EXCLUSIVE RADIOTHERAPY FOR NON SMALL CELL LUNG CANCER. A RETROSPECTIVE MULTICENTRIC STUDY

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SUMMARY

Purpose: to evaluate the daily practice of management of early inoperable lung cancer (stage I).

Materials and methods: The analysis was based on a questionnaire which was sent to participated centers. Between 1982 and 1994, 123 patients with an early stage I inoperable lung cancer were treated with definitive irradiation in the different institutions. The survival distributions were estimated by the Kaplan-Meier method. The following covarties were analyzed: age, gender, Karnofsky status, symptoms, diagnostic work-up, T stage, tumour size, tumour location, histology, respiratory and cardiac contra-indication. The univariate analysis was performed using log-rank test. Cox regression models were used to find the independent prognostic factors.

Results: The 2 and 5-year survival rates were 34% and 8% respectively. The 5-year local failure rate was 42 % for T1 and 82% for T2. In a multivariate analysis, the most important prognostic factors for survival were the performance status and the stage. After adjustment for these two covariates, the total dose delivered had no impact for the range of doses used in this series.

Conclusions: Our poor data outlined the needs for better radiation technique and for a better staging system.

INTRODUCTION

The management of early inoperable lung cancer (stage I, II) remains a controversial issue between tenants of an aggressive approach aiming at cure and those in favor of a more conservative approach, from a wait and see policy to moderate doses of radiotherapy. Furthermore, even after a curative course of radiation, results vary between different series leading from an optimistic view (radiation may be a curative modality) to a pessimistic view (only surgery may cure such patients). This was well illustrated by several surveys on lung cancer management [22]. Indeed, 5-year survival rates vary from 5 to 31% for stage I disease [3-6,8,9,12-16,19,20,21,24]. Also, there are still some questions related directly to the radiation treatment modality: total doses, volume to be treated, the role of elective mediastinal irradiation, and the place for conformal 3D radiotherapy or endoluminal brachytherapy.

During the last years, our network of «rare disease» conducted several reviews. The multicentric character of our systematic database allows us to partially avoid a possible bias of patient selection. This approach may more reflect the daily practice of radiation oncology as we registered in our study all cases treated in the participating institutions.

MATERIAL AND METHODS

A questionnaire was sent to participants of our network. Criteria were to have a stage I non-small cell lung cancer treated between 1982 and 1994 by exclusive external radiotherapy without any chemotherapy and no prior history of cancer.

Survival duration was calculated from the first day of irradiation. The survival distributions were estimated by the Kaplan Meier method. The same method was used to calculate the risk of local failure. The impact of some covariates was

analyzed: age (≤70 years vs. > 70), gender, Karnofsky index (≤ 70 vs. 70), symptoms (No vs. yes), diagnostic work-up (local only only vs. distant), T1 vs. T2, tumor size (<2cm, 2-4, >4 cm), tumor location (right versus left), histology (squamous vs. other), respiratory (no vs. yes) and cardiac contra-indication (no vs. yes). Univariate analysis for these covariates was done by non-parametric log rank tests. Cox regression models were used to determine the independent prognostic value of these covariates. A forward stepwise method was applied to select the variables to be included in the final model. The distribution of the time to local failure and of the survival without relapse was also estimated with an actuarial method. All reported p values are twotailed, with a level of significance of 5%.

This series included 123 patients, 112 men and 11 women, with a mean age of 71.8 years ranging from 50 to 88 years). Contraindications to surgery were poor respiratory functions (60 patients), old age (34 patients), cardiac function (20 patients), and general physical conditions (12 patients) but also patient refusal (9 patients). These co morbidities had an impact on their performance status: 29 had a Karnofsky index inferior to 80 and 8 patients had severe limitation with an index below 50. There were 38 T1NO and 85 T2NO tumors. For the latter, tumor size varied from 3 to 10 cm. The initial staging procedure was different from one center to another: chest CT was performed in almost all patients (106 patients) but only 53 patients had a work-up including an upper abdominal investigation by CT or echography, 25 had a brain CT or MR and 29 patients a bone scintigraphy.

Patients were treated with different radiation schedules according to the local policy including split course, continuous daily radiation doses and an hyperfractionated schedules with a 2 week interruption between the 3 radiation courses. Continuous daily irradiation delivered doses between 1.8 and 4 Gy per fraction: total physical dose and fraction size are listed in *Table 1*. The dose were asked to be reported according to the ICRU definition. For the purpose of this study, the doses were converted in tumor equivalent doses for 2 Gy per fraction without taking into account the treatment duration (10). For the 2 Gy equivalent radiation doses, 2 patients received less than 45 Gy, 56 between 46 and 59 Gy and 65 patients more than 60 Gy. Ten out of 38 T1N0 received less than 60 Gy and only 37 patients out of the 85 T2N0 received 60 Gy or more.

