Role of Radiation Therapy in the Combined-Modality Treatment of Patients With Extensive Disease Small-Cell Lung Cancer: A Randomized Study

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Purpose: **To investigate the efficacy and toxicity of cisplatin/etoposide (PE) chemotherapy (CHT) with or without accelerated hyperfractionated radiation therapy (ACC HFX RT) and concurrent daily carboplatin/etoposide (CE) in patients with extensive-disease small-cell lung cancer.**

Patients and Methods: **A total of 210 patients were treated with three cycles of standard PE. Patients with a complete response (CR) at both the local and distant levels (CR/CR) or a partial response (PR) at the local level and CR at the distant level (PR/CR) received either thoracic ACC HFX RT with 54 Gy in 36 fractions over 18 treatment days in combination with CE followed by two cycles of PE (group 1, n = 55) or an additional four cycles of PE (group 2, n = 54). Patients who experienced less response were treated nonrandomly (groups 3, 4, and 5). All patients with a CR at the distant level received prophylactic cranial irradiation.**

Results: **For 206 assessable patients, the median survival time (MST) was 9 months and the 5-year survival rate was 3.4%. Patients in group 1 had significantly better survival rates than those in group 2 (MST, 17 *v* 11 months; 5-year survival rate, 9.1% *v* 3.7%, respectively; *P* = .041). Local control was also better in group 1, but the difference was only marginally not significant (*P* = .062). There was no difference in distant metastasis-free survival between groups 1 and 2. Acute high-grade toxicity was higher in group 2 than in group 1.**

Conclusion: **The addition of ACC HFX RT to the treatment of the most favorable subset of patients led to improved survival over that obtained with CHT alone.**

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CHEMOTHERAPY (CHT) IS THE cornerstone of therapy for extensive disease (ED) small-cell lung cancer (SCLC). Various active drugs have been used to treat patients with ED SCLC, offering improvement in survival from 1.5 to 3 months and from 9 to 12 months in recent years.[1,2] However, the prognosis for patients with ED SCLC remains poor, despite the fact that up to 90% of patients experience an objective response after initial CHT. Most of them eventually relapse, for a 5-year survival rate of only 1%.

To improve these poor survival figures, many approaches have been tested. During the 1980s, 10 controlled clinical trials investigated the influence of maintenance CHT after four to six cycles of induction CHT.[3,4] There was little evidence to support the effectiveness of maintenance CHT when administered at disease progression.[5] Together with unequivocally associated increased toxicity, this led the consensus panel to recommend four to six cycles of CHT without maintenance CHT as the standard treatment approach today,[5] which has been confirmed recently by the large European Organization for Research and Treatment of Cancer Lung Cancer Cooperative Group study.[6]

Also, higher doses of CHT did not lead to improved results, but they did lead to increased toxicity, with early toxic deaths necessitating dose reductions at the beginning of the treatment.[7] The effect of dose has also been evaluated in studies using bone marrow support.[8-10] Results obtained during these studies were similar to those obtained with standard CHT, sometimes with increased toxicity.[8] Recently, weekly CHT was used with great interest.[3,9] Preliminary studies found weekly CHT to be somewhat more toxic, while treatment results were similar or slightly improved,[11] although subsequent studies showed that granulocyte colony-stimulating factors can decrease toxicity of this regimen (cisplatin, vincristine, doxorubicin, and etoposide).[12]

Although the role of radiation therapy (RT) is well defined in limited disease (LD) SCLC, the usefulness of RT in ED SCLC is much more open to debate. More than 15 years ago, a large, retrospective literature review showed that RT reduced the frequency of initial chest failure, but complete response (CR) rates, overall response rates, median survival,

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and 2-year disease-free survival were identical for patients treated with CHT alone and those treated with CHT and thoracic RT.[13] However, the majority of studies from this report originated in the 1960s and 1970s and can not be considered as the optimal RT today, because of the total tumor dose (TD), dose per fraction, and timing. Furthermore, when exploring the effectiveness of RT in ED SCLC, one must bear in mind the systemic character of ED SCLC, which may obscure possible effects of RT on survival (established on a local level), especially in an adequately chosen subgroup of patients suitable for the ''curative'' role of RT. Other issues concerning RT, such as irradiation to sites of systemic tumor or the role of prophylactic cranial irradiation (PCI), are also controversial.

