ORIGINAL ARTICLE

Treatment Outcomes of Older Participants in a Randomized Trial Comparing Two Schedules of Twice-Daily Thoracic Radiotherapy in Limited-Stage SCLC

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ABSTRACT

Introduction: Half of the patients with limited-stage SCLC (LS SCLC) are above or equal to 70 years old, but they account for less than 20% of participants in most trials. Comorbidities and reduced organ and physical function might lead to more treatment toxicity, and population-based studies indicate that fewer older than younger patients with LS SCLC receive standard chemoradiotherapy, although there is limited evidence for such a policy.

Methods: We compared baseline characteristics, comorbidity, survival, treatment completion, toxicity, health-related quality of life, and treatment outcomes between patients above or equal to 70 years old and those younger than 70 years old in an open-label, randomized phase II trial comparing twice-daily thoracic radiotherapy of 45 Gy in 30 fractions with 60 Gy in 40 fractions in LS SCLC. All patients received concurrent i.v. cisplatin (75mg/m^2) or carboplatin (AUC 5-6 mg/ml x min) day 1 and i.v. etoposide (100 mg/m^2) day 1-3 chemotherapy. This trial is registered at ClinicalTrials.gov (NCT02041845).

Results: A total of 170 patients who were above or equal to 18 years old and had performance status of 0 to 2 were randomized. Of these, 53 patients (60 Gy: 25, 45 Gy: 28) were above or equal to 70 years old and 117 (60 Gy: 64, 45 Gy: 53) were younger. There were no differences in baseline characteristics, treatment completion rates, toxicity, or response rates across the age groups. Health-related quality of life mean scores were similar during year one, but older patients reported more decline on functional scales than younger patients during year two. Overall survival was shorter for older patients, whereas there was no difference in progression-free survival or time to progression.

Conclusions: Patients above or equal to 70 years old tolerated concurrent twice-daily chemoradiotherapy and achieved similar disease control as younger patients, indicating older patients should receive the same treatment as younger patients.

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Introduction

Standard treatment for fit patients with limited-stage SCLC (LS SCLC) is concurrent platinum/etoposide chemotherapy and thoracic radiotherapy (TRT) followed by prophylactic cranial irradiation (PCI) to those who respond to chemoradiotherapy (CRT).[1–6] Five-year survival rates are 25% to 34%.[7–9]

The proportion of patients aged 70 years or older diagnosed with having SCLC increased from 23% in 1975 to 44% in 2010,[10] and as the world's population is aging, the number of older patients with lung cancer is expected to increase exponentially in the next 20 years.[11–13] There is, however, little evidence for how to treat older patients because they are underrepresented in clinical trials.[14,15] The proportion of participants aged above or equal to 70 years varies between 13% and 21% in recent clinical trials of LS SCLC.[16–19] Population-based studies reveal that the proportion of patients receiving standard CRT decreases with age,[20–24] most likely due to concerns about toxicity. A considerable proportion (up to 33%) of participants in trials of CRT in LS SCLC experience severe toxicity.[7,25–27] Comorbidities and reduced organ and physical function make older patients more vulnerable to treatment toxicity, and they might be less able to tolerate side effects when they occur.[28–31]

We conducted a randomized phase II trial comparing twice-daily TRT of 45 Gy in 30 fractions to 60 Gy in 40 fractions. All patients were to receive four courses of i.v. cisplatin (75 mg/m^2) or carboplatin (AUC 5-6 mg/ml x min.) day 1 and i.v. etoposide (100 mg/m^2) day 1-3 chemotherapy, and PCI was offered to the responders. The higher TRT dose resulted in a significantly improved 2-year survival (primary end point) (74% versus 48%; $p < 0.01$) and median overall survival (OS) (37.2 versus 22.6 mo; $p = 0.012$) without adding toxicity.[32] There was no upper age limit in this trial, and 31% of the patients were 70 years old or older.

The aim of the present study was to compare baseline characteristics, treatment completion, toxicity, health-related quality of life (HRQoL), and treatment outcomes between patients below 70 years old and those who were 70 years old or older.

