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ORIGINAL ARTICLE

Accelerated hypofractionated thoracic radiotherapy in limited disease small cell lung cancer : comparison with the results of conventionally fractionated radiotherapy

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Summary

Purpose: *To compare accelerated hypofractionated (A-HYPO) radiotherapy (RT) with conventionally fractionated (CF) thoracic RT in patients with limited-disease small-cell lung cancer (LD-SCLC).*

Methods: *Out of 217 consecutive LD-SCLC patients, treated between 1997 and 2012, 82 received CF-RT (44–60 Gy, 2 Gy/fraction) sequentially to 4-6 cycles of platinum-based chemotherapy (CHT), and 100 received A-HYPO-RT (42 Gy, 2.8 Gy/fraction). Forty-two patients (42%) received "early" (before the 3rd cycle of CHT) A-HYPO-RT, and 58 (58%) patients received "late" A-HYPO-RT. Overall survival (OS), locoregional failure risk (LRFR) and toxicities were retrospectively evaluated and compared between CF-RT and A-HYPO-RT groups (also separately for "early" and "late" A-HYPO-RT).*

Results: *Median survival times (MST) for CF-RT and A-HYPO-RT were 18 and 24 months, respectively; 3-year OS were 19.1 and 39.4%, respectively (p=0.004). Three-year LRFR in CF-RT was 47.3% and 34.0% in the A-HYPO-RT group (p=0.12). Statistically significant difference in OS (p=0.007) and LRFR (p=0.03) was observed, favoring "early" A-HYPO-RT (MST=27 months, 3-year OS=40.0%, 3-year LRFR=28.4%) over CF-RT. Use of CF-RT (relative risk/RR=1.65, p=0.02) and poor CHT compliance (RR=1.69, p=0.03) were independent prognostic factors for poor OS; "early" start of RT was a favorable although non-significant prognostic factor for LRFR (RR=0.42, p=0.05). No difference in toxicities was observed between the groups.*

Conclusions: *A-HYPO-RT results in better outcomes than CF-RT. "Early" A-HYPO-RT provides additional benefit in locoregional control and survival, without increased toxicity. These results indicate the need for a randomized study on the efficacy of A-HYPO-RT.*

Key words: *accelerated hypofractionation, dose fractionation, limited disease, radiotherapy, small cell lung cancer, timing of radiotherapy*

Introduction

The current standard of care for LD-SCLC is concurrent CHT and thoracic RT followed by prophylactic cranial irradiation (PCI) for complete or near-complete responders [1]. There is some evidence suggesting that an improvement of outcome in radiochemotherapy (RT-CHT) of LD-SCLC is related to treatment intensification by shortening the total duration of therapy [2]. However, the best way of acceleration of RT remains to be determined. Although the twice-daily RT schedule with concurrent platinum-etoposide CHT, introduced by Turrisi et al. [3], is currently considered the "gold standard" [4], this accelerated regimen has failed to be widely implemented – mainly due to its inconvenience and also to significantly increased acute esophageal toxicity [1]. As a result, despite the known detrimental effect of prolonged overall treatment time (OTT) of chest RT [2,5], the vast majority of patients still receive CF-RT in a dose range of 50.4-66Gy in 1.8-2Gy daily frac-

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tions [6-8]. Considerable shortening of the OTT, however, can be achieved by the use of accelerated, moderately hypofractionated (A-HYPO) RT schedules (i.e. 40-45Gy, 2.6-3Gy/fraction in three weeks). Since the NCI-C randomized controlled trial reported by Murray et al. [9], A-HYPO-RT has been commonly used [10-13] with good efficacy. However, three-dimensionally (3D) planned, modern conformal A-HYPO-RT has never been compared to hyperfractionated RT nor to CF-RT in a randomized setting. Although late toxicity is an important endpoint when evaluating A-HYPO-RT schedules, as the late effects in normal tissues are dependent on dose per fraction, published clinical data on the incidence and severity of A-HYPO-RT-related late side effects in LD-SCLC patients are scarce.

The optimal timing of RT related to CHT is another important, yet still unresolved issue [1]. RT (mostly: hyperfractionated) administered early in relation to the start of CHT (i.e. with the first or second cycle) improves long term results but at the expense of higher toxicity [2,5]. Early administration of A-HYPO-RT may confer the benefit of avoiding excessive toxicity while maintaining high efficacy.

The aim of our study was to compare the efficacy and toxicity of A-HYPO and CF schedules of thoracic RT in LD-SCLC patients. Additionally, to evaluate the value of the early delivery of A-HYPO-RT, the outcomes of "early" and "late" A-HYPO-RT were separately evaluated and compared with that of CF-RT.

Methods

Patients

Between 1997 and 2012, 217 consecutive LD-SCLC patients received thoracic RT with curative intent in our institution. Thirty-five patients, treated between 1997 and 2006 with hyperfractionated RT or with alternating RT-CHT schedule, were excluded from the analysis. During the same period, 82 patients received CF-RT. From 2007 – when A-HYPO-RT was adopted as a standard treatment for LD-SCLC in our institution – to 2012, 100 consecutive patients were treated with A-HYPO-RT.

The staging procedures included a complete history, physical examination, blood tests, bronchoscopy, chest computed tomography (CT), abdominal CT or ultrasound, brain CT or MRI, bone scanning and pulmonary function tests. PET-CT was not performed. All patients met the following eligibility criteria for radical RT: pathologic confirmation of SCLC, limited stage disease, a Karnofsky performance status (KPS) >70 (exceptionally: KPS =70), no contraindications to chest RT, and 1-second forced expiratory volume (FEV1) >1 liter.