In an attempt to redefine the role of RT in ED SCLC, we designed a prospective randomized trial to select the subgroup of patients with the best prognosis as the primary target group for investigation. Also, we explored the role of RT in a subgroup of patients with a less favorable prognosis.

PATIENTS AND METHODS

Eligibility criteria included a histologic or cytologic diagnosis of ED SCLC, which was defined as tumor beyond the confines of the hemithorax, mediastinum, and ipsilateral or contralateral supraclavicular nodes. Patients with tumors that could not be encompassed within a tolerable RT field were also considered to have ED SCLC,[14,15] as were patients who had an ''isolated'' pleural effusion with positive cytology. Patients with negative cytology in an isolated pleural effusion were ineligible for this study. No prior treatment or previous malignancy (except that of a skin nonmelanoma) was allowed. To be eligible, patients had to have a Karnofsky performance status score of ≥ 70, age 18 to 70 years, and adequate hematologic (WBC count $\geq 4{,}000/mm^3$, platelet count $\geq 150{,}000/mm^3$), renal (serum creatinine level < 2.0 mg/dL), and hepatic (serum bilirubin level < 2.0 mg/dL) function (unless due to liver metastases). No recent or concurrent severe, uncontrolled, cardiovascular or pulmonary disease was allowed, and no CNS metastases or other abnormality that substantially impaired mental status was allowed. This study was performed after approval was obtained from the institutional ethics committee. All patients gave informed consent.

Staging procedures included chest x-rays and tomography, bronchoscopy, bone marrow biopsy, brain, bone and liver radionuclide scans, and abdominal ultrasonography. Computed tomography scans of the thorax, brain, and abdomen and pulmonary function tests were highly recommended and were actually performed in all patients treated since 1989. Whenever necessary or possible, a cytologic examination was performed for pleural effusions, as were biopsies of suspicious lymph node metastases or soft tissue masses. All patients were jointly staged by a thoracic surgeon/pneumologist, radiation oncologist, and medical oncologist.

The design of this trial is shown in Fig 1. Eligible patients were treated with three cycles of a standard-dose cisplatin/etoposide (PE) regimen given at 3-week intervals (cisplatin 80 mg/m^2 on day 1 and etoposide 80 mg/m^2 on days 1 through 3). After three cycles of PE, complete patient reevaluation and restaging were performed, using the procedures outlined above. Patients who achieved a CR at local and distant levels (CR/CR) and those who achieved a partial response (PR)

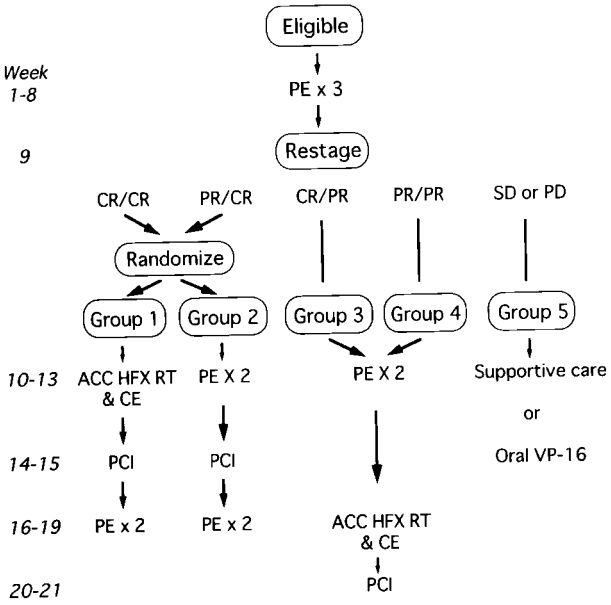

Fig 1. Treatment schema. VP-16, etoposide.

within the thorax accompanied by CR elsewhere (PR/CR) were randomized to receive either accelerated hyperfractionated radiation therapy (ACC HFX RT) and concurrent low-dose daily CHT consisting of carboplatin and etoposide (CE), 50 mg each, given on each RT day, followed by PCI and then by two additional cycles of PE (group 1) or four additional cycles of PE and PCI (group 2). Patients who achieved their worst response, ie, those who achieved CR or PR within the thorax but only a PR elsewhere (CR/PR, group 3; PR/PR, group 4), were treated with two additional PE cycles followed by the same ACC HFX RT and CE treatment and, in the case of CR at distant level, PCI as well. Those with stable disease or disease progression (group 5) were either observed until death (treated with supportive care only) or treated with orally administered etoposide, 50 mg/m^2, on days 1 through 21 every 28 days for a total of six cycles or until further progression (on oral etoposide).

