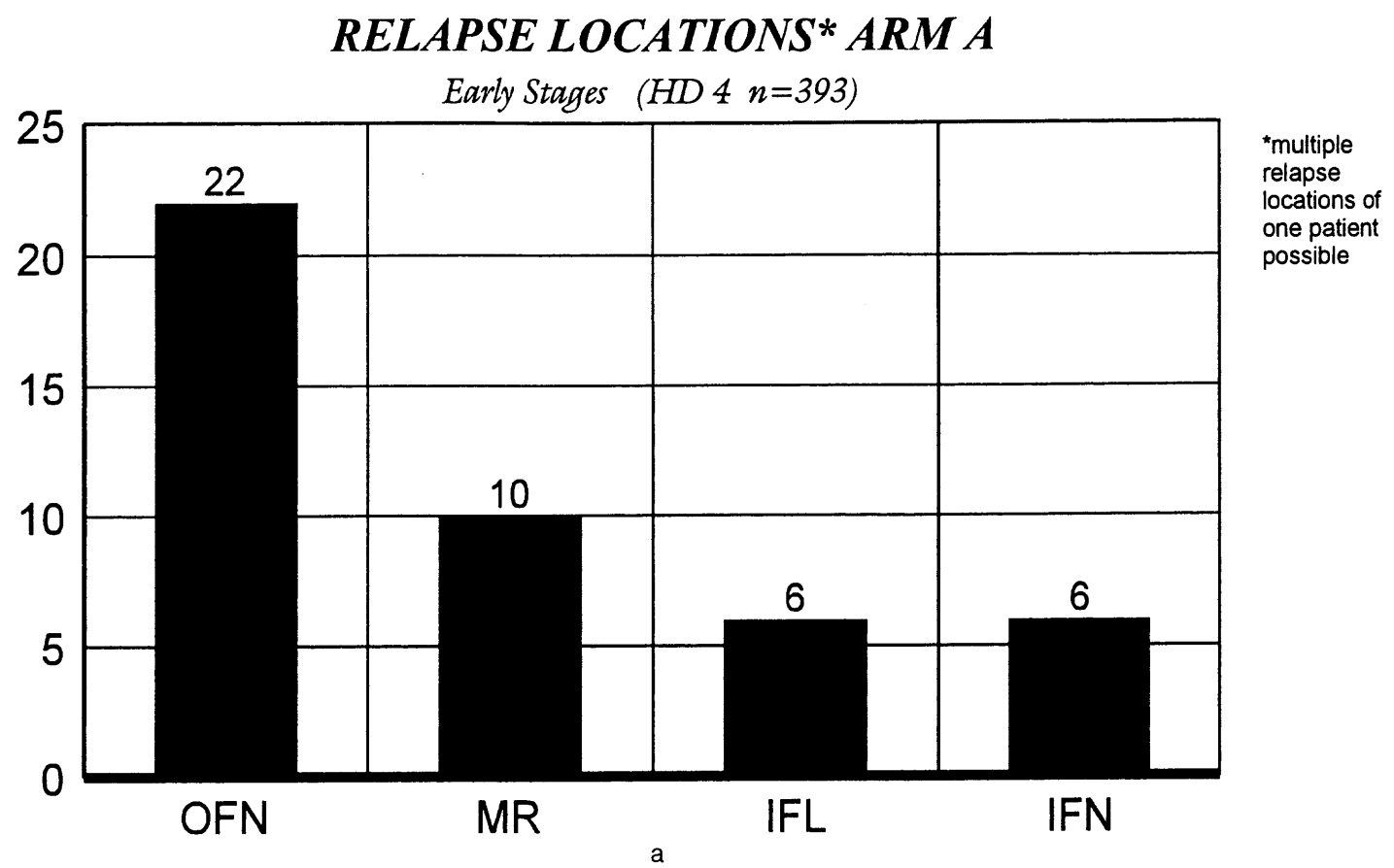
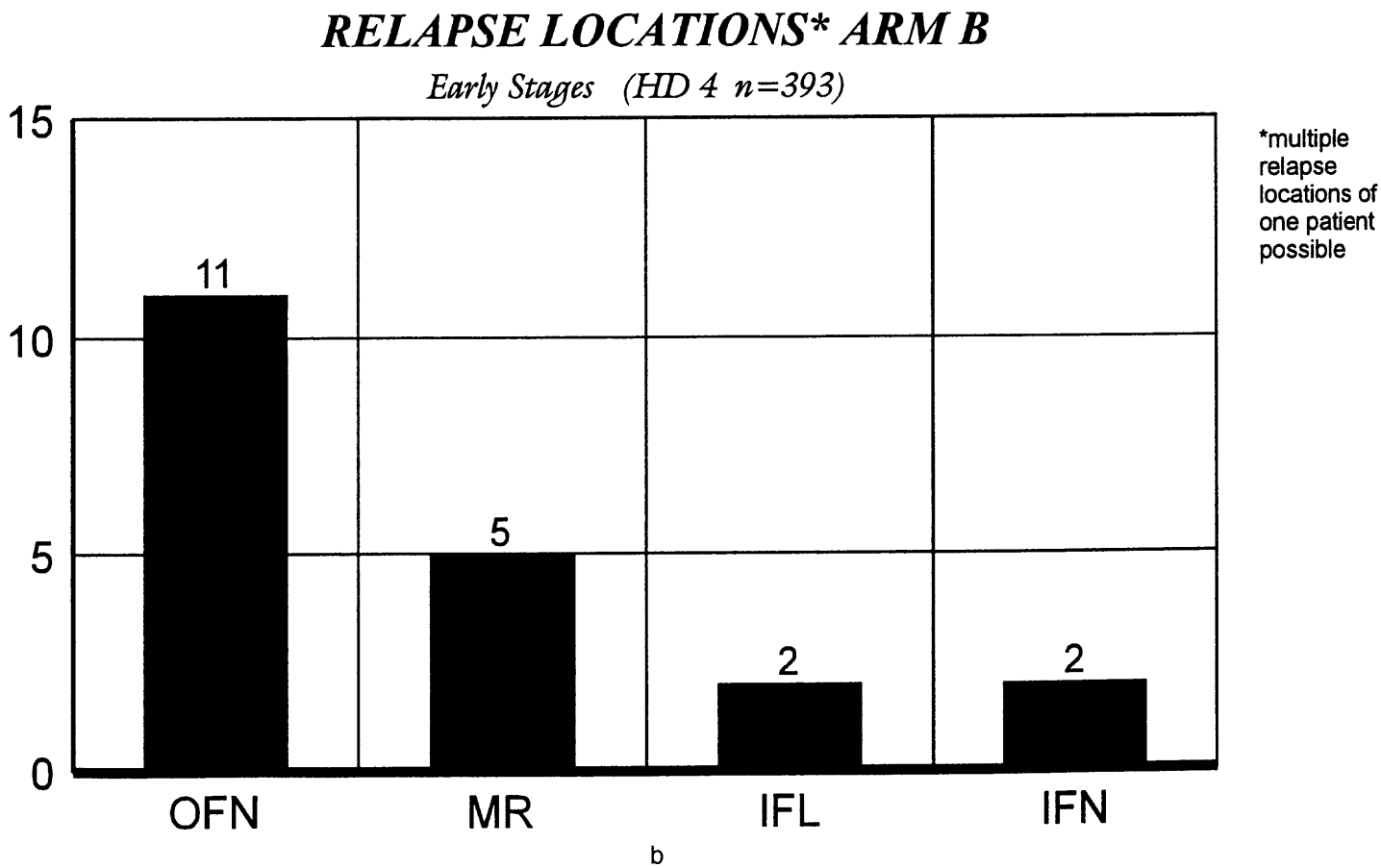