Materials and Methods

Design and Approval

This open-label, randomized phase 2 trial was approved by the Regional Ethics Board in Gothenburg, Sweden, the Regional Committee for Medical Research Ethics, Central Norway, and the National Committee on Health Research Ethics in Denmark.

This subgroup analysis of patients 70 years old or older was preplanned. The primary end point was OS. Secondary end points were toxicity and HRQoL, whereas exploratory end points included response rates, progression-free survival (PFS), and time to progression (TTP).

Patients and Treatment

Details on trial design are published earlier.[32] Between July 2014 and June 2018, 170 patients at 22 Scandinavian hospitals diagnosed with having LS SCLC were included in this randomized, controlled phase 2 study. Median follow-up was 49 months, and all patients were followed up for a minimum of 2 years at the time of the primary analyses. All deaths considered related to the treatment occurring any time during the study period or any death occurring within 4 weeks after completion of the study treatment was reported as a fatal event. Patients aged above or equal to 18 years with performance status (PS) of 0 to 2 received four courses of i.v. cisplatin (75 mg/m^2) or carboplatin (AUC 5-6 mg/ml) day 1 and i.v. etoposide (100 mg/m^2) day 1-3 chemotherapy and were randomized to receive TRT of 45 Gy in 30 fractions or 60 Gy in 40 fractions. Whole-body 18F-fluorodeoxyglucose positron emission tomography computed tomography (FDG PET-CT) was mandatory for staging, and TRT target volumes were limited to FDG PET-CT positive lesions. PCI of 25 to 30 Gy in 10 to 15 fractions was offered to those who responded to CRT. Relapses were treated according to each hospital's routine.

Assessments

Comorbidity was assessed at inclusion using the Charlson Comorbidity Index (CCI),[33] and divided into three groups (CCI 0, 1, $\geq$2), as this categorization is frequently used in studies of patients with cancer.[23,34–36]

Stage of disease was assessed according to TNM version 7,[37] toxicity according to the Common Terminology Criteria for Adverse Events (version 4.0),[38] and treatment response according to the Response Evaluation Criteria in Solid Tumors (version 1.1).[39]

Patients reported HRQoL on the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire—Core 30 (QLQ-C30) version 3 and its lung cancer module, the Quality of Life Questionnaire—Lung Cancer 13 (QLQ-LC13).[40,41] The QLQ-C30 consists of five multiple-item functional scales (social, emotional, cognitive, role, and physical), three multi-item symptom scales (fatigue, pain, and nausea/vomiting), six single-item symptom scales (insomnia, constipation, diarrhea, loss of appetite, dyspnea, and financial impact), and one multi-item scale (global QoL). The QLQ-LC13 measures