Concerning the clinical target volume, there was a wide variation between the centers and the data for the different possible lymph node areas (ipsi and contralateral hilum, lower and upper mediastinum, supraclavicular lymph nodes) were not always available: only the information for the mediastinum and the supraclavicular lymph nodes were well reported. When an elective mediastinal irradiation was performed, the volume was later reduced to boost only the gross tumor volume using oblique or lateral fields. Seventy-two patients had an irradiation including an elective mediastinal irradiation to a dose at least of 45 Gy, 10 received less than 45 Gy and 41 patients had no mediastinal irradiation. Only 18 patients had an irradiation of the supraclavicular nodes.

Table 1. Relation between total dose and fraction size.

Fraction size in Gy

Total Dose (Gy)	< 2	2 - 2.2	2.3 - 2.6	2.7 - 2.9	3 - 3.5	4	
< 40		1			1		2
40 - 49			1		1	9	11
50 - 52	1		2		5		8
53 - 57	1	6	1	28			36
58 - 62	1	12	1		37		51
63 - 67		7	1				8
68 - 74		6	1				7
	3	32	7	28	44	9	123

RESULTS

The 2 and 5-year survival rates were respectively 34% and 8% and the 2 and 5-year survival without relapse 29% and 7%. The 2-year survival rate dropped from 52% for T1 tumor to 21% for T2 lesions and the 5-year survival rate from 13% to 1%. Altogether 6 patients were alive 5 years after the treatment including 5 T1 and 1 T2. No difference was observed at 2 years between patients receiving less than 60 or more than 60 Gy: the 2 year survival rates were 30% for doses between 46 and 59 Gy and 32% for doses of 60 Gy or more.

Local recurrence as component of failure was observed in 36 patients while distant metastases were seen in 24 patients. No difference was observed in term of locoregional relapse between T1 and T2 while T2 had more distant metastases (18.3% vs. 9.8%) *(Table 2)*. If the risk of local recurrence is expressed in an actuarial way, the 5-year local failure rates were respectively 42% for T1 and 82% for T2 *(Fig. 1).* In this series, we did not observe any influence of the total dose delivered either for the whole series, T1 or T2. The total dose of irradiation had no impact on the tumor control for the whole series, T1 or T2 tumor *(Table 3).* However, only one relapse was observed amongst the 11 patients with a tumor smaller than 2 cm, all had received doses in excess of 55 Gy.

A mediastinal relapse was observed in 6 cases either alone (one patient) or with a local relapse (5 patients). The patient with only a mediastinal relapse had received less than 45 Gy to the mediastinum. Amongst the 5 patients with a local and mediastinal relapse, three had no mediastinal irradiation and 2 had received more than 45 Gy to the mediastinum. There was no single supraclavicular failure.

In univariate analysis, the only significant prognostic factors on survival were the performance status, the stage and the tumor size; gender and tumor localization had also an influence with better observed survival for female and right side lesions without reaching statistical signify-cation *(Table 4).* In a multivariate analysis, only performance status (p= 0.003) and stage (p=0.02) were important prognostic factors. The total dose had no influence on the survival.

Table 2. Stage I lung cancer : pattern of relapse.

	All	T1	T2
	123	38	85
Local	25	6	19
Local + Mediastinal	5	2	3
Local + Distant	4	2	2
Mediastinal only	1		1
Distant met.	19	6	13
Loc+Mediastinal+Met.	1		1

Table 3. Locoregional relapses versus equivalent 2 Gy total doses (numbers in parentheses refers to the total number of patients).

	0-45 Gy	46-59 Gy	60 Gy or more
All	50% (1/2)	20% (11/56)	37% (24/65)
T1	0	30% (3/10)	25% (7/28)
T2	50% (1/2)	18% (8/46)	43% (16/37)