No dose reductions were allowed for the first three cycles of PE. Dose reductions and/or treatment delays were allowed during any subsequent treatment. Adjustments in drug dosage were made according to nadir and treatment-day blood counts. A 25% reduction in the dosage of both drugs was made if the nadir granulocyte count was less than 0.5×10^9/L or the nadir platelet count was less than 75×10^9/L. A similar reduction was made if the pretreatment granulocyte count was between 1.5 and 2.0×10^9/L or the pretreatment platelet count was between 100 and 125×10^9/L. If the pretreatment granulocyte count or platelet count fell below these levels that required a 25% dosage reduction, treatment was delayed for 1 week until the blood counts recovered.

RT was administered with 6 to 10 MV photons from linear accelerators in groups 1 through 4 (Fig 1). The target volume included all gross disease and ipsilateral hilum with a 2-cm margin and the entire mediastinum with a 1-cm margin. Both supraclavicular fossae were routinely irradiated, and anteroposterior/posteroanterior fields were used to deliver 36 Gy in 24 fractions in 12 treatment days over 2.5 weeks. After this, the anterior, lateral, and/or posterior oblique fields were used to give an additional 18 Gy in 12 fractions in 6 treatment days. The total TD was 54 Gy in 36 fractions in 18 treatment days in 3.5

weeks. Doses were specified at middepth at the central axis for parallel-opposed fields and at the intersection of the central axes for oblique techniques. The maximum dose was 36 Gy for the spinal cord and the entire heart, 54 Gy for the esophagus, and 18 Gy for the contralateral lung. Two daily fractions of 1.5 Gy were used with an interfraction interval of 4.5 to 6 hr. No dose corrections were made for lung inhomogeneities.

During ACC HFX RT, 50 mg of carboplatin and 50 mg of etoposide were given on each RT day between the two daily fractions (3 to 4 hr after the first one, ie, 1 to 2 hr before the second one).

In groups 1 and 2, PCI was administered to the whole brain at a TD of 25 Gy in 10 daily fractions in 2 weeks via two parallel-opposed lateral fields. Patients in groups 3 and 4 also received PCI, but only those patients who achieved CR at a distant level. Palliative RT with 30 Gy in 10 daily fractions was offered to patients with metastatic tumors when appropriate.

Patients were examined fully at the end of their treatment (groups 1 through 4), every month for 6 months after the end of the treatment, every 2 months for 2 years thereafter, and every 4 to 6 months thereafter. Restaging at the time of progression was performed using the diagnostic tools outlined above.

Patients were evaluated for response after three cycles of PE (week 9), then after either ACC HFX RT or two additional PE cycles (week 15), and at the end of treatment (week 21). CR was defined as the disappearance of all disease for at least 4 weeks, including negative bone marrow examination results, and the absence of new lesions (for all measurable or assessable disease). For bone metastasis, bone lesions visible on plane radiographs were required only to be improved or stable, and no finding on radionuclide bone scan could have interfered with the designated type of response. For measurable disease, PR was defined as a 4-week reduction of greater than 50% of the sum of the products of the cross-sectional diameters of all measurable disease, together with the absence of new lesions. For assessable lesions, PR was defined as a decrease in tumor size for at least 8 weeks. Stable disease was defined as a reduction of less than 50% or an increase of less than 25% in the sum of the products of the cross-sectional diameters of all measurable lesions and no clear pattern of either regression or progression of disease for at least 8 weeks. Disease progression was defined as an increase of greater than 25% in the sum of the products of the cross-sectional diameters of measured lesions, together with an increase in assessable disease or the appearance of new lesions.

Patients who died during cycles 1 through 3 were considered induction deaths and were included in all analyses. CHT-induced toxicity was evaluated using the criteria of the Eastern Cooperative Oncology Group. Toxicity attributable to ACC HFX RT was evaluated according to the criteria of the Radiation Therapy Oncology Group/European Organization for the Research and Treatment of Cancer.

CR and PR rates of 25% each in patients who received standard-dose PE were anticipated.[16] In order to allow detection of an increase in the CR rate to 50%, with a one-sided significance of .05 and power of 80%,[17] randomization of 106 patients (both CR/CR and PR/CR) was planned. To obtain a population of 106 such patients, 212 patients were needed at the outset of the study. With the same significance and power,[18] this number of patients (106) could also allow detection of a 1.8- to two-fold increase in median survival time (MST). No interim analysis was planned during the trial and no early stopping rules were used.

