High-dose Radiation Therapy alone for Inoperable Non-small cell Lung Cancer

Experience with Prolonged Overall Treatment Times

Henning Willers, Florian Würschmidt, Henry Bünemann and Hans-Peter Heilmann

From the Hermann-Holthusen-Institute of Radiotherapy at St. George Hospital, Hamburg, Germany (F. Würschmidt, H. Bünemann, H.-P. Heilmann), and Department of Radiation Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, USA (H. Willers)

Correspondence to: Dr. Henry Bünemann, Hermann-Holthusen-Institut für Strahlentherapie, AK St. Georg, Lohmühlenstr. 5, 20099 Hamburg, Germany,Tel.: + 49 40 20982362, Fax: + 49 40 247546.

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The purpose of this study as to determine the impact of overall treatment time on long-term survival after high-dose radiation therapy alone for inoperable non-small cell lung cancer (NSCLC). Between 1978 and 1990, 229 patients with stage I–III disease and Karnofsky Performance Scores of 80–100 received a conventionally fractionated total dose of 70 Gy through a split-course technique. After a first treatment course of 40 or 50 Gy, a restaging was performed and only patients without any contraindications, such as newly diagnosed distant metastases or serious deterioration of performance status, were given a second course. In 83% of patients this break lasted for 4–6 weeks. Overall treatment time ranged between 7 and 24 weeks (median 12 weeks). Median follow-up time was 6.6 years (range 4.0–9.3 years). Actuarial overall survival rates at 2 and 5 years were 28% and 7% respectively. Complete radiological tumor response was observed in 31% of patients, and was found to be the strongest positive predictor of survival with 2- and 5-year rates of 50% and 12% respectively compared with 17% and 4% for patients without complete response. Treatment duration was not found to be a significant prognostic factor in univariate or multivariate analysis. For overall treatment times of 7–11 weeks ($n = 50$), 12 weeks ($n = 79$) and > 12 weeks ($n = 100$), 5-year survival was 4%, 6%, and 8%, respectively ($p = 0.6$).To conclude, in our experience and in contrast to other studies, prolonged overall treatment times in radiation therapy alone for inoperable NSCLC had no negative impact on long-term survival. It is hypothesized that accelerated tumor cell repopulation is absent in a significant number of these patients with the time-factor playing no apparent role for outcome of treatment.

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For squamous cell carcinomas of the upper respiratory and digestive tracts, there have been numerous studies that prolongation of overall treatment time being associated with e.g. reduced local tumor control rates have been reported (1–3). Studies testing altered fractionation regimens have suggested a potential benefit at reduced treatment duration (4, 5). Repopulation of tumor clonogens during therapy has been considered to be responsible for these observations, although there still appears to be some controversial discussion in the literature (6). For non-small-cell carcinoma of the bronchus, there also exist indications that the time factor may play a role for outcome of radiation therapy (4, 7, 8). The time factor does probably not affect the entire treatment population, but only a subgroup of patients whose tumors have the potential for accelerated repopulation during therapy and who, therefore, would benefit from acceleration of treatment (9). Accordingly, patients with slowly proliferating tumors could be treated in longer overall times. The purpose of the present study is to determine the impact of overall treatment time on long-term survival of patients with technically or medically inoperable non-small-cell lung cancer who had been treated at our institution with high-dose split-course radiation therapy. Further details of this treatment regimen as well as prognostic factors and outcome have been reported previously (10).

MATERIAL AND METHODS

The basis of this analysis consists of 229 patients with inoperable non-small cell lung cancer (NSCLC) and favorable performance status, treated at our institution with curatively intended radiation therapy of 70 Gy during the period 1978–1990. Criteria for exclusion of patients from this analysis were: additional chemotherapy or surgical resection, no histological diagnosis of tumor type, Karnofsky performance status (KPS) less than 80%, distant metastases at diagnosis, and T4/N3 disease (since 1987,

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with revision of the staging system). Weight loss was not an exclusion criterion.