Chemotherapy

CHT consisted of 4-6 courses (median 4) of cisplatin+etoposide (PE) or carboplatin+etoposide (CE) at 21-day intervals. In A-HYPO-RT group, the CHT course that included RT was prolonged to 28 days. Ten patients (12%) in the CF-RT group and 3 patients (3%) in A-HYPO-RT group received another type of CHT due to toxicity or other reasons, as listed in Table 1. Two patients (2.4%) in the CF-RT group received non-platinum-based CHT.

Radiotherapy

CF-RT started after 4-6 cycles of CHT and consisted of 44-60Gy (median 56) in 2Gy/fraction, 5 days/week. For 41 (50%) patients, the elective fields were planned with two-dimensional (2D) technique, using anterior-posterior/posterior-anterior fields and treated up to 44Gy, whereas the boost fields were 3D-planned and treated up to a median of 56Gy. The boost volumes included the gross tumor and pathologic mediastinal/hilar (and unilateral supraclavicular in 1 patient) lymph nodes (LNs) with a 1-2 cm margin. LNs with a short axis diameter ≥1 cm on CT were considered pathologic. The elective area encompassed the bilateral mediastinal and ipsilateral hilar LNs (supraclavicular regions were treated electively in one patient).

A-HYPO-RT was 3D-planned and consisted of 42Gy in 2.8Gy/fractions (15 fractions/3 weeks). Details of this technique were published previously [14]. Briefly, the "concomitant boost" technique was used: elective volume and tumor volumes were treated during the same fraction, with total dose to elective volume of 39Gy, 2.6Gy/fraction. All patients were treated with 6MV photons. The boost volume included the gross tumor with a 5 mm margin and the whole nodal stations with pathologically enlarged LNs. Elective volume included the ipsilateral hilum, nodal stations 7, 4R, 4L, 6, 3A, 2R, 2L, and 5 for the left side tumors. In case of "bulky mediastinal disease" (i.e. an involvement of more than two mediastinal nodal stations or a single LN with a short axis diameter ≥3 cm), the elective volume was additionally enlarged to encompass stations 1R, 1L and supraclavicular areas. The nomenclature of nodal stations followed the recommendations of Mountain and Dressler [15]. The mean lung dose could not exceed 20Gy. Less than 35% of the lung volume was to receive more than 20Gy. The maximum dose to the spinal cord was constrained to 40Gy.

As the majority of patients were treated with CHT outside our institution, the timing of delivery of A-HYPO-RT in relation to CHT was dependent on referral by clinical oncologists and varied as follows: "early" A-HYPO-RT, defined as given before the 3rd cycle of CHT, was administered to 42 patients, and the remaining 58 patients received "late" A-HYPO-RT (i.e. delivered be-

Table 1. Treatment characteristics of the A-HYPO-RT group (100 patients) and the CF-RT group (82 patients)

Characteristics	*A-HYPO-RT Group Number of patients (equals %)*	*CF-RT Group Number of patients (%)*	*p value*[†]
Use of PCI			0.08
Yes	52	37 (45)	
No	48	45 (55)	
Type of CHT			0.05
PE	78	66 (80.5)	
KE	19	6 (7.5)	
PN	1	0	
CAV	0	1 (1)	
Other (mostly combinations of above)	2	9 (11)[*]	
Number of CHT cycles			0.009
≤3	22	7 (8.5)	
>3	78	75 (91.5)	
Delivery of RT			0.0001
Early^	42	0	
Late[‡]	58	82 (100)	
RT planning			0.0001
2D	0	0	
2D – elective volume, 3D – boost volume	0	41 (50)	
3D	100	41 (50)	
Timing of RT and CHT			1.0
Sequential	100	82 (100)	
RT between 1st and 2nd or 2nd and 3rd cycle of CHT (early sequential RT)	42	0	
RT after CHT	58	82 (100)	
RT dose and fractionation			0.06[#]
42 Gy in 15 fractions of 2.8 Gy″ (BED = 60 Gy)	98	0	
• 39 Gy in 15 fractions of 2.6 Gy (BED = 55.4 Gy)	1	0	
• 49.8 Gy in 18 fractions″ (BED = 66.4 Gy)	1	0	
44-60 Gy of 2 Gy, median 56 Gy (median BED = 60.2 Gy; range 51.4 – 63.6 Gy)	0	82 (100)	

*two patients received non-platinum-based chemotherapy; ^ "early" radiotherapy was defined as terminated before the 3rd cycle of chemotherapy; [‡]"late" radiotherapy was defined as started after the 3rd cycle of chemotherapy; with 39 Gy, 2.6 Gy/fraction to elective volume; 42 Gy, 2.8 Gy/fraction+3 additional fractions, each of 2.6 Gy; [#] for BED 60 vs>60 Gy. [†] chi-square test. PCI : prophylactic cranial irradiation; RT: radiotherapy; CF-RT: conventionally fractionated RT; A-HYPO-RT: accelerated hypofractionated RT ; CHT: chemotherapy; 2D: two-dimensional radiotherapy planning; 3D: three-dimensional radiotherapy planning; PE: Cisplatin + Etoposide; CE: Carboplatin + Etoposide; PN: Cisplatin+Vinorelbine; CAV: Cyclophosphamide +Doxorubicin +Vincristine; BED: biologically effective dose.

tween 3rd and 4th cycle of CHT or after the end of all 4 CHT cycles).

