ORIGINAL PAPERS

DOSE ESCALATION USING 3-DIMENSIONAL CONFORMAL RADIOTHERAPY IN MANAGEMENT OF NON-SMALL CELL LUNG CANCER; PRELIMINARY RESULTS ON 22 PATIENTS

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ABSTRACT

Purpose: To determine the feasibility of radiation dose escalation > 70 Gy to Gross Tumour Volume (GTV) using 3-Dimensional Conformal Radiotherapy (3-DCRT).
Methods and Materials: From December 1997 to November 1998, 22 patients with non-small cell lung cancer (NSCLC) were included. Tumour stage was I in 3 cases, II in 6 cases, III in 10 cases, and there were 3 locoregional recurrences after surgery. A 3-D treatment planning system with BEV was used for all patients. Patients underwent limited elective nodal irradiation of 56 Gy. The GTV with 1 cm margin received a dose of at least 70 Gy. Acute and late toxicity were estimated according to the RTOG/EORTC score.
Results: The mean follow-up was 217 (80-360) days. Seventeen patients received 74 Gy, two had 72 Gy, and one had 70 Gy. In one patient with the largest irradiation volume a toxic death due to radiation pneumonitis occured. Except this fatality acute toxicity was acceptable. Seventeen patients were evaluable for response. There were 3 (18%) complete responses, all in patients staged I and II, seven (41%) partial responses, 5 (29%) non-responses and two (12%) local progressions. Two local progressions and two distant failures occured in stage III patients.
Conclusions: Dose escalation >70 Gy using 3-DCRT in management of NSCLC is feasible with acceptable acute toxicity.

INTRODUCTION

Radiotherapy is one of the major modalities used in the treatment of non-small cell lung cancer (NSCLC), however a local control rate following conventional radiation therapy remains poor. In view of the poor efficacy of radiotherapy in management of NSCLC there is a clear need for improvement in the therapeutic ratio of this method. Radiation dose escalation is one of the means used for enhancement of the local control disease, but this technique may cause a prohibitive toxicity. Three-dimensional conformal radiotherapy (3-DCRT) enhances the therapeutic ratio by increasing the probability of cure due to increased target dose and decreased toxicity through minimizing the radiation dose to healthy tissues. Recent technological advances in the areas of treatment planning and delivery systems have made possible to achieve both effects in several clinical studies (Emami et al., 1991; Armstrong et al., 1997; Robertson et al., 1997; Derycke et al., 1997). In this study the possibility of implementation of a 3-DCRT in view of dose escalation in management of NSCLC has been investigated.The purpose was to determine the feasibility of radiation dose escalation >70 Gy to gross tumour volume (GTV) using a 3-DCRT. In addition, the survival rate and the pattern of locoregional failure have also been examined.

MATERIAL AND METHODS

Twenty two patients, 6 females and 16 males, aged 50-75, numbered 1 to 22, were included in

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the study between December 1997 and November 1998. The histology type was found to be squamous cell carcinomas in 13 patients, bronchio-alveolar carcinoma in one patient, large cell carcinomas in two patients and 6 non-small cell carcinomas without further specification. Tumour stage according to the TNM UICC classification was I in 3 cases, stage II in 6 cases, IIIA in 7 cases, IIIB in 3 cases. Three locoregional recurrences were observed after surgery (rT2N1M0, rT0N2M0, rT3N2M0). Table 1 shows the number of patients, age, sex, histology, stage, performance status and weight loss. Ten patients were found to be inoperable because of medical problems (cardio-pulmonary diseases), and 12 patients were unresectable. Patients with stage III of the disease were not eligible for chemo-radiotherapy protocols, which is a routine treatment policy in these cases in our department, because of significant medical problems involved. Pre-treatment evaluation included a physical examination, complete blood count, chest X-ray, bronchoscopy, CT scan of the chest and upper abdomen, CT or MRI of the brain and bone scan. The clinical trial was approved by the Ethical Committee of the Institute, with prior informed consent of all patients having been obtained.