Patient and tumor characteristics

The study comprised of 196 males and 33 females with a median age of 67 years (range 27–83 years). Distribution of KPS was: 80% (n = 77), 90% (n = 112), and 100% (n = 40). In 74% of patients, the diagnosis of squamous cell carcinoma was made. Adenocarcinomas, large cell carcinomas and others (without small cell components) were found in 26% of the patients. From 1978 to 1986 (n = 148), the distribution of UICC-stage was: I (31%), II (14%) and III (55%). From 1987 to 1990 (n = 81) it was: I (24%), II (12%) and IIIA (T3/N2) (64%). Diagnostic and staging examinations included: chest x-ray, computerized tomography (CT) of the chest (since 1980), bronchoscopy, abdominal ultrasound or CT, bone scan, and routine laboratory screening. Mediastinoscopy was optional. Brain CTs were performed only if cerebral metastases were suspected.

Treatment characteristics

Radiation techniques have been described in detail previously (10). Briefly, the majority of patients was treated with 8 MeV photons. The initial target volume included the primary tumor with safety margins of about 2 cm and hilar and mediastinal lymph nodes. The supraclavicular fossas were not treated routinely. The boost volume included the tumor bearing regions at the start of treatment with a reduced safety margin of about 1.5 cm. Reference dose was given to the 100% isodose encompassing the target volume. Irradiation was performed through a split-course technique (2 Gy fractions, 5 fractions per week): A first course delivering 40 Gy (as of 1990, 50 Gy were given) was followed by a restaging during a treatment break. The original purpose for introduction of this restaging was to identify patients with newly developed distant metastases, to allow for tumor shrinkage in order to achieve a favorable new target volume, and to have the option to critically reconsider the treatment intention before delivery of the second treatment course of 30 Gy (or 20 Gy as of 1990). Furthermore, the break allowed for recovery of patients in reduced performance status. During the study period 1978–1990, 43 patients who had initially started treatment with curative intent were excluded from the second course because of newly diagnosed distant metastases (35% of patients), serious deterioration of performance status or severe intercurrent disease (30%), no signs of tumor shrinkage or progression (21%) and other reasons (14%). In most patients (83%), duration of break was 4–6 weeks (median 5 weeks; range 0–17 weeks). The corresponding overall treatment times ranged from 7 to 24 weeks (median 12 weeks).

Statistics

The endpoint of analysis was overall survival. Data on local and distant failures could not be obtained for all patients. Normal tissue toxicity has been reported previously and found to be acceptable (10). Time to last follow-up date or death was calculated from start of treatment. For patients alive at last observation date, median follow-up time was 6.6 years (range 4.0–9.3 years). Life-table probabilities were determined with the Kaplan-Meier method and statistical inferences on actuarial curves with the log rank test. The 95% confidence limits were calculated assuming binomial distributions. Multivariate analysis was performed using Cox's proportional hazard regression. All variables were forced into the multivariate model. All comparisons were made with two-sided tests. The risk of obtaining a statistically significant result by chance increases with the number of tests performed (a total of 19 cited in this publication). A conservative way to adjust for this type I error is the Bonferroni method (11). Thus, the new α-level for an individual test, in order to keep the overall significance level of the analysis at 5%, can be estimated to be $p = 0.05/19 = 0.003$.

RESULTS

Actuarial overall survival rates at 1, 2, 3, 4, and 5 years were 62% (95% confidence limits, 56 to 68%), 28% (22 to 35%), 14% (10 to 19%), 10% (6 to 15%) and 7% (4 to 11%) respectively. Complete radiological tumor response (usually documented approximately 4–6 weeks after end of treatment, or later if indicated) was achieved in 31% of patients. Complete response was found to be the strongest positive predictor of survival (Table 1). Patients with this early local control had a 2-year survival rate of 50% (38 to 62%) and a 5-year rate of 12% (6 to 22%), compared with only 17% (11 to 24%) and 4% (1 to 8%) for uncontrolled tumors respectively ($p < 0.001$).