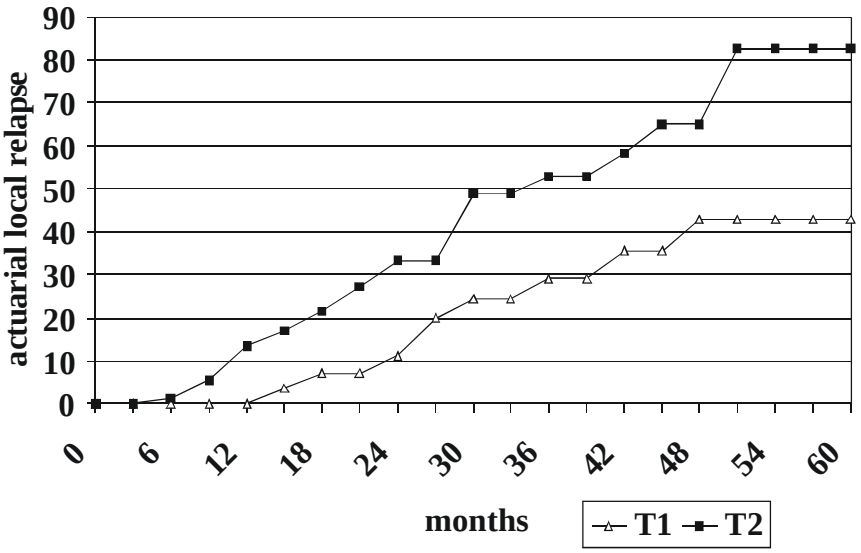

Fig. 1. T1 - T2 NO NSC LUNG Ca: Exclusive RT Actuarial Risk of Local Relapse.

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Table 4. Prognostic factors for stage I non small cell lung cancer: an univariate analysis.

Covariate	N	2 Years rate	5 Years rate	p
Age				
≤ 70 yrs	56	38%	7%	0.45
> 70	65	30%	8%	
Sex				
Male	110	31%	7%	0.10
Female	11	55%	14%	
Karnofsky				
≤ 70	29	21%	3%	0.01
> 70	65	38%	9%	
Symptoms				
No	66	33%	10%	0.62
Yes	28	41%	5%	
Diagnostic work-up				
Local only	60	35%	4%	0.99
Distant test	61	32%	15%	
Staging				
T1	38	52%	16%	< 0.01
T2	83	25%	4%	
Tumor size				
< 2 cm	23	44%	28%	0.02
2 - 4 cm	62	37%	4%	
> 4 cm	36	21%	6%	
Tumor localisation				
Right	60	27%	3%	0.12
Left	59	38%	13%	
Histology				
Squamous	90	30%	9%	0.63
Other	31	43%	4%	
Respiratory contra-indic.				
No	57	30%	20%	0.21
Yes	60	39%	9%	
Cardiac contra-indic.				
No	97	37%	8%	0.39
Yes	20	25%	13%	

DISCUSSION

This series includes unselected patients treated in different institutions over Europe and is a good illustration of the daily practice in the management of early non-small cell lung cancer. Those results remain within the limits of a large review made by the Cochrane group: the 2-year survival rates range from 22 to 72% and the 5-year survival rate from 0 to 42%. Results may appear very dismal in contrast to some series from single institutions but outlined the pessimistic point of view of the community when dealing with inoperable lung cancer *(Table 5)* [3-9,12 -14,16,19,20,24].

Table 5. Irradiation for early NSC lung.

Authors	N° of pts	Radiation scheme Gy	weeks	Elective nodal irradiation	Survival rate (%) 3 years	5 years
Burt et al (1989)	133	50 - 55	3	No		20
Cheung et al (2000)	102	48	4	No	35	16
Coy and Kennely (1980)	141	50 - 57	4	Yes	18	10
Dosoretz et al (1992)	152	50 - 70	5 - 7	Yes		10
Gauden et al (1995)	347	50	4	Yes		27
Gouders et al	123	40 - 70		Yes (59%)	18	5
Graham et al (1995)	150	60	6	Yes		14
Krol et al (1996)	108	60 - 65	6 - 7 s	No	31	15
Morita et al (1997)	66	55 - 74	6 - 7	Yes		31
	83			No		15
Noordijk et al (1988)	50	60	6 - 7 s	No		16
Sandler et al (1990)	77	60	6	Yes	21	17
Sibley et al (1998)	141	64	5 - 7	Yes (73%)		13
Slotman et al (1996)	31	48		No	42	8
Zhang et al (1989)	44	55 - 70	6 - 7	Yes		16
(s = split course)						

Why are the results so dismal in contrast to some of the reported series in literature? Several explanations are possible related either to the initial staging procedure or to the radiation technique itself. Indeed in the current series, many patients had a staging procedure limited to a chest CT. It was very rare to perform a brain CT or MR and even an upper abdominal investigation was only performed in one out of three patients. Those findings are in good concordance with a survey of radiation practice performed in 1994: in daily practice CT of the brain was performed in less than 50% of the centers with a great variation between countries (from 62% in France to 5% in Great Britain) [22].