No of patient, age, sex	Histology	Stage	KPS	Weight loss
P1, 72, M	NSCLC	IIIA	80	NO
P2, 75, M	SCC	IIIB	80	<10%
P3, 50, F	NSCLC	IIIA	80	<10%
P4, 70, M	SCC	rIIIA	90	NO
P5, 74, M	NSCLC	II	90	<10%
P6, 52, M	SCC	IIIA	70	>10%
P7, 63, M	SCC	IIIA	80	<10%
P8, 60, M	SCC	IIIB	90	NO
P9, 69, F	SCC	I	80	<10%
P10, 69, M	BAC	rIIIA	90	NO
P11, 67, M	NSCLC	I	80	NO
P12, 67, F	NSCLC	II	80	<10%
P13, 61, M	SCC	II	90	<10%
P14, 53, F	SCC	II	80	<10%
P15, 67, F	LCC	IIIA	70	>10%
P16, 68, M	SCC	IIIA	80	>10%
P17, 64, M	LCC	IIIB	80	NO
P18, 73, M	SCC	I	70	NO
P19, 66, M	SCC	II	80	<10%
P20, 63, M	SCC	IIIA	70	>10%
P21, 69, M	SCC	rII	70	>10%
P22, 66, F	NSCLC	II	90	NO

Abbreviations: M=male, F=female, NSCLC= non-small cell lung cancer without specification, SCC= squamous cell carcinoma, BAC=bronchio-alveolar carcinoma, LCC= large cell carcinoma

Table 1. Patient's characteristics

A 3-D treatment planning system (TMS-Helax) was used for all patients after computed tomography including the entire lung volume. CT scans were done at 1 cm intervals through regions with no visible involvement and at 5 mm slices through the GTV. Three different clinical target volumes were contoured, of which the PTV1 was the largest one and included PTV2, which in turn included PTV3, as described below. PTV1 included GTV and the region of subclinical disease (uninvolved ipsilateral hilar, mediastinal, subcarinal nodes, - generally ipsilateral groups 2,3,4,5,6,7,10 and heterolateral groups 4 for the left side and heterolateral group 4, 5 for the right side according to the classification of AJCC and ATS) with 1-1.5 cm margins within lungs and 2 cm margins within mediastinal tissues. PTV2

included GTV, uninvolved ipsilateral hilar (group 10), subcarinal (group 7), lower paratracheal (group 4) and aortico-pulmonary window nodes (group 5) with 1 cm margins within lungs and 2 cm within mediastinum. PTV3 consisted of GTV with 1 cm margins. GTV was defined as tumour visible at CT and bronchoscopy plus the lymph nodes with a diameter on CT scans larger than 2 cm. PTV1 received a dose of 40-44 Gy, and the dose to PTV2 reached 56 Gy. PTV3 was irradiated to the highest possible dose of not less than 70 Gy. The dose was prescribed to the isocentre, located at the geometric centre of the PTV. Specific dose constraints for critical structures were observed. The dose to the spinal cord did not exceed 50 Gy. At least 50% of the lung volume received less than 20 Gy and the mean dose for both lungs outside the PTV3 was inferior to 20 Gy. The length of the oesophagus receiving over 60 Gy did not exceed 10 cm. The entire heart volume received less than 40 Gy. The critical structures tolerance was inferred from the DVH analysis. The maximum rate of dose inhomogeneity for PTV3 was set at 10%. Beam incidences were established using the BEV. Optimization tools were used for each stage of the treatment (irradiation of each PTV) in order to meet the criteria for tolerance and deliver the maximum achievable dose to PTV3. Custom blocks were used to minimise the dose delivered to healthy adjacent tissues. Figure 1 shows example of added dose plan in coronal section. Figures 2, 3, 4 show dose distribution in transversal section for PTV1, PTV2 and PTV3 respectively. The dose per fraction was 2 Gy (corrected for tissue inhomogeneity), delivered once a day, five times per week. In all patients, 4 MV photons were used. Port films checks were made every week. All patients were evaluated once per week during treatment. During the follow-up, patients were seen initially 6 weeks after treatment, and then every 3 months. Evaluation included physical examination with assesement of the Karnofsky Performance Status (KPS) and measurements of weight, complete blood counts, liver functions tests and chest X-rays. CT of the thorax was performed within three months after the end of radiotherapy and then every 6 months. Acute and late toxicity was estimated according to the criteria of the RTOG/EORTC scoring system (Cox et al., 1995).