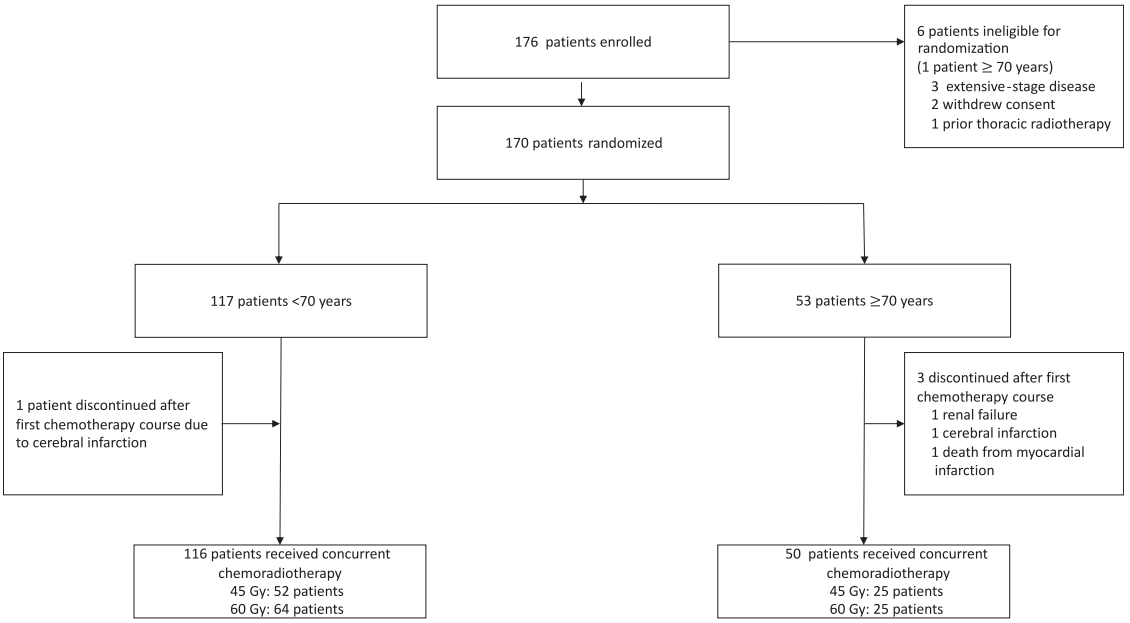


Figure 1. Patient selection.

dyspnea on a multiple-item scale. The single-item scales measure hair loss, hemoptysis, cough, sore mouth, neuropathy, dysphagia, pain (in the chest/arms/shoulder/other parts), and use of pain medication. A higher score on global QoL and functional scales reflects a better HRQoL, and a higher score on the symptom scales represents a worse HRQoL.

Patients completed the questionnaires on paper at week 0 (inclusion), week 4 (before TRT), week 8 (end of TRT), week 12 (response evaluation), week 16 (end of PCI), every 10 weeks on year one, every 3 months on year two, and at progression. Raw scores (the average of the items that contribute to the scale) were transformed to a scale from 0 to 100 according to the European Organisation for Research and Treatment of Cancer scoring manual.[42] Mean scores for each scale or single item were compared between the age groups at each time point. A difference in mean score of 10 or more was considered clinically relevant.[43] Global QoL, physical function, dysphagia, and dyspnea were defined as the primary HRQoL end points. Global QoL and physical function were measured on multi-item scales on the QLQ-C30, whereas the QLQ-LC13 was used to measure dyspnea on a multi-item scale and dysphagia on a single-item scale.

Analyses

OS, PFS, and TTP were estimated using the Kaplan-Meier method. Survival was compared with univariable and multivariable Cox proportional hazards regression models. Logistic regression was used for univariable and multivariable analyses of 2-year survival. Pearson's chi-square test or Fisher's exact test was used to compare baseline characteristics, toxicity, and overall response rates. Multivariable models were adjusted for TRT schedule, sex, age ($<$70 y versus $\geq$70 y), performance status (0 versus 1 versus 2), stage of disease (I–II versus III), presence of pleural fluid (yes versus no), and CCI score (0 versus 1 versus $\geq$2). Reported p values are two sided, and a p less than 0.05 was considered statistically significant. All analyses were performed using SPSS version 27.

Results

Participants

All 170 participants were included in the present efficacy analyses (60 Gy: 89, 45 Gy: 81). Of these, 117 (69%) were below 70 years, 53 (31%) above or equal to 70 years, 20 (12%) above or equal to 75 years, and five (3%) above or equal to 80 years.

Among the 166 patients who commenced TRT and were included in the toxicity analyses, 116 (70%) (60 Gy: 64, 45 Gy: 52) were below 70 years and 50 (30%) (60 Gy: 25, 45 Gy: 25) were above or equal to 70 years (Fig. 1).

Overall, median age was 65 years (36–82 y), 97 (57%) were women, 166 (98%) were current or former smokers, 152 (89%) had Eastern Cooperative Oncology Group performance status of 0 to 1, 142 (84%) had stage III disease, and 13 (8%) had pleural effusion. There were no statistically significant differences in baseline characteristics between younger and older patients (Table 1).