Differences between treatment groups in patient characteristics, response rate, and mean number of toxicities were mostly evaluated using the χ^2 test. Student's *t* or Welch's *t* test was used to examine the differences in the mean duration of response and in the mean number of acute toxic events in a patient. Survival and relapse-free survival rates were calculated by the Kaplan-Meier method, and the differences between groups in survival curves were analyzed by the log-rank test. All these statistical analyses were carried out by one of us (Y.S.) using a computer program (HALBAU 4; Gendaisuugakusha, Kyoto, Japan).

RESULTS

This single-institution study was performed at University Hospital, Kragujevac, Yugoslavia, between January 1988 and June 1993. A total of 210 patients were entered onto this study and all of them were from Yugoslavia. Four patients were excluded from analysis because of the occurrence of second (bladder) cancer, voluntary discontinuation of their treatment within the first cycle of CHT, stroke, and myocardial infarction. The second cancer and treatment discontinuation occurred during the first week of treatment and the stroke and myocardial infarction occurred before the onset of treatment. A total of 206 patients were fully assessable for toxicity and survival. Patient characteristics are listed in Table 1. There was no difference in the distribution of various variables among the five treatment groups.

For all 206 patients, the MST was 9 months and the yearly survival rates at 1, 2, 3, 4, and 5 years were 38%, 19%, 9.7%, 4.9%, and 3.4%, respectively. Survival according to treatment group is shown in Fig 2. Patients in group 1 achieved best results that were significantly better than those in the other treatment groups. Also, except for no significant difference between groups 3 and 4, all the other differences

Table 1. Patient Characteristics

Characteristic	Total of All Patients	Group 1	2	3	4	5	*P*
Sex							
Male	124	33	32	21	17	21	
Female	82	22	22	13	11	14	.99
Age, years							
Median	59	59	59	58	60	59	.99
Range	38-71	38-70	39-71	41-70	44-69	41-69	
KPS score							
70	31	8	8	7	4	4	.99
80	37	10	10	5	5	7	
90	80	20	23	12	13	12	
100	58	17	13	10	6	12	
Weight loss							
$\geq$ 5%	95	25	23	16	12	19	.85
$<$ 5%	111	30	31	18	16	16	
No. of metastatic sites							
1	97	23	25	18	14	17	.91
2	87	27	23	12	11	14	
3	17	4	5	3	2	3	
4	4	1	1	1	0	1	
5	1	0	0	0	1	0	

Abbreviation: KPS, Karnofsky performance status.

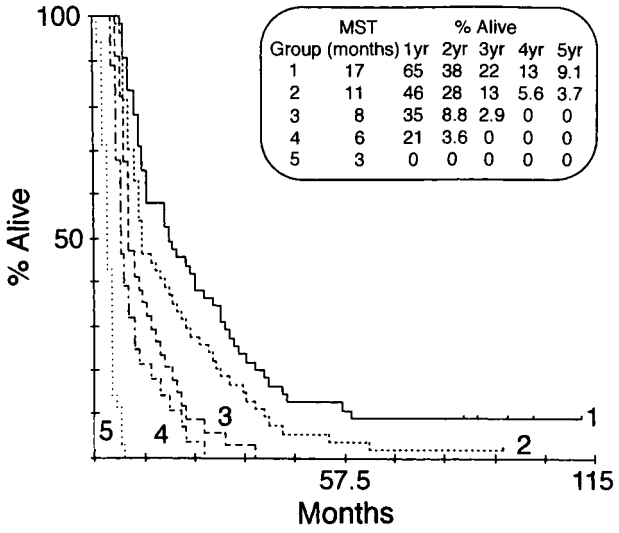

Fig 2. Overall survival in group 1 (——), group 2 (- - - -), group 3 (– – – –), group 4 (- · - · - ·), and group 5 (· · · ·).