The biologically effective dose (BED) formula, proposed by Fowler [16], was used to compare the effect of different fractionation schedules:

$$BED = nd [1 + d (\alpha/\beta)] - \ln 2 (T - Tk),$$

where n = number of fractions, d = dose per fraction, α/β=10 for SCLC, T = total irradiation time, Tk = time of onset of accelerated tumor repopulation, which we assumed to be 28 days.

PCI – 25Gy in 2.5Gy/fractions – was offered to complete or near-complete responders, after completion of treatment. Neurodegenerative changes, dementia syndrome, alcoholism, epilepsy, cerebrovascular diseases and age >75 years were considered relative contraindications to PCI.

Toxicity

Acute lung toxicity was scored using the Southwest Oncology Group (SWOG) scale [17]. Late pulmonary, acute and late esophageal toxicity were reported according to the Radiation Therapy Oncology Group (RTOG) scale [18]. In CF-RT group, late esophageal toxicity was determined by the need for esophageal dilation or any condition (i.e. necrosis, fistula, perforation) requiring surgery. Thus, according to the RTOG scale [18], only severe (grade ≥3) late esophageal toxicities were recorded in that group.

Statistics

Survival outcomes, locoregional failure risk (LRFR), pulmonary and esophageal toxicity were retrospectively evaluated and compared between A-HYPO-RT and CF-RT groups. Additional analysis was per-

Table 2. Clinical characteristics of the A-HYPO-RT group (100 patients) and the CF-RT group (82 patients)

Characteristics	*A-HYPO-RT GROUP Number of patients (equals percentage)*	*CF-RT GROUP Number of patients (%)*	*p value‡*
Gender			
Male	52	47 (57)	0.46
Female	48	35 (43)	
Age (years)	Median: 59 Range: 41 – 81	Median: 59 Range: 44 – 78	0.44
KPS^			
90–100	85	81 (99)	0.005
80	12	1 (1)	
70	3	0	
Comorbidity*			
Yes	73	41 (50)	0.002
No	27	41 (50)	
Side			
Right	49	47 (57)	0.25
Left	51	35 (43)	
Bulky disease#			
Yes	66	46 (56)	0.17
No	34	36 (44)	
Upper mediastinal involvement (groups 1-2)			0.001
Yes	42	16 (19.5)	
No	58	66 (80.5)	
N stage			
N0	6	15 (18)	0.005
N1	6	6 (8)	
N2	45	36 (44)	
N3	38	15 (18)	
No exact data	5	10 (12)	

* Comorbidity was defined as a chronic disease requiring long-term drug therapy and/or another malignant neoplasm;#Bulky disease was defined as an involvement of three or more lymph node stations or a single lymph node enlargement >3cm in short axis; ^before radiotherapy;‡ chi-square test; RT: radiotherapy; CF-RT: conventionally fractionated RT; A-HYPO-RT: accelerated hypofractionated RT; CHT: chemotherapy; KPS: Karnofsky performance status

formed to compare the results and toxicity of "early" and "late" A-HYPO-TRT with that of CF-RT. Locoregional failure (LRF) was defined as a relapse at the primary tumor site or in the initially involved nodal stations, whichever occurred first. Regional nodal failure occurring without LRF was defined as an isolated nodal failure (INF), regardless of distant metastases (DM) occurrence. The chi-square test was used to determine and compare the distribution of patient characteristics across the analyzed groups. OS and LRFR were estimated using the Kaplan-Meier method. OS was defined as the interval between the start of CHT and the date of death from any cause or last follow-up. LRFR was calculated from the start of CHT to the occurrence of LRF (last follow-up and death without LRF were censored). Univariate (log-rank) and multivariate (Cox regression model) analyses were used to evaluate the influence of patient, tumor and treatment related factors on OS and LRFR. The clinical variables included in univariate analysis were as follows: age (<65 vs ≥65), gender (male vs female), KPS (90-100 vs 70-80), the presence of "bulky disease" (yes vs no), RT schedule (CF-RT vs A-HYPO-RT), RT timing ("early" vs "late"), the use of PCI (yes vs no), and the number of CHT cycles (≤3 vs >3). The chi-square test was used to compare the distribution of the incidence and severity of RT-induced toxicity between groups. A p value <0.05 was considered statistically significant. SPSS Statistical software package v.20 (SPSS Inc, Chicago, Ill) was used for statistical analyses.

Results

Patients and treatment

Table 2 summarizes the characteristics of 182 patients, divided into two groups: CF-RT (N=82) and A-HYPO-RT (N=100). Median follow up was 31 months (range 11-88) for the living patients.

There were statistically significant differences between A-HYPO-RT and CF-RT groups in the distribution of patients' KPS (p=0.005) and the number of CHT cycles (p=0.009), in favor of the

CF-RT group. Seventy-five patients (91.5%) in the CF-RT group received at least 4 cycles of CHT vs 78 patients (78%) in A-HYPO-RT group (p=0.009). Similarly, between "early" A-HYPO-RT and CF-RT groups significant differences were noticed in KPS (p=0.02) and the number of CHT cycles (p=0.0001), favoring the of CF-RT group. Between "late" A-HYPO-RT and CF-RT groups significant difference was noticed only in KPS distribution (p=0.0001). Within the A-HYPO-RT group, the difference in the proportion of patients who received ≥4 cycles of CHT vs 3 or less was statistically significant, favoring "late" A-HYPO-RT group (67 vs 86%, respectively; p=0.03).