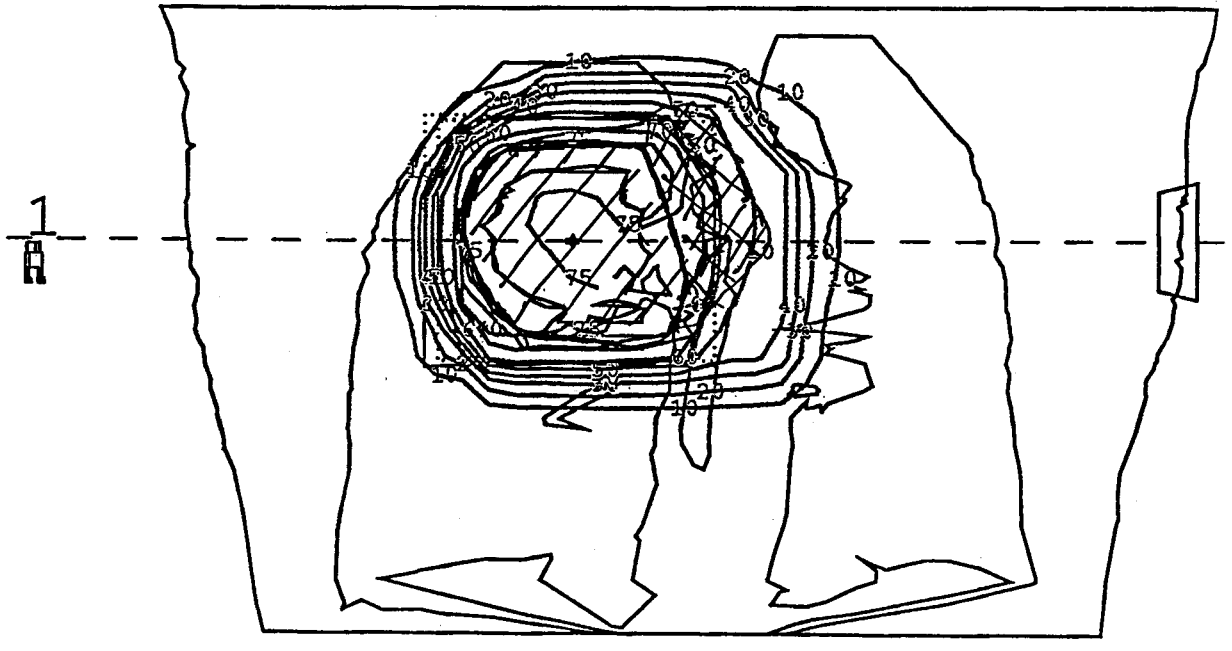

Fig. 1. Added dose plan for PTV1, PTV2, PTV3; example of dose distribution in coronal section