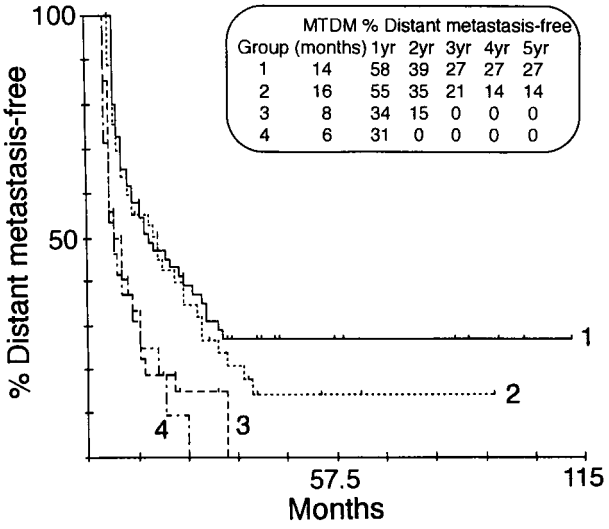

Fig 4. DMFS in group 1 (——), group 2 (- - - -), group 3 (– – – –), and group 4 (- · - · - ·).

were significant at the level of .05. It is worth emphasizing the better outcome of patients treated with combined CHT and ACC HFX RT compared with patients treated with CHT only ($P = .041$); the 5-year survival rates were 9.1% and 3.7% for groups 1 and 2, respectively.

Local recurrence-free survival (LRFS) is shown in Fig 3. The difference between groups 1 and 2 is only marginally not significant, with median time to local recurrence of 30 and 22 months, respectively, and 5-year LRFS of 20% and 8.1%, respectively ($P = .062$). In groups 3 and 4, no 4-year local recurrence-free survivors were observed.

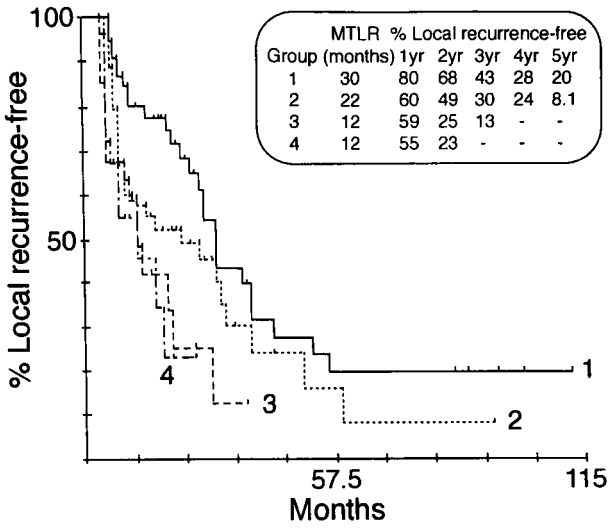

Fig 3. LRFS in group 1 (——), group 2 (- - - -), group 3 (– – – –), and group 4 (- · - · - ·).

Distant metastasis-free survival (DMFS) (freedom from progression of distant metastasis) is shown in Fig 4. Although group 2 patients treated with CHT alone achieved longer median time to distant metastasis than group 1 patients treated with combined CHT and RT (16 *v* 14 months, respectively), they had poorer 5-year DMFS (14% *v* 27%, respectively), and the difference was not significant ($P = .35$). In groups 3 and 4, no 3-year distant metastasis-free survivors were observed.

Because LRFS was only marginally insignificant and DMFS was not significantly different between groups 1 and 2, we then performed first relapse-free survival analysis, the results of which are shown in Fig 5. Patients in group 1 achieved better results than those in group 2 regarding both median time to first relapse (13 *v* 9 months, respectively) and 1- to 5-year first relapse-free survival ($P = .045$).

Table 2 shows the local CR rate in groups 1 and 2 at weeks 9, 15, and 21. At week 9, after three cycles of induction PE, there was an unexpectedly high CR rate at distant sites (52%). At that time, there was no difference in the local CR rate between the two groups, but at week 15, when either ACC HFX RT and CE (group 1) or two additional cycles of PE (group 2) were administered, the CR rate was significantly higher in group 1 than in group 2 ($P = .000007$), and it persisted until week 21 ($P = .00005$). Actual CR rates for groups 1 and 2 were 96% and 66%, respectively. Duration of response (mean ± SD) was 22 ± 26 months in group 1 and 14 ± 16 months in group 2 ($P = .055$). In groups 3 and 4, it was 7 ± 7 months and 6 ± 5 months, respectively.