Fig. 5. Impact of protocol violations (PV) on freedom from treatment failure (FFTF) courses, where patients without PVs are living significantly ($p < 0.0418$) better with 82% FFTF at 5 years than the PV-assigned group with only 70%.



a



b

Fig. 6. (a, b) Analysis of recurrences with regard to irradiated volumes, where most events were found outside of treated volumes (off field new OFN), then along the margins of treated volumes (MR), then formally within involved field-volumes (in field local IFL), and, finally, formally within extended field volumes (infield new IFN), using a cumulative display, to count multiple recurrences in single patients, too. Interestingly, only two formal recurrences throughout extended field volumes in ARM B, turned out to be no true recurrences at all after 30 Gy extended field-radiotherapy (EF-RT).

where too small volumes and too narrow safety margins were mainly found along the mediastinum and axillae. Furthermore, ARM A revealed more (n = 30) relapses than ARM B (n = 15), almost due to similar volume-PV-distributions in RQC. This evidently resulted in a slightly better long-term effect for patients in ARM B than in ARM A, which is significant with regard to FFTF, but nonsignificant regarding OAS. This unexpected effect reveals the readiness of the radiotherapists to be more generous in EF-volume planning at a lower treatment dose of 30 Gy compared to 40 Gy.

In conclusion, this prospective randomized trial demonstrates, to date, that fractionated total dose of 30 Gy is sufficient to eradicate subclinical disease, permanently, next to involved nodal areas. This finding is consistent with recent retrospective findings in the international literature (14).

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