Table 1. Baseline Characteristics

Baseline Characteristics		<70 y (n = 117)		≥70 y (n = 53)		p
		n	%	n	%	
Age	Median (range)	61 (36-69)		74 (70-82)		
Thoracic radiotherapy	45 Gy	53	45	28	53	
	60 Gy	64	55	25	47	0.36
Sex	Female	67	57	30	57	0.94
Performance status	0	57	49	21	40	
	1	51	44	25	47	
	2	9	8	7	13	0.38
Stage	I-II	20	17	8	15	
	III	97	83	45	85	0.75
Pleura fluid	Yes	9	8	4	8	0.97
Smoking history	Never	2	2	1	2	
	Former	34	29	21	40	
	Current	81	69	30	56	0.34
	Unknown			1	2	
Pack years	Median (range)	35 (10-114)		31 (4-273)		
Charlson Comorbidity Index total score	0	52	44%	19	36%	
	1	35	30	15	28	
	≥2	30	26	19	36	0.37

CCI Score

Overall, 71 patients (42%) had no comorbidity (CCI 0) (<70 y: 44%, ≥70 y: 36%), 50 (29%) had a CCI of 1 (<70 y: 30%, ≥70 y: 28%), and 49 (29%) had a CCI of greater than or equal to 2 (<70 y: 26%, ≥70 y: 36%). There were no statistically significant differences in CCI scores between the two age groups ($p = 0.37$) (Table 1).

Treatment Completion

Most of the patients (90%) completed all four courses of chemotherapy (<70 y: 92%, ≥70 y: 85%; $p = 0.46$). There were no statistically significant differences in the proportions who had reductions of chemotherapy doses or delays of chemotherapy courses (<70 y: 85%, ≥70 y: 92%; $p = 0.19$), completed TRT as planned (<70 y: 95% versus ≥70 y: 92%; $p = 0.37$), or received PCI (<70 y: 85% versus ≥70 y: 75%; $p = 0.13$) or second-line therapy (<70 y: 51% versus ≥70 y: 38%; $p = 0.10$) (Table 2).

Grade 3 to 4 Toxicity

Overall, grade 3 to 4 toxicity was reported for 89% of the patients who commenced TRT. There were no statistically significant differences in the proportions who experienced any grade 3 to 4 toxicity (<70 y: 85%, ≥70 y: 92%, $p = 0.31$), grade 3 to 4 hematological toxicity (<70 y: 82%, ≥70 y: 92%; $p = 0.11$), or grade 3 to 4 nonhematological toxicity (<70 y: 52%, ≥70 y: 48%; $p = 0.74$). Furthermore, there were no significant differences in the proportions who experienced neutropenic infections (<70 y: 31%, ≥70 y: 36%; $p = 0.53$) or any of the most important radiotherapy-related toxicities,

Table 2. Treatment Completion and Response Rates

Treatment Completion and Response Rates	<70 y (n = 117)		≥70 y (n = 53)		p
	n	%	n	%	
Completed TRT as planned	111	95	49	92	0.37
Completed 4 cycles of chemotherapy	108	92	45	85	0.46
No dose reduction or delay of chemotherapy	18	15	4	8	0.19
Carboplatin instead of cisplatin for >1 course	41	35	24	45	0.23
Prophylactic cranial irradiation	100	85	40	75	0.13
Second-line therapy	60	51	20	38	0.10
Overall response rate	94	80	37	70	0.13

TRT, thoracic radiotherapy.

Table 3. CTCAE Grade 3 to 5 Toxicity in Patients Who Commenced Thoracic Radiotherapy

Patients Who Commended TRT	<70 y (n = 116)		≥70 y (n = 50)		
Toxicity	Grades 3-4	Grade 5	Grades 3-4	Grade 5	*p*
Any toxicity	99 (85)	2 (2)	46 (92)	2 (4)	0.31
Any hematological toxicity	95 (82)	1 (2)	46 (92)	1 (2)	0.11
Any nonhematological toxicity	60 (52)	1 (2)	24 (48)	1 (2)	0.74
Esophagitis	24 (21)		9 (18)		0.69
Pneumonitis	2 (2)		1 (2)	1 (2)	0.90
Anemia	19 (16)		10 (20)		0.57
Thrombocytopenia	25 (22)		15 (30)		0.24
Neutropenia	94 (81)		40 (80)		0.93
Neutropenic infection	36 (31)		18 (36)	1 (2)	0.53
Thrombocytopenic bleeding	1 (1)				0.14
Infection	5 (4)		2 (4)		0.14
Kidney failure	16 (14)		4 (8)		0.42
Nausea	8 (7)		1 (2)		0.80
Fatigue	1 (1)				0.85
Erythema			1 (2)		0.13
Headache	1 (1)		1 (2)		0.36
Neuropathy	1 (1)				0.43
Myelopathy	1 (1)				0.51
Myocardial infarction	1 (1)				0.51
Aortic dissection	1 (1)				0.51
Ototoxicity	2 (2)		1 (2)		0.31
Thromboembolism	2 (2)		1 (2)		0.80

Note: All values are n (%).
CTCAE, Common Terminology Criteria for Adverse Events; TRT, thoracic radiotherapy.

pneumonitis (<70 y: 2%, ≥70 y: 2%; $p = 0.90$), or esophagitis (<70 y: 21%, ≥70 y: 18%; $p = 0.69$) (Table 3).