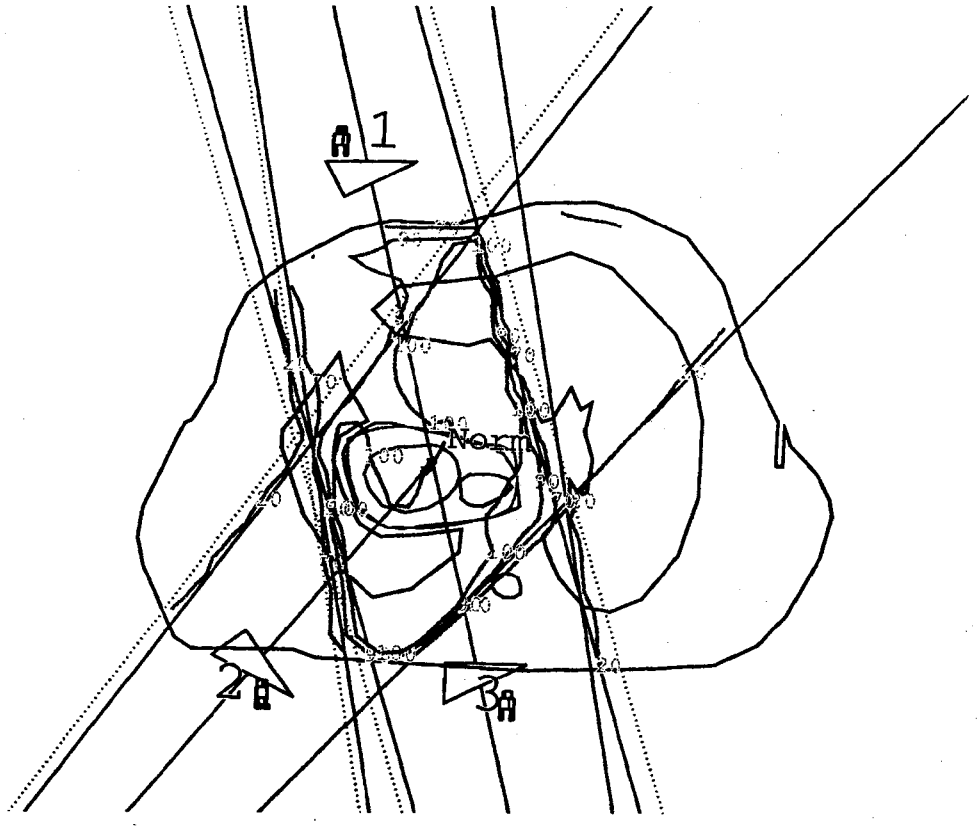

Fig. 2. Dose distribution for PTV1 in transversal section.

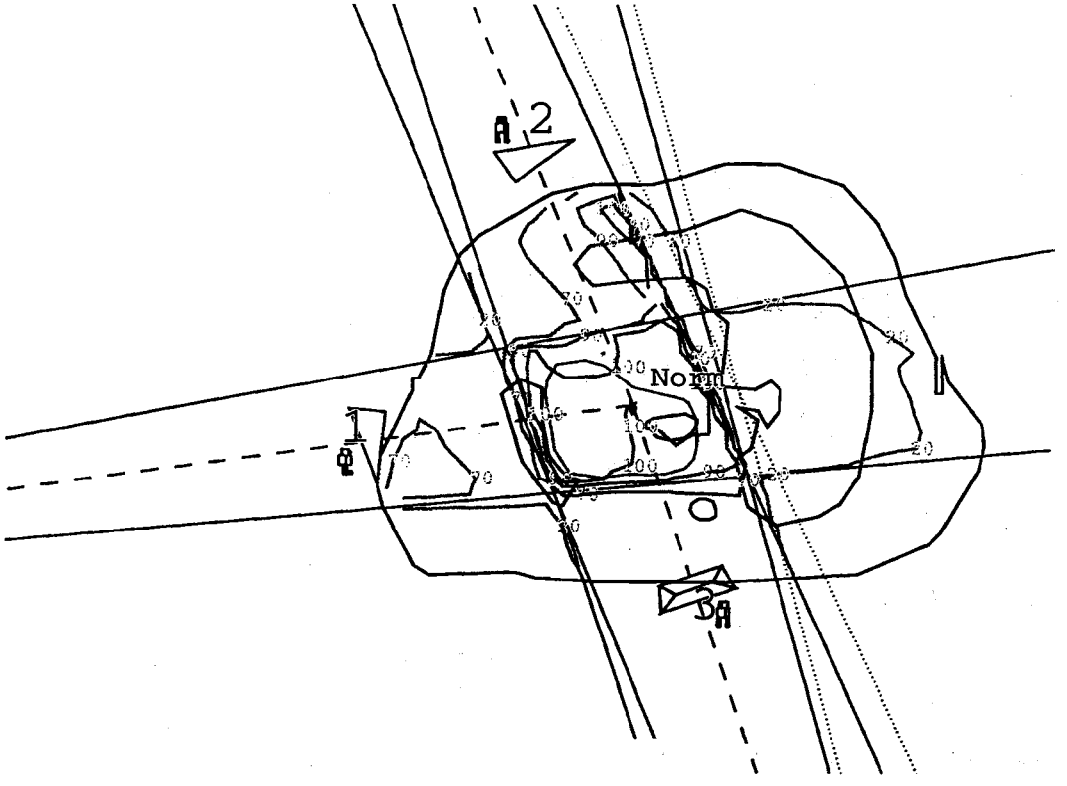

Fig. 3. Dose distribution for PTV2 in transversal section.