Acute, high-grade (≥ grade 3), treatment-related toxicities are shown in Table 3. Although hematologic toxicity

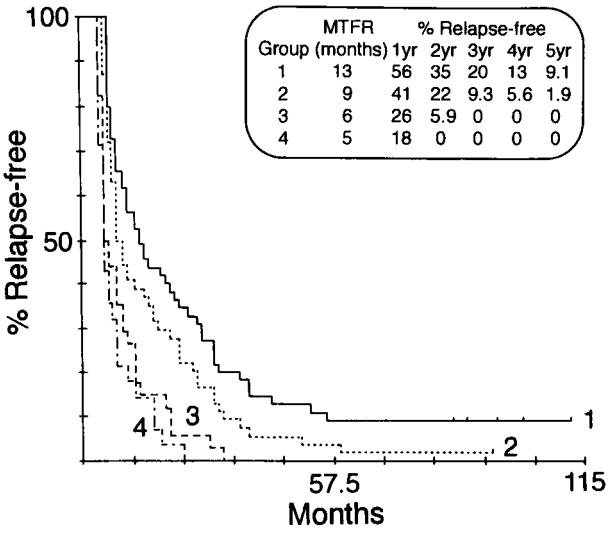

Fig 5. First relapse-free survival in group 1 (——), group 2 (- - - -), group 3 (– – – –), and group 4 (- · - · - -).

was more frequent in group 2 than in group 1, the difference was not significant, and that was the case for all groups with regard to leukopenia, trombocytopenia, and anemia. There was no difference between groups 1 and 2 in regard to the incidence of high-grade infection ($P = .64$), but there was an overall significant difference among the five groups ($P = .048$) because of the high incidence of grade 5 infection in group 5. Because more cycles of CHT were administered to patients in group 2, nausea and vomiting were significantly more frequent in that group than in group 1 ($P = .0038$), as was the case with alopecia ($P = .000003$). High-grade kidney toxicity was observed only in group 2. Acute, high-grade (≥ grade 3), RT-induced esophageal toxicity was observed only in groups of patients who received RT (groups 1, 3, and 4, with rates of 27%, 30%, and 25%, respectively). On the other hand, although patients in groups 1, 3, and 4 experienced RT-induced, high-grade bronchopulmonary toxicity, it was infrequent; therefore, the difference between these groups and groups 2 and 5, who did not receive RT, was not significant (group 1 *v* group 2,

Table 2. Response at Local Level in Groups 1 and 2 After Week 9

	Week 9		Week 15		Week 21	
Group	No. of Patients/ Total No. of Patients	%	No. of Patients/ Total No. of Patients	%	No. of Patients/ Total No. of Patients	%
1	26/55	47	53/55	96	53/55	96
2	24/54	44	33/54	61	35/53*	66
P	.77		.000007		.00005	

NOTE. All patients in groups 1 and 2 had CR at the distant level.

*One patient in group 2 had died of toxicity by week 21.

Table 3. Acute High-Grade Toxicity

	Grade 3		Grade 4		Grade 5			
Toxicity/Group	No. of Patients	%	No. of Patients	%	No. of Patients	%		*P*
Leukopenia								
1	17	31	7	13	—		1 *v* 2	.18
2	22	40	11	20	—		All	.33
3	12	36	4	12	—			
4	10	36	4	14	—			
5	11	31	11	31	—			
Thrombocytopenia								
1	9	16	6	11	—		1 *v* 2	.23
2	15	27	8	14	—		All	.81
3	6	18	3	9	—			
4	5	18	3	11	—			
5	9	26	4	11	—			
Anemia								
1	3	5	3	5	—		1 *v* 2	.39
2	5	9	6	11	—		All	.21
3	2	6	2	6	—			
4	1	4	1	4	—			
5	7	20	1	6	—			
Infection								
1	7	13	5	9	1	2	1 *v* 2	.64
2	11	20	5	9	2	4	All	.048
3	4	12	2	6	1	3		
4	5	18	1	4	1	4		
5	1	3	—		6	17		
Nausea and vomiting								
1	2	4	3	5	—		1 *v* 2	.0038
2	11	20	8	14	—		All	.0076
3	3	9	1	3	—			
4	1	94	1	4	—			
5	7	20	1	3	—			
Alopecia								
1	5	99	2	4	—		1 *v* 2	.000003
2	20	36	12	22	—		All	.000003
3	4	12	1	3	—			
4	2	7	1	4	—			
5	7	20	5	14	—			
Kidney								
1	—		—		—		1 *v* 2	.0010
2	11	20	1	2	—		All	.000019
3	—		—		—			
4	—		—		—			
5	—		—		—			
Esophageal								
1	11	20	4	7	—		1 *v* 2	.00020
2	—		—		—		All	.00023
3	8	24	2	6	—			
4	6	21	1	4	—			
5	—		—		—			
Bronchopulmonary								
1	3	5	—		—		1 *v* 2	.082
2	—		—		—		All	.28
3	2	6	—		—			
4	1	4	—		—			
5	—		—		—			