Fatal Events

There were six fatal events during the study treatment period. Three patients above or equal to 70 years (one from myocardial infarction, one from neutropenic infection, and one from pneumonitis) and three patients below the age of 70 years (one from aortic dissection, one from thrombocytopenic bleeding, and one from cerebral infarction) died. Of these, one patient in each age group died from a thromboembolic event before TRT was commenced. The proportion of fatal events did not differ significantly between the two age groups (<70 y: 3 of 117 [2.6%], ≥70 y: 3 of 53 [5.7%], $p = 0.31$) (Table 3).

Response to Treatment, PFS, and TTP

The overall response rate was 77% and did not differ between the age groups (>70 y: 80%, ≥70 y: 70%; $p = 0.13$) (Table 2).

Overall, PFS was 15.0 months (95% confidence interval [CI] 10.2–19.9) with no significant difference between the age groups (<70 y: 15.9 mo [95% CI 8.5–23.3], ≥70 y: 12.2 mo [95% CI 7.5–17.0], $p = 0.13$) (Fig. 2*B*).

For the whole cohort, TTP was 16.0 months (95% CI 10.1–21.8). There was no significant difference between the age groups (<70 y: 18.6 mo [95% CI 10.4–26.8], ≥70 y: 15.8 mo [95% CI 8.6–23.0], $p = 0.96$) (Fig. 2*C*).

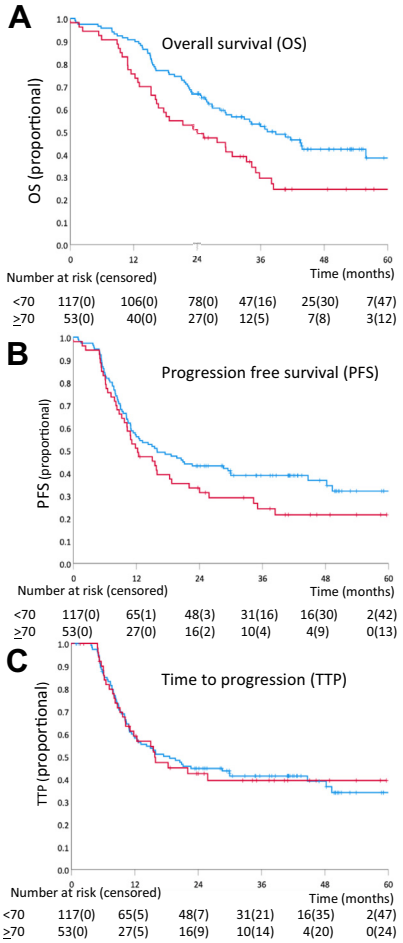
There were no statistically significant differences in PFS or TTP between TRT schedules in either age group (Supplementary Fig. 1).

OS and Two-Year Survival

For the whole cohort, two-year survival rate was 62% and median OS was 33.2 months. There was no statistically significant difference in two-year survival (<70 y: 67% [95% CI 57–75], ≥70 y: 51% [95% CI 37–65]; $p = 0.061$), but median OS was longer among younger patients (<70 y: 37.2 mo [95% CI 27.6–46.8], ≥70 y: 24.0 mo [95% CI 12.9–35.2]; $p = 0.009$) (Fig. 2*A*).

In univariable analysis with age as a continuous variable, there was a trend toward shorter survival with increasing age (hazard ratio 1.03, 95% CI 1.00–1.05; $p = 0.055$).