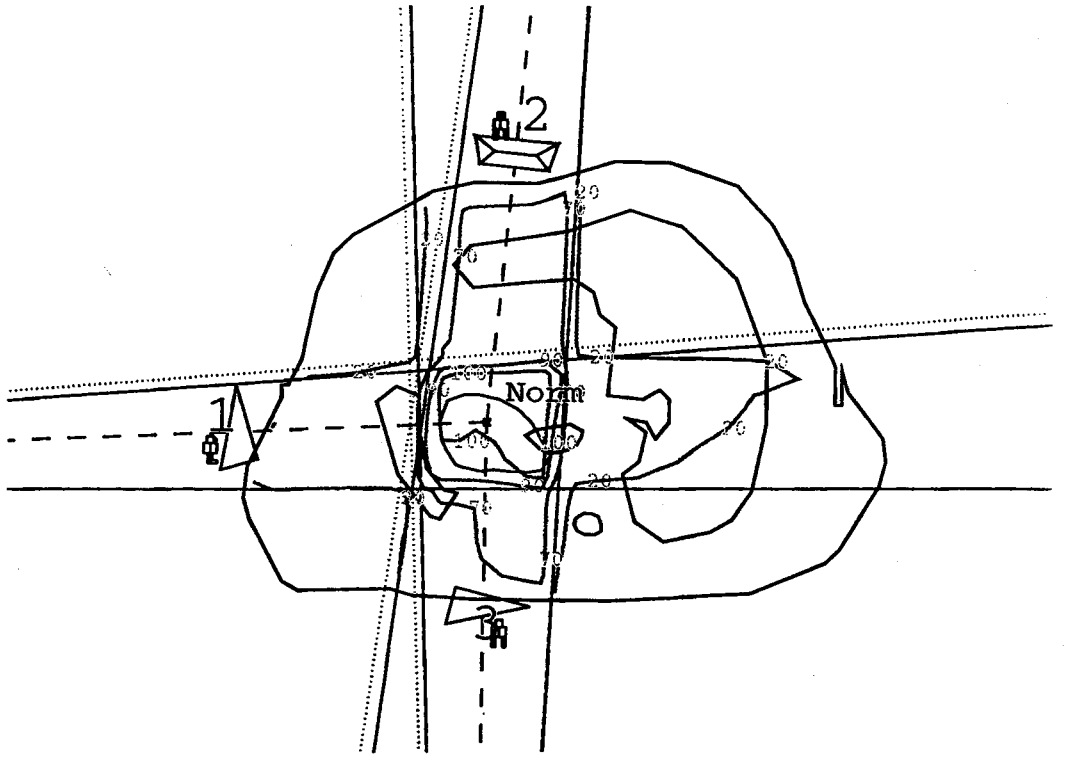

Fig. 4. Dose distribution for PTV3 in transversal section.

RESULTS

The mean follow-up was 217 days ranging from 80 to 360 days. Two patients were excluded from analysis, because they did not receive the prescribed dose. One of them did not complete the treatment because of dissemination which occured during radiation therapy and in the other because of a significant error in treatment delivery. The details of the radiation therapy plan and technique, toxicity and treatment results of evaluable 20 patients are summarized in table 2.

Treatment plan evaluation

A dose superior to 70 Gy to PTV3 could be attained with the 3-DCRT technique without exceeding the predetermined limits of critical structures tolerance (except for a mean dose for both lungs). Seventeen patients received 74 Gy, two patients had 72 Gy and one had 70 Gy. In the latter case a total dose was not limited by the predetermined tolerance criteria but by the presence of concurrent heavy chronic respiratory disease. Limits of 10% of dose inhomonogeity within PTV3 were not reached in 45% of the accepted treatment plans. This was caused by too low photons energy (4MV) used (only available in our institution for this purpose during the study). The maximum dose to the spinal cord was lower than 50 Gy, whereas one patient received 52 Gy due to a technicians error. At least 50% of the lung volume received <20 Gy in all patients. The level of the mean dose to the lungs fixed below 20 Gy was exceeded in 5 cases. All these five patients had stage III disease, and three of them had a tumour located in the inferior lobe. The mean volumes of PTV3 and PTV1 in this group were 251.6 cc and 617 cc respectively, whereas in the group of patients with the mean dose to both lungs below 20 Gy the volumes for PTV3 and PTV1 were 169 cc and 453 cc respectively. The mean dose to both lungs tended to increase with increasing irradiated volumes. Dose constraints for heart and oesophagus were observed in all patients.