$P = .082$; all five treatment groups, $P = .28$). There were 57 acute grade 3 toxic events in 55 patients of group 1 and 94 acute grade 3 toxic events in 54 patients of group 2 ($P = .0000$). There were 31 acute grade 4 toxic events in group 1 and 51 acute grade 4 toxic events in group 2 ($P = .019$). Acute grade 3 + 4 toxic events in group 1 were therefore less frequent (88/55) than those in group 2 (145/54) ($P = .0000$). However, there was no difference in either late grade 3 (2/55 *v* 0/54, $P = .16$), late grade 4 (1/55 *v* 0/54, $P = .32$), or combined late grade 3 + 4 (3/55 *v* 0/54, $P = .082$) toxicity between groups 1 and 2.

Delays in scheduled treatment (RT or CHT) after the third cycle of PE were observed in six patients (11%) in group 1 for 3 to 9 days (median, 5 days), in 13 patients (23%) in group 2 for 6 to 15 days (median, 10 days), in six patients (18%) in group 3 for 6 to 12 days (median, 9 days), in five patients (18%) in group 4 for 5 to 11 days (median, 8 days), and in five patients (15%) in group 5 for 5 to 9 days (median, 6 days). The difference between groups 1 and 2 was not significant ($P = .070$), nor was there a significant difference among the five treatment groups ($P = .47$). Reductions in the dose of CHT due to toxicity at any time during treatment were observed in five (9%), 11 (20%), six (17%), five (18%), and five patients (14%) in the five treatment groups. The differences between groups 1 and 2 and among all five groups were not significant ($P = .096$ and $P = .56$, respectively).

The number of patients who required hospital admission due to any toxicity during treatment was six (11%), 11 (20%), eight (23%), six (22%), and five (14%) for the five groups. The difference between groups 1 and 2 and among all five groups was not significant ($P = .17$ and $P = .50$, respectively).

Interruptions in ACC HFX RT were observed in all groups that received it (groups 1, 3, and 4) solely because of myelosuppression. Interruptions were observed in three patients (5%) in group 1 for 4 to 6 days, in five patients (15%) in group 3 for 5 to 10 days, and in four patients (14%) in group 4 for 6 to 10 days ($P = .27$). There was 1 hospital admission (2%) for management of myelosuppression in group 1, two (6%) in group 3, and two (7%) in group 4 ($P = .45$). Although some patients experienced grade 3 and 4 acute esophageal toxicity, it was always observed after the end of ACC HFX RT and was not, therefore, the reason for interruptions in the course of ACC HFX RT.

DISCUSSION

ED SCLC is a frustrating challenge for thoracic oncologists. In contrast to LD SCLC, in which clear improvement in prognosis was observed in recent years with the combination CHT and concurrent RT,[9-22] treatment of ED SCLC is still beyond reasonable hope for improvement. An MST of approximately 10 months and a 5-year survival rate of approximately 1% to 2% are consistently reproduced no matter what new and promising approach is tested. Maintenance CHT, high-dose CHT, multiple-drug regimens, and alternating CHT have faced the same fate.[3,7-12] Recent years also witnessed a number of studies of new and modern drugs and combinations[23-26] that still need to be proved superior to ''old-fashioned'' CHT, such as PE and cyclophosphamide/doxorubicin/vincristine, which are still standard treatments in the majority of institutions all over the world.

In ED SCLC, RT was mostly used palliatively to ameliorate symptoms at the local or distant level. Only rarely was it used in the initial combined-modality approach with curative intent.[27] The rationale for this was that ED SCLC is a systemic disease and local/regional therapy such as RT does not have a curative role in its treatment. However, even patients who were experiencing CR after a few cycles of CHT subsequently relapsed at either the local (intrathoracic) level alone or at the local level accompanied with distant metastasis. It is possible that this temporary benefit of induction CHT may be fortified and improved by introducing RT, provided these patients live long enough to verify this hypothesis. This patient group should, therefore, include those with the least burden of tumor cells, ie, mostly patients with either clinical CR/CR or PR/CR.