For analysis, overall treatment times were arbitrarily grouped according to the median. The impact of overall time groups of 7–11 weeks (n = 50) vs. 12 weeks (n = 79) vs. > 12 weeks (n = 100) on survival is displayed in the Fig. 1. Survival curves were not statistically different with 5-year rates being 4% (1 to 13%), 6% (2 to 14%), and 8% (4 to 15%) respectively ($p = 0.6$). Table 2 shows the distribution of potential prognostic factors among these time groups. There is some imbalance for variables sex and tumor stage with a slightly higher portion of female and stage I + II patients in the longest time group (> 12 weeks). Since these parameters were not identified as statistically significant prognosticators (Table 1), the relevance of their imbalance remains unclear. When we evaluated the impact of overall treatment time in these subgroups by looking at male patients, stage I + II patients and stage III patients, again, long overall times did not lead to a significant decrease in survival rates (Table 3). Also, further

Table 1

Potential prognostic factors of overall survival after radiation therapy alone for NSCLC

Parameters	No. of patients	Survival rates (%) at		Analysis (p-values)	
		2 years	5 years	Univariate	Multivariate
Complete tumor response					
Yes	72	50	12	<0.001	<0.001
No	157	17	4		
Sex					
Male	196	26	5	0.027	0.030
Female	33	39	18		
Age					
≤67 years*	116	23	3	0.006	0.074
>67 years	113	32	11		
Histology					
SCC	169	27	6	0.9	0.4
Others	60	30	8		
UICC-stage					
I+II	96	29	11	0.1	0.5
III**	133	26	7		
Treatment duration					
≤12 weeks*	129	26	6	0.4	0.9
>12 weeks	100	30	8		
Treatment period					
1978–86	148	30	6	0.8	0.9
1987–90	81	24	8		

SCC = squamous cell carcinoma.
* for variables sex and treatment duration cut-off at the median.
** since 1987 T4/N3 disease excluded.

subgroup analysis (data not shown) and multivariate analysis (Table 1) did not reveal any negative impact of prolonged treatment. Finally, patients with a treatment duration of more than 12 weeks achieved a similar complete response rate (33%) as those treated in a shorter overall time (30%) (Fisher's exact test, p = 0.7).

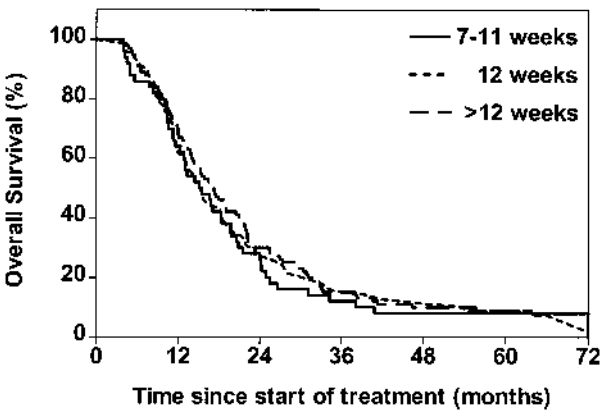

Fig. 1. Impact of overall treatment times of 7–11 weeks (n = 50) vs. 12 weeks (n = 79) vs. >12 weeks (n = 100) on survival after radiation therapy with 70 Gy. Survival curves are not statistically different (p = 0.6, log rank test). Two-year and 5-year survival rates are: 22%, 28%, 30%, and 4%, 6%, 8%, respectively.

DISCUSSION

Five-year survival after radiation therapy for locoregionally advanced inoperable NSCLC has been reported to be less than 10% (12–15). Accordingly, our experience with patients treated with split-course irradiation alone to a total dose of 70 Gy revealed a 5-year survival rate of 7% (95% confidence limits, 4 to 11%). While one approach to improve this poor survival consists of the combination of chemotherapy and radiation in order to reduce mainly the incidence of distant failure (16), another approach is to improve locoregional treatment, e.g. via altered fractionation regimens or conformal therapy (4, 14, 17). The available clinical data are suggestive of a positive correlation between local control and at least short-term survival (12, 14, 15, 17). In the hyperfractionation studies, escalation of total dose to 69.6 Gy has translated into improved 2-year survival rates in the order of 20–35%, although not yet into long-term survival (16–20). The survival rates after conventional irradiation with 70 Gy at our institution are comparable to these results. Furthermore, the present analysis showed improved 2-year survival of 50% (38 to