Toxicity evaluation

Acute toxicity includes any toxicity occuring at any time during the treatment, and the first 90 days after the end of the radiotherapy. Any toxicity occuring after this period of time was defined as late toxicity.

The Karnofsky Performance Status was increased in 10% (2 patients), unchanged in 70% (14 patients), and decreased in 20% (4 patients). Deterioration in KPS was associated with tumour progression in 3 patients, and in one patient it was due to intercurrent liver failure. Weight decreased in 20%, being associated with tumour progression and non treatment related. There was no acute esophageal toxicity in 35% of patients, grade 1 occured in 40%, 20% experienced grade 2, and only one patient (5%) developed grade 3, which caused treatment interruption of 8 days. To date

no late esophageal toxicity has been observed.

Acute pulmonary toxicity was assessed in 16 patients. Four patients were excluded from the analysis. Two of them experienced rapid clinical and radiological tumour progression and it was impossible to distinguish the symptoms of the disease from treatment toxicity. Two patients died of an interrcurrent disease before the end of the acute toxicity evaluation period (one cardiac failure and one non tumour and treatment related liver failure). Of the 16 evaluable patients four experienced radiation pneumonitis. Three patients were scored as grade 2 RTOG/EORTC acute pulmonary toxicity, and all required corticosteroid therapy. In one patient radiation pneumonitis had fatal evolution (grade 5 RTOG/EORTC) despite corticosteroid therapy from the third to the sixth week after the end of radiotherapy. The CT of the chest performed 4 days before the toxic death showed partial regression of the tumour and the image of radiation pneumonitis covered the previous radiation area. To date the evaluation of late pulmonary toxicity has been performed only in 6 patients who met two conditions: follow-up over 6 months without local disease progression. There were no severe late pulmonary complications that were attribuable to the treatment for this group of patients. Only one patient had grade 2 toxicity according to the RTOG/EORTC, on all clinical and radiographic findings (increase in steroids used for chronic respiratory disease and moderate fibrosis). In two patients, moderate fibrosis, as in grade 2 toxicity according to RTOG/EORTC scale, was found without any clinical radiation-induced pulmonary symptoms. There were no signs of pulmonary toxicity in the remaining three cases. Statistical evaluation of the relation of the mean dose to both lungs and/or the pulmonary volume receiving dose superior to 20 Gy and the pulmonary toxicity was not feasible because of the small number of events that occured. Hovewer, one fatality occured in a patient with the highest mean dose to both lungs, exceeding the fixed dose constraint by 25%.

To date neither radiation-related cardiotoxicity nor radiation myelopathy were observed.

Treatment responses and failure patterns

Of 20 patients, 17 (85%) were evaluable for response. Treatment results are summarised in Table 2.

Number	Total dose (in Gy)	Volume of PTV1	Volume of PTV3	Mean dose to both lungs	APT	LPT	Response to treatment
P1	74	815	400	25	5		PR
P2	74	569	192	22	2	2	PR
P3	74	438	196	21	2	NE	PR
P4	70	302	117	11	0	2	NR
P5	74	322	111	17.5	0	0	CR
P6	74	658	283	15	NE	NE	PROGR
P7	74	637	262	21.5	0	NE	PR
P8	74	627	208	21	0	2	PR
P9	74	226	75	19	0	0	CR
P10	72	750	141	13	0	0	NR
P11	74	520	61	19	0	NE	PR
P12	72	555	304	19	NE	NE	NE
P13	74	439	189	15.5	0	NE	NR
P14	74	380	135	18	NE	NE	NE
P15	74	366	191	16	NE	NE	PROGR
P16	74	438	206	17	2	NE	NR
P17	74	560	231	15.5	0	NE	PR
P18	74	555	208	14	0	NE	CR
P19	74	311	104	14	0	NE	CR
P20	72	417	178	17	0	NE	NE
P21	treatment not completed (metastatic disease progression)						
P22	error in treatment delivery						

Abbreviations: APT=acute pulmonary toxicity according to EORTC/RTOG score, LPT=late pulmonary toxicity according to EORTC/RTOG score, NE=non evaluated
CR=complete response, PR=partial response, NR=non-response, PROGR= progression