Apart from that, there were no significant differences in the distribution of patient characteristics and prognostic parameters (i.e. age, sex, presence of bulky disease, use of PCI, type of CHT: platinum-based vs non-platinum, BED of RT) among compared subgroups.

Data on weight loss were incomplete for A-HYPO-RT group, and thus were not analyzed.

OS

Median survival time (MST) for the whole group of 182 patients was 19 months (95%CI: 17-21); the actuarial 3-year OS rate was 30.9%. The actuarial 3-year OS rate was 19.1% in CF-RT group and 39.4% in A-HYPO-RT group, with MST of 18 (95%CI: 14-21) and 24 months (95%CI: 16-32), respectively; p=0.004 (Figure 1). In "early" A-HYPO-RT group, the 3-year OS rate was 40.0% vs 19.1% in the CF-RT group (MST=27 months; 95%CI: 15-39) vs 18 months; 95%CI: 14-21), respectively; p=0.007 (Figure 2). In "late" A-HYPO-RT group, the 3-year OS rate was 38.7% vs 19.1% in the CF-RT group (MST=22 months; 95%CI: 14-29) vs 18 months (95%CI: 14-21), respectively; p=0.05 (Figure 3).

In univariate analysis (Table 3), RT schedule was the only significant prognostic factor for OS (p=0.004) – the use of CF-RT was associated with poor prognosis. "Early" RT timing (p=0.05) and the use of PCI (p=0.05) showed a non-significant trend toward improved OS. Multivariate analysis (Table 4) confirmed CF-RT to be an independent factor of poor prognosis (RR=1.65, 95%CI: 1.08-2.51; p=0.02) and revealed that poor CHT compliance (i.e. delivery of 3 or less cycles of CHT) was significantly associated with poor OS (RR=1.69,

Table 3. Results of univariate analysis of prognostic factors for OS and LRFR

Factors	*Number of patients*	*OS*			*LRFR*	
		3-year (%)	*MST (mo)*	*p value*	*3-year (%)*	*p value*
Age, years						
< 65	128	30.1	19	0.43	44.3	0.35
≥ 65	54	25.9	19		31.7	
Gender						
Male	99	27.8	18	0.27	41.2	0.65
Female	83	29.4	21		41.1	
KPS						
90-100	166	29.5	24	0.72	43.2	0.14
70-80	16	17.9	19		28.4	
Bulky disease						
Yes	112	27.1	20	0.64	41.1	0.33
No	70	31.9	20		39.8	
RT schedule						
CF-RT	82	19.1	18	0.004	47.3	0.12
A-HYPO-RT	100	39.4	24		34.0	
RT timing						
Early	42	40.0	27	0.05	28.4	0.04
Late	140	27.1	18		45.4	
PCI						
Yes	89	30.0	21	0.05	41.1	0.31
No	93	27.7	16		37.3	
CHT cycles				0.13		0.35
≤3	29	23.1	14		36.0	
>3	153	30.5	20		41.6	

OS: overall survival, MST: median survival time, LRFR: locoregional failure risk, mo: months, RT: radiotherapy, CF-RT: conventionally fractionated RT, A-HYPO-RT: accelerated hypofractionated RT, CHT: chemotherapy, PCI: prophylactic cranial irradiation, KPS: Karnofsky performance status

95%CI: 1.05-2.72; p=0.03). Timing of RT and the use of PCI were not prognostic in multivariate analysis for OS.

Patterns of failure

DM represented the most common pattern of failure in both groups. DM as a first site of failure occurred in 39 (47%) and 28 (28%) patients in the CF-RT and A-HYPO-RT group, respectively (p=0.01). Among them, 19 patients (23%) in the CF-RT group and 17 (17%) in the A-HYPO-RT group experienced brain metastases as a first site of failure (p=0.28). INF occurred in 3 (3.5%) and 4 (4%) patients in the CF-RT and A-HYPO-RT group, respectively (p=0.9).

LRFR

LRFR at 3 years was 47.3% in the CF-RT group and 34.0% in the A-HYPO-RT group (p=0.12; Figure 4). In the "early" A-HYPO-RT group, LRFR at 3 years was 28.4%, and differed significantly from CF-RT group (p=0.03; Figure 5). In the "late" A-HYPO-RT group 3-year LRFR was 45.1 vs 47.3% in the CF-RT group (p=0.58; Figure 6).

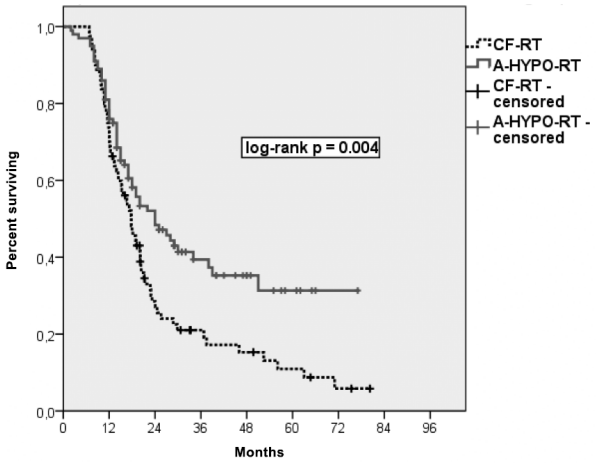
Univariate analysis (Table 3) identified the "early" start of RT as the only significant prognostic factor for better locoregional control (p=0.04). In multivariate analysis (Table 5), "early" RT appeared as a strong but non-significant prognostic factor for LRFR (RR=0.42, 95%CI: 0.17-1.01; p=0.05), whereas RT schedule, CHT compliance meant as delivery of more than 3 cycles of CHT and KPS had no significant association with survival.