Table 2

Distribution of potential prognostic factors among overall treatment time groups

Parameter	Overall treatment time groups		
	7–11 weeks (n = 50)	12 weeks (n = 79)	>12 weeks (n = 100)
Age (median & range)	66 (27–79)	66 (44–83)	69 (41–81)
Sex (%)			
Male	88	91	80
Female	12	9	20
KPS (%)			
100	16	18	18
90	52	44	51
80	32	38	31
Histology (%)			
SCC	66	72	79
Others	34	28	21
UICC-stage (%)			
I+II	34	39	48
III	66	61	52
Complete tumor response (%)			
Yes	34	28	33
No	66	72	67

KPS = Karnofsky performance status, SCC = squamous cell carcinoma.

62%) and 5-year survival of 12% (6 to 22%) for patients in whom a complete radiological response after treatment was observed.

While realizing the importance of local treatment outcome for survival, it has to be considered whether, and as to which extent, a potential tumor cell repopulation during therapy adversely affects survival. Cox et al. (7) retrospectively analyzed the consequences of treatment interruptions in the RTOG Hyperfractionation Protocol 83-11. The adverse effect of a treatment delay of more than four days on survival was seen entirely in those patients who received at least 69.6 Gy. This was most pronounced in 197 patients with favorable prognostic factors (KPS 90-100, weight loss $< 5\%$, no N3-stage): All 22 patients with delays were dead after two years. In a retrospective analysis on 153 patients, Koukourakis et al. (8) calculated a reduced 2-year local progression-free probability with increasing treatment duration (up to 10 weeks). Vice versa, the results of CHART, delivering 54 Gy at 1.5 Gy three times daily over 12 consecutive days, have suggested a potential benefit from reduction of treatment duration (4, 21). Results of the phase III trial demonstrated a 9% higher survival for the CHART arm compared with conventional arm delivering 60 Gy at 2 Gy fractions, i.e. 29% vs. 20% after 2 years (4).

In contrast, our experience with overall treatment times of up to half a year in a group of prognostically favorable patients failed to show any suggestion of a negatively affected outcome. One would expect that such long treatment times with presumably considerable repopulation of tumor clonogens during therapy would bring the long-term survival rates down to 0%. It is unlikely that this difference had been overlooked in our dataset of 229 patients with a median follow-up time of more than 6 years. For example, the power of detecting a difference in 5-year survival rates of 6% versus 0% can be estimated to be 0.73 (based on overall time groups 7–12 weeks and >12 weeks in Table 1 respectively, with all patients evaluable and at $\alpha = 0.05$). It is tempting to speculate that accelerated tumor cell repopulation does not occur in a large number of patients leading to these unexpectedly high survival rates. However, we cannot exclude the possibility that exclusion of patients during treatment breaks in statistical analysis contributes to the favorable prognosis of patients receiving full radiation dose over extended periods of time. Also, we are fully aware of the problems generally associated with analysis of clinical data (11, 22, 23). Therefore, any conclusions should be drawn carefully.

Our results are consistent with the literature data showing that curative radiation therapy alone for inoperable NSCLC generally yields 5-year survival rates of about 6–8%. In our experience and in contrast to other studies, however, prolonged overall treatment times had no negative impact on long-term survival. It is hypothesized that accelerated tumor cell repopulation is absent

Table 3

Impact of treatment duration: subgroup analysis

Parameters		Survival rates (%) at	
Overall time groups		2 years	5 years
Males			
7–11 weeks	n = 44	20	7
12 weeks	n = 72	25	6
>12 weeks	n = 80	29	8
UICC-stage I+II			
7–11 weeks	n = 17	29	6
12 weeks	n = 31	26	10
>12 weeks	n = 48	31	15
UICC-stage III			
7–11 weeks	n = 33	18	9
12 weeks	n = 48	29	8
>12 weeks	n = 52	29	4

$p > 0.5$ in every subgroup.

in a significant number of these patients with the time-factor playing no apparent role for outcome of treatment. It will be very interesting to see whether our currently employed treatment schedule of delivering 70 Gy over 7 weeks without a planned break will yield increased survival rates when compared with the historic split-course regimen.

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