The T stage or the tumor size is an important prognostic factor. In the current series, the 5-year survival rate dropped from 13% for T1 to 1% for T2N0. This is in agreement with most published series. There is also a need for better defining T2: in the current series, T2 included tumors as large as 10 cm. This may explain partially the poor survival and local control and outlines the necessity to move slowly away from the classical TNM classification: tumor volume should be taken into account especially when dealing with radiation treatment. The second explanation may be the suboptimal radiation technique: doses vary from 32 to 74 Gy while some patients were even treated with a split course schedule. In the current

series, higher biological dose yield better survival and local control for T1N0 tumor. It is interesting that improving the radiation schedule may lead to better survival: in the CHART (Continuous, Hyperfractionated, Accelerated, Radiation Treatment) randomized trial, an analysis of stage I disease showed a 4-year survival rate of 12% after 60 Gy in 6 weeks and 18% for the CHART protocol [1,17]. Another approach could be to use a chemoradiation program either with an induction schedule or a concurrent approach. Several trials have demonstrated a benefit due to an improvement in the control of the metastatic disease with an induction schedule or due to a better local control when a concurrent approach is used [1,7,11,18]. However, most patients treated in those trials have usually stage III disease, a good performance status and a complete initial staging evaluation.

The clinical target volume remains a controversial issue: should the irradiation be limited to the gross tumor volume or should an elective mediastinal irradiation be performed? In the paper of Morita including 149 patients there was some suggestion for better survival for patients receiving mediastinal irradiation: the 5-year survival rate rose from 15% to 31% in case of elective mediastinal irradiation [13]. Nevertheless, this was partially related to the initial tumor location (near to the mediastinum) and to the histological subtype (adenocarcinoma vs. squamous cell ca). Sibley et al noticed an improved local control 2 years after a prophylactic mediastinal irradiation without better overall survival [19]. In different series, there was no elective mediastinal irradiation and mediastinal failures were rare: Slotman et al reported 3 locoregional relapses in a series of 31 patients, Krol et al 4 out of 50 patients and Cheung et al 4 out of 102 patients [4,12,20]. Furthermore, inoperable stage I patients have often very poor lung functions and the volume of irradiation is mostly determined by the patient lung function. This volume may also be influenced by the quality of the initial staging procedure. Mediastinosocopy was not routinely performed and the radiation oncologist based his judgment on the chest CT. In the future PET scan may be a useful tool to help us to better delineate our target volume: 73 patients had a CT, a PET scan and a surgical resection. Radiation volumes were defined by CT and PET scans and compared to the surgical data; PET changed the CT defined volume in 45 out of 73 patients and did not include in 8 cases all the positive lymph nodes (5 misinterpretations of lymph node localization and 3 cases of minimal disease) [23].

Tumor control is directly related to the total dose and the tumor size whereas the late morbidity is directly influenced by the total dose, the fraction size and the volume irradiated. Tolerance of normal lung is one of the limiting factors when irradiating a patient suffering from lung cancer. This is particularly the case for patients with a contraindication to surgery due to poor lung functions. On the other side, the probability of local control is directly influenced by the total dose delivered. So, this group of patients should be a good candidate for 3D conformal radiotherapy.

In conclusion, the poor results achieved in the current series of patients just reflect the lack of an aggressive management including a suboptimal initial workup and radiation technique. The data available in literature shows clearly that radiation may be a curative modality providing an adequate radiation schedule with the aim of delivering biological equivalent doses in excess of 60 Gy, while keeping in mind the tolerance of normal tissues. Better radiation techniques are mandatory for early T1N0 tumors.

REFERENCES

1. Arriagada R, Le Chevalier T, Quoix E, Ruffie P, de Cremoux H, Douillard JY, et al. Effect of chemotherapy on locally advanced non-small lung carcinoma: a randomized study of 353 patients. Int J Radiat Oncol Biol Phys 1991;20: 1183-90.

2. Bentzen SM, Saunders MI, Dische S, Parmar MK. Updated data for CHART in NSCLC: further analyses. Radiother Oncol 2000;55:86-7.

3. Burt PA, Hancock BM, Stout R. Radical radiotherapy for carcinoma of the bronchus: an equal alternative to radical surgery? Clin Oncol 1989;1:86-90.

4. Cheung PC, Mackillop WJ, Dixon P, Brundage MD, Youssef YM, Zhou S. Involved-field radiotherapy alone for early stage non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2000;48:703-10.

5. Coy P, Kennelly GM. The role of curative radiotherapy in the treatment of lung cancer. Cancer 1980;45:698-702.

6. Dosoretz DE, Katin MJ, Blitzer PH, Rubenstein JH, Salenius S, Rashid M, et al. Radiation therapy in the management of medically inoperable carcinoma of the lung: results and implications for future treatment strategies Int J Radiat Oncol Biol Phys 1992;24:3-9.