Table2. Number of patients (according to table 1), details on radiation therapy technique, treatment toxicity and results

Two patients were excluded because of death from an intercurrent disease before the response assessement. In one patient the follow-up period was too short. Of evaluable patients, three (18%) - two in tumour stage I and one in stage II - achieved complete radiological response. In one patient, the complete response was confirmed by bronchoscopy and biopsy. Seven (41%) patients had a partial radiological response, defined as superior to 50% tumour regression. In 5 (29%) patients no change of their tumour size has been noted. In two (12%) patients, both in stage IIIA with a weight loss superior to 10% prior to treatment local tumor progression occured. The response to treatment was evaluated 6 weeks, 3 months and 6 months after treatment completion. In two patients the evaluation of the response to treatment was hampered by the appearence of radiation-related lung condensations in the treated volume wrongly suggesting a tumour growth which occured between the sixth week and the third month. At evaluation within six months this finding was verified and finally progression of lung fibrosis with partial response to treatment was diagnosed. To date no progression has been observed within the treated volumes, except for two above mentioned cases of progression immediately following radiotherapy. Distant metastases occured within the first 3 months of the follow-up in two patients with partial thoracic response to radiotherapy. The initial stage of both patients was IIIA. One patient with no radiological response to treatment relapsed in the seventh month outside the radiological field, in the homolateral supraclavicular region and underwent salvage radiotherapy with complete response. Seventeen of 22 patients included in the study (77%) are alive with a median follow-up of 220 days (range: 80-360). One died from acute toxicity, two from an intercurrent disease and two from distant relapse. Follow-up data are not mature, and it is not possible at this point to draw any firm conclusions concerning survival.

DISCUSSION

The rationale for the 3-DCRT is founded on the results of many clinical and laboratory studies concluding that enhancement of local control results in a decreased metastatic spread and increased survival in several types of cancer (Leibel et al., 1991; Suit, 1992). This approach is particularly attractive in the management of NSCLC because of poor local control rate with conventional doses and techniques of radiotherapy and high morbidity of thoracic irradiation. Several studies on the use of 3-DCRT with or without dose escalation with different degrees of technological advances in the technique used in the management of NSCLC have been published in the last decade (Emami et al., 1991; Armstrong et al., 1997; Robertson et al., 1997; Derycke et al., 1997). Our study in this field has been based on 3-D planning system using BEV for the selection of beam directions and DVH for plan evaluation. However, in the treatment delivery such tools as asymmetric jaws, dynamic wedges, multileaf collimators, portal imaging have not been yet available. A 3-DCRT has been performed with cerrobend blocks and conventional hard wedges. Despite the absence of some tools making treatment delivery more accurate, our study enabled us to familiarise our staff with a new approach in radiotherapy of the thoracic tumours and acquire own experience in this field.

The definition of a clinical target volume in 3-DCRT remains controversial. Some authors treated uninvolved mediastinal areas at least with „prophylactic" doses (Armstrong et al., 1997), others included only involved areas (Robertson et al., 1997). Taking into account the high probability of microscopic nodal invasion of mediastinal nodes, S. Derycke et al. (Derycke et al., 1997) included in the CTV the nodal areas with the probability of invasion exceeding 10% according to the work of Minet et al. (Minet et al., 1993). The elective nodal irradiation largely contributes to toxicity. The major dose-limiting effect of radiotherapy for NSCLC is radiation pneumonitis strongly dependent on the volume of the irradiated lung (Martel et al;, 1994). In our department in view of the limiting treatment toxicity the above described scheme of limited elective nodal irradiation has been elaborated for this study. As in the work of Derycke et al. (Derycke et al., 1997), we based the rationale of our radiotherapy scheme on the probability of mediastinal nodal invasion in NSCLC derived from thoracic surgery experience (Lewinski, 1965; Kiricuta et al., 1994). The uninvolved nodal areas with the probability of invasion superior to 10% according to surgical data were irradiated by 40-44 Gy and those with the probability of invasion exceeding 20% received 56 Gy. Target volumes thus defined were significantly reduced as compared with „classical" elective fields, currently used in many departments for the irradiation of NSCLC with curative intent (Rocmans et al., 1991). In our study, one patient relapsed in homolateral supraclavicular region outside the port. He presented initially a metastatic involvement of mediastinal nodes (group 4) and if a principle of classical elective nodal irradiation had been adopted, a region of relapse would have been initially irradiated. The patient was successfully

irradiated at relapse. The impact of relapse on survival remained unclear. The necessity of elective nodal irradiation needs further investigations in phase III study and at least a careful monitoring of pattern of loco-regional failure is called for.