To investigate the role of RT in ED SCLC, we designed this study with the primary aim of identifying the subgroup of patients most likely to benefit from this treatment modality. Naturally, these patients should have been in the best-prognosis subgroup; therefore, we chose only patients with CR at distant sites (their status on the local level could have been either CR or PR [CR/CR and PR/CR]). With this approach, we ensured that this subgroup of patients would have had a reasonable outcome, even if treated with CHT alone. With the use of RT, we were able to investigate the effect of RT on the local level (in all cases, the distant level was CR) by fortifying the effect of CHT (CR) or improving it (PR) with eradication of CHT-resistant tumor cells that were likely to predominate in cases of PR (after three cycles of PE). In a way, this approach resembles the one we already tested in LD SCLC, since after three cycles of PE, a subset of patients had only macroscopic intrathoracic disease with CR at distant sites and were, therefore, similar (in regard to tumor cell burden) to patients with LD SCLC at the beginning of their treatment. In that study,[19] ''initial'' administration of the same ACC HFX RT to patients who had no distant metastasis was beneficial. Furthermore, in a group of patients treated with ''delayed'' RT, a significant effect of RT on the local level was also noted and materialized in an increase in intrathoracic CR, when compared with

that obtained with CHT only. It seems that this hypothesis worked well in patients with ED SCLC who achieved not just CR/CR but PR/CR as well. In group 1, the median time to local recurrence was 30 months and the 5-year LRFS rate was 20% (corresponding figures for patients in group 2 are 22 months and 8.1%, respectively), which led to the improvement in survival, with an MST of 17 months and a 5-year survival rate of 9.1% (corresponding figures for patients in group 2 are 11 months and 3.7%, respectively). It proved that RT given as ACC HFX RT is capable of eradicating drug-resistant tumor cells, showing, again, that there is no complete cross-resistance between these two treatment modalities in SCLC.[19,20]

Exclusive CHT also proved to be more toxic than PE plus ACC HFX RT. Although there was no difference in the incidence of hematologic toxicity, in the group treated with CHT only, nausea and vomiting, alopecia, and kidney toxicity were more frequent, with nausea and vomiting and alopecia always being extremely important to patients. On the other side, esophageal toxicity was more frequent in RT-treated groups, but it was managed to an extent that it did not interrupt ACC HFX RT, since it always peaked after the end of ACC HFX RT and was largely resolved until the next cycle of PE (in group 1) or after the end of treatment (groups 3 and 4). Acute grade 3 and/or 4 toxic events were significantly more frequent in group 2 than in group 1, but this was not the case for late (RT-induced) toxicity, which was infrequently observed during this study.

Recently, Ihde et al[7] reported in a National Cancer Institute randomized study on the use of two cycles of PE given either as a standard-dose or high-dose regimen followed by standard-dose PE in cycles 3 and 4. In cycles 5 through 8, patients with CR continued with PE, and all other patients received either cyclophosphamide/doxorubicin/vincristine or a combination CHT regimen based on in vitro drug sensitivity testing of tumor cell lines established from individual patients. There were no differences between the high- and standard-dose groups in either CR rate (23% *v* 22%) or MST (10.7 *v* 11.4 months). Hematologic toxicity was significantly more common in the high-dose group. These results are quite similar to those obtained in our group 2 patients (treated with PE only), who had an MST of 11 months. Similar percentages of long-term survivors and similar incidences of both hematologic and nonhematologic toxicities are seen in these two studies when similarly treated patients are compared. Additionally, the toxicities are much more frequent than those observed in group 1 patients of the current study (treated with ACC HFX RT), which is another advantage of our study that used ACC HFX RT in group 1. It seems, therefore, that the introduction of ACC HFX RT in a subset of patients most likely to benefit from intensive treatment such as this type of RT is, according to the improved results, due mainly to the increase in local control.

In conclusion, introduction of ACC HFX RT in the general treatment plan for patients with ED SCLC offers promising results. The best results were obtained in the best-prognosis subgroup of patients, ie, those who achieved either CR/CR or PR/CR after induction CHT consisting of three cycles of standard PE CHT. These results were achieved through improvement obtained at the local level, confirming previous observations in this disease localized to the thorax.[19,20] However, more patients are needed to further investigate this effect in patients with ED SCLC.

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