Toxicity

Table 6 shows a comparison of the incidence and severity of RT-induced toxicity for the CF-RT patients and the A-HYPO-RT group divided into "early" and "late" A-HYPO-RT subgroups. There were no statistically significant differences in acute and late pulmonary and esophageal toxicity between the compared groups, although the risk of grade 2 RTOG acute esophageal toxicity was quantitatively higher in the "early" A-HYPO-RT group.

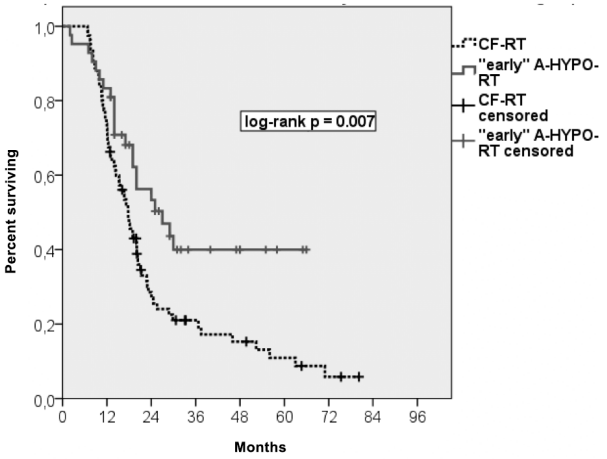
Discussion

A-HYPO-RT schedules may confer a survival benefit compared with prolonged CF-RT. Although hyperfractionated RT has produced the best reported survival ever with a 5-year OS rate of 26%



Number at risk:							
CF-RT:	82	60	26	22	19	17	15
A-HYPO-RT:	100	76	52	46	44	43	43

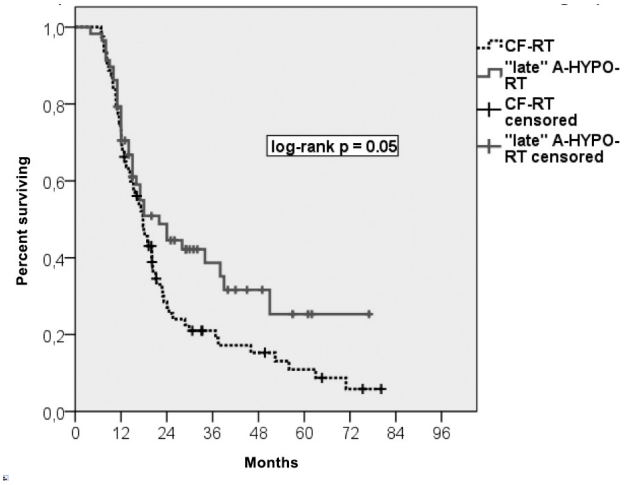
Figure 1. Comparison of overall survival between A-HYPO-RT and CF-RT groups.



Number at risk:						
CF-RT:	82	60	26	22	19	17
"early" A-HYPO-RT:	42	35	24	20	20	20

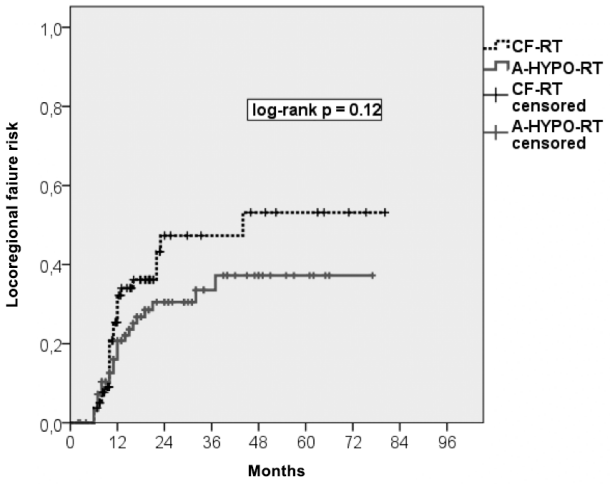
Figure 2. Comparison of overall survival between "early" A-HYPO-RT and CF-RT groups.

[3], an improvement of survival from hyperfractionated RT is probably related to shortened duration of RT rather than hyperfractionation itself [19,20]. From radiobiological standpoint, "carefully regulated hypofractionation" (i.e. keeping the overall treatment time/OTT close to Tk by the use of dose per fraction calculated for equal late BED, to ensure a constant level of late complications)



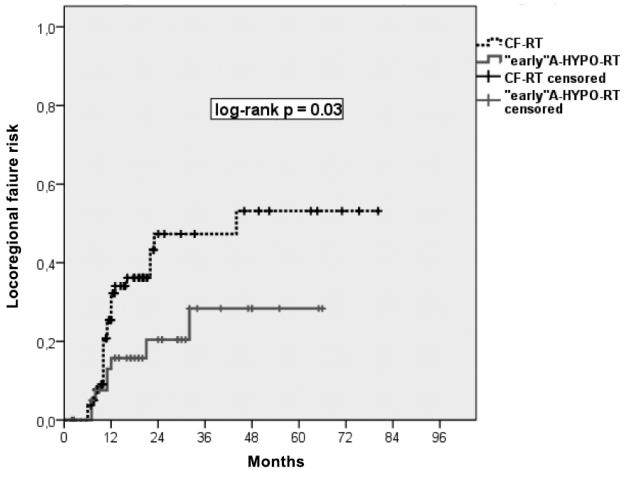
Number at risk:						
CF-RT:						
82	60	26	22	19	17	
"late" A-HYPO-RT:						
58	41	28	26	24	23	