In multivariable analyses of OS, TRT of 60 Gy ($p = 0.009$), female sex ($p = 0.035$), age below 70 years ($p = 0.046$), and a lower CCI score ($p = 0.002$) were significantly associated with increased survival time. TRT of 60 Gy ($p = <0.001$), stages I to II disease ($p = 0.045$), and a lower CCI score ($p = 0.037$) were associated with improved 2-year survival rate.



	Median OS	95% CI	HR	95% CI	p
< 70 years	37.2	27.6–46.8	1		
≥ 70 years	24.0	12.9–35.2	1.71	1.14–2.56	0.009

	Median PFS	95% CI	HR	95% CI	p
< 70 years	15.9	8.5–23.3	1		
≥ 70 years	12.2	7.5–17.0	1.35	0.92–1.99	0.13

	Median TTP	95% CI	HR	95% CI	p
< 70 years	18.6	10.4–26.8	1		
≥ 70 years	15.8	8.6–29.0	1.0	0.6–1.5	0.96

Figure 2. (*A*) OS, (*B*) PFS, and (*C*) TTP according to age groups. CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; TTP, time to progression.

Among younger patients, the higher TRT dose provided a survival benefit (60 Gy: 54 mo, 45 Gy: 44 mo; $p = 0.018$), whereas this was not the case among older patients (60 Gy: 44 mo, 45 Gy: 35 mo; $p = 0.42$) (Supplementary Fig. 1).

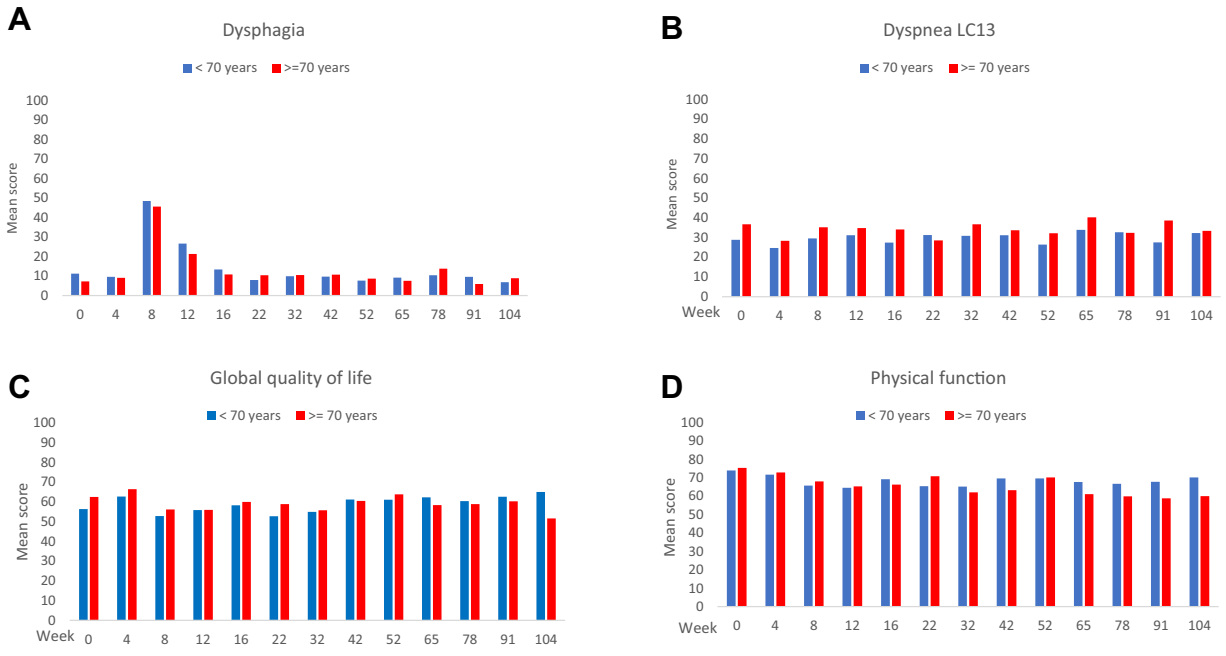
Health-Related Quality of Life

Of the patients commencing TRT, 150 (88%) completed at least one HRQoL questionnaire. The completion rate ranged from 59% to 80% of patients alive at different time points and was comparable for the two age groups (Fig. 3*E*).