7. Furuse N, Fukuoka M, Kawahara M, Nishikawa H, Takada Y, Kudoh S, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine and cisplatin in unresectable stage III non-small cell lung cancer. J Clin Oncol 1999;17:2692-9.

8. Gauden S, Ramsay J, Tripciony L. The curative treatment by radiotherapy alone of stage I non-small cell lung cancer. Chest 1995;108:1278-82.

9. Graham PH, Gebski VJ, Langlands AO. Radical radiotherapy for early nonsmall cell lung cancer Int .J Radiation Oncol Biol Phys 1995;31:261-6.

10. Joiner MC, Bentzen SM. Time-dose reltionships: the linear-quadratic approach in Basic Clinical Radiobiology G. Steel (Ed) Arnold London page 126, 2002.

11. Komaki R, Scott CB, Sause WT, Johnson DT, Taylor SG, Lee JS, et al. Induction cisplatin/vinblastine and irradiation versus irradiation in unresectable squamous cell lung cancer: failure patterns by cell type in RTOG 88-08/ECOG 4588 Int J Radiat Oncol Biol Phys 1997;39:537-44.

12. Krol ADG, Aussems P, Noordijk EM, Hermans J, Leer JWH. Local irradiation alone for peripheral stage I lung cancer: could we omit the elective regional nodal irradiation ? Int J Radiat Oncol Biol Phys 1996;34:297-302.

13. Morita K, Fuwa N, Suzuki Y, Nishio M, Sakai K, Tamaki Y, et al. Radical radiotherapy for medically inoperable non-small cell lung cancer in clinical stage I: a retrospective analysis of 149 patients. Radiother Oncol 1997;42:31-6.

14. Noordijk EM, Van Poest Clement E, Hermans J, Wever AMJ, Leer JWH. Radiotherapy as an alternative to surgery in elderly patients with resectable lung cancer. Radiother Oncol 1988;13:83-9.

15. Rowell NP, Williams CJ. Cochrane Lung Cancer Collaborative Review Group Radical radiotherapy for stage I/II non-small cell lung cancer in patients not sufficiently fit for or declining surgery (medically inoperable): A systematic review Lung Cancer 2000;29 suppl1:165-6.

16. Sandler HM, Curran WJ, Turrisi AT. The influence of tumor size and pretreatment staging on outcome following radiation therapy alone for stage I non small cell lung cancer. Int J Radiat Oncol Biol Phys 1990;19:9-13.

17. Saunders M, Dische S, Barrett A, Harvey A, Griffiths G, Parmar M0. Continuous, hyperfractionated, accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small cell lung cancer: mature data from the randomised multicentre trial. Radiother Oncol 1999;52:137-48.

18. Schaake-Koning C, van den Bogaert W, Dalesio O, Feesten J, Hoogenhout J, Van Houtte P, et al. Effects of concomitant cisplatin and radiotherapy on inoperable non-small cell lung cancer. N Eng L J Med 1992;326:524-30.

19. Sibley GS, Jamieson TA, Marks LB, Anscher MS, Prosnitz LR. Radiotherapy alone for medically inoperable stage I non-small-cell lung cancer: the Duke experience. Int J Radiat Oncol Biol Phys 1998; 40:149-54.

20. Slotman BJ, Antonisse IE, Njo KH. Limited field irradiation in early stade (T1-2,N0) non-small cell lung cancer. Radiother Oncol 1996;41:41-4.

21. Talton BM, Constable WC, Kersh CR. Curative radiotherapy in non-small cell lcarcinoma of the lung. Int J Radiat Oncol Biol Phys 1990;19:15-21.

22. Van Houtte P, Gregor A, Philips P. An international survey of radiotherapy practice for radical treatment of non-small cell lung cancer. Lung Cancer 1994;11: 129-38.

23. Vanuytsel LJ, Vansteenkiste JF, Stroobants SG, De Leyn PR, De Wever W, Verbeken E, et al. The impact of 18 F-fluoro-2-deoxy-D-glucose positron emi-ssion tomography (FDG-PET) lymph node staging on the radiation treatment volumes in patientswith non-small cell lung cancer. Radiother Oncol 2000;55:317-24.

24. Zhang HX, Yin WB, Yang ZY, Zang ZX, Wang M, Chen DF, et al. Curative radio-therapy of early operable non small cell lung cancer. Radioth Oncol 1989;14:89-94.