Figure 3. Comparison of overall survival betwwen "late" A-HYPO-RT and CF-RT groups



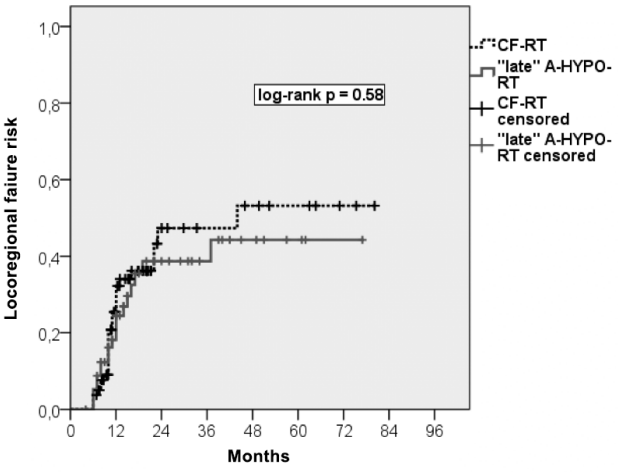
Number at risk:						
CF-RT:						
82	42	20	18	16	15	
A-HYPO-RT:						
100	68	48	42	41	40	

Figure 4. Locoregional failure risk in CF-RT and A-HYPO-RT groups.



Number at risk:						
CF-RT:						
82	42	20	18	16	15	
"early" A-HYPO-RT:						
42	31	22	18	18	18	

Figure 5. Locoregional failure risk in CF-RT and "early" A-HYPO-RT groups.



Number at risk:						
CF-RT:						
82	42	20	18	16	15	
"late" A-HYPO-RT:						
58	37	26	25	23	22	

Figure 6. Locoregional failure risk in CF-RT and "late" A-HYPO-RT groups.

would increase tumor control probability in rapidly proliferating tumors, without enhancement of complications [16]. However, although high quality outcome data do exist for A-HYPO-RT [9,10], this regimen has never been directly compared to others in a randomized control trial. To date, there has been only one retrospective study on 215 LD-SCLC patients treated in a single institution over 10 years, that investigated the impact of changing the RT regimen from A-HYPO-RT (40Gy, 2.67Gy/fraction) to CF-RT (50Gy, 2Gy/fraction) on patient outcomes and toxicity [11]. No statistically signif-

Table 4. Multivariate analysis of prognostic factors for OS

Factors	*Relative risk*	*95% confidence interval*	*p value*
RT schedule: CF-RT vs A-HYPO-RT	1.65	1.08 – 2.51	0.02
RT timing: early vs late	0.78	0.46 – 1.35	0.38
PCI: yes vs no	0.75	0.53 – 1.08	0.12
CHT cycles: ≤3 vs >3	1.69	1.05 – 2.72	0.03

OS : overall survival, RT: radiotherapy; CF-RT: conventionally fractionated RT; A-HYPO-RT : accelerated hypofractionated RT; CHT: chemotherapy; PCI: prophylactic cranial irradiation

Table 5. Multivariate analysis of prognostic factors for LRFR

Factor	*Relative risk*	*95% confidence interval*	*p value*
RT schedule: CF-RT vs A-HYPO-RT	1.00	0.54 – 1.86	0.98
RT timing: early vs late	0.42	0.17 – 1.01	0.05
KPS^: 90-100 vs 70-80	1.03	0.97 – 1.08	0.19
CHT cycles: ≤3 vs >3	1.05	0.46 – 2.37	0.91

^ before radiotherapy; LRFR: locoregional failure risk; RT: radiotherapy; CF-RT: conventionally fractionated RT; A-HYPO-RT: accelerated hypofractionated RT; CHT: chemotherapy; PCI: prophylactic cranial irradiation; KPS: Karnofsky performance status

icant differences were found with respect to OS or the overall rate of first failure in the chest, although an absolute difference in the chest failure rate of 11% favored the 40Gy cohort. Acute treatment toxicity was measured by the incidence and duration of toxicity-related breaks; no statistically significant difference was found between both groups [11]. In our study, the use of CF-RT was an independent prognostic factor of poor survival, but not for LRFR. A benefit in locoregional control has been shown only for "early" start of RT. Moreover, the benefit in locoregional control and survival in the "early" A-HYPO-RT group has been achieved without significant excess in acute and late treatment-related toxicity, suggesting that such a schedule can be safely implemented into the routine clinical practice, and constitute a reasonable alternative for patients unsuitable for accelerated hyperfractionated RT. Better performance status of patients in CF-RT group (p=0.005, Table 2) may suggest more strict eligibility criteria for definitive RT in this group. A-HYPO-RT group consisted of 100 consecutive patients with KPS ≥70, thus selection criteria were not so rigorous. This can be considered as an additional advantage, indicating that the presented A-HYPO-RT schedule can be used in a wider population of patients. A negative consequence of less strict qualification criteria in A-HYPO-RT group was probably the lower proportion of patients who completed the planned CHT, compared to the CF-RT; the proportions of patients who received at least 4 cycles of CHT were 78 and 91.5%, respectively; p=0.009; Table 1. This could have negatively influenced the outcomes in A-HYPO-RT group, as CHT compliance was shown to be an independent prognostic factor for survival (RR=1.69, 95%CI: 1.05-2.72; p=0.03). Despite the improvement in locoregional control with the use of "early" RT (RR=0.42, 95%CI: 0.17-1.01; p=0.05), timing of RT was not prognostic in multivariate analysis for OS. This finding is in line with the results of the meta-analysis performed by Spiro et al. [10] that first raised the issue of the optimal delivery of CHT. The authors conducted a meta-analysis of 8 trials and concluded that the optimal delivery of CHT is necessary to derive any benefit from the "early" use of RT [10].