There were no clinically relevant differences in mean scores for dyspnea or dysphagia between the age groups at any time point. There were no differences in global QoL or physical functioning between the age groups during the first year. For patients aged 70 years or older, there was a clinically relevant decline in physical functioning during the second year which was not reported by the younger age group (Fig. 3*A*–*D*). The older patients also reported a similar decline in role and social functioning and an increase in fatigue. For cognitive functioning, there was a clinically relevant decline for both age groups, but the reduction was larger among older patients. Emotional functioning remained stable for older patients, whereas younger patients reported marked better emotional functioning on the second year after treatment (Supplementary Fig. 2).

Discussion

In this preplanned subgroup analysis of our trial of high-dose versus standard-dose twice-daily TRT in LS SCLC, we found that older patients completed TRT to the same degree as their younger counterparts, and they did not experience more severe radiotoxicity. There was no difference in completion of chemotherapy, and the frequencies of severe hematological toxicity, neutropenic infections, or fatal events were not different between older and younger patients. These findings were supported by the HRQoL analyses which did not reveal any clinically relevant differences between younger and older patients during the first year of follow-up. Patients



E

Week	0	4	8	12	16	22	32	42	52	65	78	91	104
<70 years	70	65	59	76	69	73	74	72	70	77	72	76	65
≥70 years	77	65	61	80	80	68	73	76	68	63	69	61	59

% completion rate of HRQoL questionnaires

Figure 3. Mean scores for (*A*) dysphagia and (*B*) dyspnea as reported on the QLQ-LC13 questionnaire and (*C*) global quality of life and (*D*) physical function reported on the C30 questionnaire split for age groups. (*E*) % completion rate among patients alive. HRQoL, health-related quality of life; QLQ-LC13, Quality of Life Questionnaire—Lung Cancer 13.

above 70 years old had a shorter OS, but there were no differences in overall response rates, PFS, or TTP.

This is one of few studies of older patients with LS SCLC receiving CRT based on prospectively collected data, the only study in which all patients received twice-daily TRT, the only including high-dose, twice-daily TRT, and to best of our knowledge, the only to include patient-reported outcomes. Eligibility criteria for our trial were liberal with respect to comorbidity, and we allowed patients with performance status of 2.

According to a pooled analyses of 11 randomized controlled trials of CRT of LS SCLC, older patients complete treatment less often than younger patients and discontinue treatment due to death, adverse events, and treatment refusal more often than their younger counterparts.[16] Schild et al.[18] and Christodoulou et al.[19] found that older patients received less chemotherapy, whereas in the CONVERT trial, older patients received less radiotherapy but not less chemotherapy. In our study, fewer older patients completed four cycles of chemotherapy and doses were reduced more often than among younger patients, though the differences were not statistically significant. Nevertheless, compared with other subgroup analyses of older patients with LS SCLC receiving CRT, the completion rates of both chemotherapy (85% versus 64%–78%) and radiotherapy (92% versus 73%) in our trial are among the highest reported.[16–19]

Several studies report the frequency of treatment toxicity split for age groups. Some have found more hematological toxicity among older patients, but similar to what we observed, older patients do not seem to have more radiotoxicity than younger patients,[16,17,19,23] except in one study that found more deaths from pneumonitis among older patients.[18] Nevertheless, studies are not necessarily comparable due to differences in staging procedures, target volume definitions, and radiotherapy planning techniques. In contrast to our findings, most other studies report more fatal events (6%–10% versus 0.5%–3%) among older patients.[16–18] The exception is the CONVERT trial,[19] in which 4% of older patients, similar to what we observed, died during the study treatment period.