Treatment results obtained with "early" A-HYPO-RT (MST=27 months, 3-year OS=40.0%) are among the best reported outcomes in the literature achieved with either another HYPO-RT or even hyperfractionated RT schedules and are much better than ever reported for CF regimen (Table 7). In light of this, it becomes tempting to compare A-HYPO with hyperfractionated RT in a randomized setting, especially because that such a comparison has never been performed before. There has been only one retrospective study reported to date that examined the survival outcomes of 41 patients treated using the Turrisi regimen compared to 38 patients treated with A-HYPO-RT (40Gy, 2.67Gy/fraction). There was no statistically significant survival difference between both groups (median survival 26 vs 21 months, 5-year OS 25 vs 20% for the Turrisi scheme and A-HYPO-RT, respectively; p=0.24) [13].

Table 6. Treatment toxicity

Treatment toxicity	*Toxicity grade* 2	3	4	*p value* #
	Number of patients (%)			
Acute esophageal toxicity‡				
"early" A-HYPO-RT	12 (28.5)	0	0	1 vs 3: p = 0.11 2 vs 3: p = 0.74 A-HYPO-RT§ vs CF-RT: p = 0.2
"late" A-HYPO-RT	12 (20.5)	0	0	
CF-RT	15 (18)	0	0	
Late esophageal toxicity‡				
"early" A-HYPO-RT	1 (2)	0	0	NA
"late" A-HYPO-RT	2 (3)	0	0	
CF-RT†	NA†	0	0	
Acute pulmonary toxicity^				
"early" A-HYPO-RT	1 (2)	0	0	1 vs 3: p = 0.34 2 vs 3: p = 0.72 A-HYPO-RT§ vs CF-RT: p = 0.73
"late" A-HYPO-RT	1 (1.7)	0	0	
CF-RT	5 (6)	0	0	
Late pulmonary toxicity‡				
"early" A-HYPO-RT	4 (9.5)	0	0	1 vs 3: p = 0.07 2 vs 3: p = 0.18 A-HYPO-RT§ vs CF-RT: p = 0.8
"late" A-HYPO-RT	1 (1.7)	0	0	
CF-RT	5 (6)	0	0	
Treatment-related deaths				
"early" A-HYPO-RT		2 (4)		1 vs 3: p = 0.20 2 vs 3: p = 0.88 A-HYPO-RT§ vs CF-RT: p = 0.47
"late" A-HYPO-RT		1 (1.7)		
CF-RT		1 (<1)		

^: according to the Southwest Oncology Group (SWOG) scale [17] ‡ : according to the Radiation Therapy Oncology Group (RTOG) scale [18] † : only severe (≥ grade 3 RTOG) late esophageal toxicities were recorded in CF-RT group; # : estimated with the use of the Chi-Square test; 1="early" A-HYPO-RT , 2="late" A-HYPO-RT, 3= CF-RT; §: for the whole group of 100 patients; CF-RT: conventionally fractionated RT; A-HYPO-RT: accelerated hypofractionated RT; NA: data not available

HYPO-RT schedules have historically been avoided in curative-intent therapy because of expectation of severe delayed toxicity. However, data on late toxicity of any schedule of thoracic RT in LD-SCLC patients are very limited and there are virtually no such data available for HYPO-RT schedules. Therefore, the detailed evaluation of late pulmonary adverse effects following A-HYPO-RT is the strong point of our study, although the retrospective nature of this analysis implies a low level of evidence.

There are also several limitations in this study. The first and most important limitation, apart from its retrospective design, results from the fact that since the A-HYPO-RT schedule was implemented in 2007, all consecutive patients have been treated that way. In this respect, patients treated with CF-RT can be considered as a kind of "historical control". Fifty percent of these patients have the elective fields planned with 2D technique, whereas in A-HYPO-RT group these techniques were not allowed. Thus, the survival advantage of the A-HYPO-RT over CF-RT might be overestimated. However, our results compare favorably to the results of any published CF-RT trial, so the survival benefit can be indeed of a highly relevant magnitude. Non-concurrent delivery of RT and CHT is another important limitation of our study, as the optimal treatment sequencing is concurrent [1,19,35]. For prolonged CF-RT regimens, however, "sequential" necessarily means "late" RT, whereas A-HYPO-RT can be delivered "early" – in the gaps between CHT cycles. Such an "early sequential" schedule may still be valid in many clinical situation, especially in the limited resources setting or outside specialized tertiary referral centers, where CHT and RT are not conducted at the same center.

Table 7. Summary results from the main published trials on chemoradiotherapy for limited-disease small cell lung cancer

Study [ref.]	*Patients, N*	*Treatment schedule*	*Results*		
			MST (months)	*3-y OS (%)*	*3-y LRFR (%)*
		Randomized studies			
Murray1993 [9]	308	40Gy/ 15 fr / 2.67 Gy, concurrent RT-CHT • "early" RT • "late" RT	 21.2 16	 29.7 21.5	 50 53
Jeremic 1997 [21]	103	54 Gy/ 36 fr b.i.d./ 1.5 Gy, concurrent RT-CHT • "early" RT • "late" RT	 34 26	 48 39	 27 39
Gregor 1997 [22]^	334	50 Gy/ 20 fr / 2.5 Gy: • alternating RT-CHT • sequential RT-CHT	15# 14 15	14# 12 15	NG NG NG
Work 1997 [23]	199	• 40-45 Gy/ 22 fr / 2 Gy, alternating RT-CHT • "early" RT • "late" RT	 10.5 12	 13 12	 2y 72 2y 68
Perry 1998 [24]^	270	50 Gy/ 25 fr / 2 Gy, concurrent RT-CHT • "early" RT • "late" RT	 13 14.7	 7.2 13.8	 NG NG
Turrisi 1999 [3]	417	Concurrent RT-CHT • 45 Gy/ 30 fr b.i.d./ 1.5 Gy • 45 Gy/ 25 fr / 1.8 Gy	20# 23 19	5-y 23# 5-y 26 5-y 16	 5y 42 5y 75
Bonner 1999 [25,26]	310	Concurrent RT-CHT • 48 Gy/ 32 fr b.i.d./ 1.5 Gy (2.5 weeks gap) • 50.4 Gy/ 28 fr / 1.8 Gy	20.6# 20.6 20.6	28.9# 29 34	 32 39
Skarlos 2001 [27]	81	45 Gy/ 30 fr b.i.d./ 1.5 Gy, concurrent RT-CHT • "early" RT • "late" RT	 17,5 17	 22 13	 NG NG
Takada 2002 [28]	228	45 Gy/ 30 fr b.i.d./ 1.5 Gy • concurrent RT-CHT ("early" RT) • sequential RT-CHT ("late" RT)	 27.2 19.7	 29.8 20.2	 NG NG
Spiro 2006 [10]	325	40 Gy/ 15 fr / 2.67 Gy, concurrent RT-CHT • "early" RT • "late" RT	 13.7 15.1	 16 22	 NG NG
		Prospective phase II studies			
Bogart 2004 [29]	63	70 Gy/ 35 fr / 2 Gy, concurrent RT-CHT	22.4	2-y 48	NG
De Ruysscher 2006 [30]	27	IFRT: 45Gy/ 30 fr b.i.d./ 1.5Gy, concurrent RT-CHT	21	2-y 33	NG
Van Loon 2010 [31]	60	IFRT: 45Gy/ 30 fr b.i.d./ 1.5Gy, concurrent RT-CHT	19	2-y 35	NG
Komaki 2012 [32]	71	61.2 Gy/1.8Gy (concomitant boost)/ 5 weeks, concurrent RT-CHT	19	2-y 36.6	NG
		Retrospective studies			
Videtic 2003 [11]	215	Concurrent RT-CHT • 40 Gy/ 15 fr / 2.67 Gy (57% of patients) • 50 Gy/ 25 fr / 2 Gy (43% of patients)	14.7 14.7 15.1	2-y 22.7 2-y 27.1 2-y 15.8	NG
Ng 2007 [33]	90	Concurrent RT-CHT (87% of patients) or sequential RT-CHT (13% of patients) • 45 Gy/ 30 fr b.i.d. / 1.5 Gy (63% of patients) • 50 Gy/ 25 fr / 2 Gy (37% of patients)	14.2†	2-y 24.8	NG
Xia 2012 [34]	108	IFRT: • 56 Gy/ 40 fr b.i.d./ 1.4 Gy, alternating RT-CHT (50% of patients) • 55 Gy/ 22 fr / 2.5 Gy, concurrent RT-CHT (50% of patients)	27	2-y 55.1	NG

Continued on next page

Giuliani 2012 [12]	227	Concurrent RT-CHT (80% of patients) or sequential RT-CHT (20% of patients) • 40 Gy/ 15 fr / 2.67 Gy (91% of patients) • 45 Gy/ 30 fr b.i.d. / 1.5 Gy (6% of patients) • 50 Gy/ 25 fr / 2 Gy (3% of patients)	22‡	5-y 25‡	33‡
Bettington 2013 [13]	79	Concurrent RT-CT • 40 Gy/ 15 fr / 2.67 Gy (48% of patients) • 45 Gy/ 30 fr b.i.d. / 1.5 Gy (52% of patients)	21 26	5-y 20 5-y 25	NG
		Present study			
2014	182	Sequential RT-CHT CF-RT: 44- 60 Gy/ 2 Gy, median: 56 Gy A-HYPO-RT: 42 Gy/ 15 fr /2.8 Gy "early" A-HYPO-RT "late" A-HYPO-RT	18 24 27 22	19.1 39.4 40.0 38.7	47.3 34 28.4 45.1

RT: radiotherapy; CHT: chemotherapy; MST: median survival time; LRFR: actuarial locoregional failure risk; IFRT: involved field RT; CF-RT: conventionally fractionated RT; A-HYPO-RT: accelerated hypofractionated RT; fr: fraction; b.i.d: twice daily; y: year; NG: not given.^ : non-platinum-based CHT; : PET-CT-based IFRT; # : for both arms; ″ : no statistically significant difference between the two RT schedules; † : MST for the group of patients treated with prophylactic cranial irradiation – 21 months; ‡ : all RT schedules analyzed together

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