Results of studies of the impact of age on survival in LS SCLC are not consistent. In the Intergroup 0096 trial, younger patients had a higher 5-year OS,[17] whereas a pooled analyses of 11 randomized controlled trials of CRT in LS SCLC concluded that older patients had worse

OS and PFS.[16] In contrast, older patients in the CONVERT trial and the trial by Schild et al.[18] and Christodoulou et al.[19] had similar survival as younger patients. Most studies report a median OS of 13.5 to 17.8 months for patients 70 years old or older,[13,16–18,20,24,44] except the CONVERT trial, which reported similar survival as in our study (2-y OS: 53%, median OS: 29 mo).[19] More importantly, population-based studies strongly indicate that older patients who receive CRT live much longer than those who receive chemotherapy alone.[20,44] Notably, the 2-year survival rate of 51% and median OS of 24 months for patients older than 70 years in our study is similar to overall results in many population-based studies and trials of LS SCLC independent of age.[16,24–27,45]

In our study, there was no statistically significant difference in PFS across the age groups and TTP was similar for older and younger patients, possibly indicating the treatment effect on the SCLC was similar for both age groups, that the survival difference might reflect that fewer older patients received relapse therapy, and that some deaths among the older patients were due to other causes than SCLC (competing risk). Considering that most relapses occur within 1 to 2 years and that locoregional tumor control results in less symptoms and better QoL, we believe that these data suggest that older patients benefit from CRT even if survival is shorter than that for younger patients. Furthermore, studies conclude that older patients consider local control and QoL as important as survival.[46,47]

Few studies of LS SCLC have included HRQoL, and we are not aware of other studies of this population which have compared HRQoL across age groups. We did not find any differences in patients reported HRQoL during the first year of follow-up, but older patients reported a larger decrease in functional scales and higher score of fatigue than younger patients during year two. Furthermore, they had a larger decline in cognitive functioning. One possible explanation is that CRT affects older patients more over time than younger patients. There are concerns that PCI causes cognitive deficits, and studies reveal that the impact increases with age.[48–50] Nevertheless, during the second year of the study period, the number of completed questionnaires decreased in both age groups and 32% to 38% of the questionnaires were completed by patients with recurrent disease. Furthermore, a high proportion in the older age group had comorbidities (64%). Thus, it is not possible to assess whether the changes in HRQoL were due to disease progression, long-term side effects of CRT, or deterioration of concurrent diseases or conditions.

The main limitation of our study is the sample size that limits the ability to perform meaningful subgroup analyses. Most importantly, it is difficult to assess whether older patients benefit from the 60 Gy schedule. Among older patients, participants in the high-dose arm had a numerically longer median OS, PFS, and TTP than in the control arm, and considering that older patients did not have more toxicity than younger patients, our study indicates that also older patients should be offered the higher TRT dose. Even though the sample size is limited, more than 31% of the patients in our trial were 70 years old or older, which is a higher proportion than in most studies of CRT in LS SCLC (13%–21%)[16–19] and numerically within the same range as previous studies (n = 50–67 patients).[17–19] Furthermore, the proportion of patients 70 years old or older is similar to a population-based study of patients with LS SCLC receiving CRT from the Netherlands.[24]

Even though the proportion who experienced severe toxicity was not higher among older patients, the study was not designed to assess how long patients had side effects or how much supportive care was needed, and we cannot rule out that the impact on patients' functional level was different between the age groups. This might explain why chemotherapy was more often discontinued and doses were more often reduced among older patients, though the difference was not statistically significant. That being said, severe toxicity is also very common among younger patients with LS SCLC who receive CRT, and it is important to monitor all patients closely and provide timely and sufficient supportive care for patients to be able to complete this potentially curative treatment.

We did, however, not collect data on patients considered ineligible for the trial (screen failures), and most likely, the proportion of elderly patients enrolled was lower than that for younger patients. Thus, it is possible that the older patients in our study were more fit than the average patient with LS SCLC older than 70 years.

In conclusion, we found that patients 70 years old or older were able to complete chemotherapy and twice-daily TRT, overall and in the high-dose arm. They tolerated the therapy well, toxicity was transient, and HRQoL was preserved on the first year after therapy, though older patients reported a larger decline in HRQoL functional scales during year two than younger patients. Survival was shorter for older patients, but considering there were no statistically significant differences in PFS or TTP, our study indicates that older patients with LS SCLC should be offered similar, twice-daily TRT, as younger patients.

CRediT Authorship Contribution Statement

Kristin Toftaker Killingberg: Project administration, Data curation, Validation, Formal analysis, Original draft, Writing—review and editing.

Bjørn Henning Grønberg: Conceptualization, Funding acquisition, Project administration, Methodology, Data curation, Writing—review and editing, Supervision.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2023.01.012.

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