The lung tissue tolerance is one of the most important dose-limiting factors in radiotherapy of thoracic tumours. On the basis of clinical data, Emami et al. (Emami et at., 1991) fixed a TD50 (end-point radiation pneumonitis) at 24.5 Gy (2 Gy per fraction) for the whole lung. Consequently, it has become a common procedure to limit the dose to the pulmonary tissue to 20 Gy to at least 50% of the lung volume. The estimation of the dose-volume relation has now become more efficient as a result of large availability of DVH. It has recently been shown that the mean dose to both lungs inferred from DVH appears to be a good predictor of the lung toxicity (Theuws et al., 1998). In our study, we evaluated the DVH derived parameters in order to predict the toxicity. The follow-up period was found to be too short, and a number of events not sufficient for any further conclusions. However, the fact that a fatality occured in a patient with the highest mean dose for both lungs supports the concept that a mean dose constraint fixed at 20 Gy should not be exceeded. If it is not possible the treatment policy must be modified. We decided that we shall include in the future patients who need irradiation of such large volumes (nodal stage III in the lower lobe). The analysis of pulmonary toxicity in our group of patients is particularly difficult, because sixteen (80%) of them presented chronic pulmonary disease, and 95% were heavy smokers. Damage to the pulmonary tissue prior to radiotherapy seems to cause a decrease in the tolerance level. This would require special treatment planning techniques using functional DVH based on pulmonary perfusion from single photon emission computed tomography (SPECT). The pulmonary function tests (PFT), prior to radiotherapy, seem to have a predictive value in the determination of radiation-induced whole lung dysfunction (Marks et al., 1997). The assessement of pulmonary toxicity using clinical and/or radiological criteria, is of particularly limited value in patients with concurrent respiratory diseases, because of the difficulties in differentiation of symptoms of radiation-induced respiratory damage from a non-treatment related worsening of a chronic medical problem. Additionally, there is no clear correlation between radiological and clinical findings after radiotherapy (Arriagada et al., 1989). PFT were not available for the majority of analysed patients. At present, we continue our study with simultaneous evaluation of pre-RT PFT and the same procedure repeated every 6 months during the follow-up period.

The planned 10% maximum dose inhomonogeity within the PTV3 was not achievable in 45% patients, mainly due to low energy of the photons used (4MV). For high energy of photons (over 10 MV) the treatment planning systems tend to underestimate the increase of the penumbra region due to changes in photon and electron transport in the lung. However, Emami et al. showed that there was no difference between the dose distribution when 4 vs.18 or 4 vs.10 MV photons beams were used. The effect of increased percentage depth dose for high energy beams tends to disappear when multiple beams are used (Emami et al., 1991). In our study the large volumes receiving dose of 56 Gy limited the number of beams used with the aim avoiding overirradiation of large pulmonary volumes. The use of conformal radiotherapy is an advantage only in the case of small target volumes.

The high rate of complete responses in stage I and II of NSCLC (50%) provide encouragement for the continuation of the study in the early tumour stages . This is in accordance with other published data suggesting the maximum benefit from conformal radiotherapy with dose escalation in early-stage NSCLC. (Kupelian et al., 1996). No patient in stage III had radiological complete response. However, partial responses and „non-responses" need very careful interpretation, because a short-term radiological response in radiotherapy of NSCLC is not a meaningful endpoint. There is no evident correlation between radiotherapy response, particularly that assessed by radiological means, and survival. In the study of Mirimanoff et al. (Mirimanoff et al., 1998) 46% of 24 long-term survivors (more than 3 years) were partial responders and 29% of them did not respond and there was even progressive disease in one case. Early appearance of radiation-induced fibrosis makes an estimation of response very difficult. We have also encountered the same problem of evaluation of radiological tumor response during the follow-up. Five treatment failures (two distant, one regional and two local progression) occured in patients in stage III only. Fifty-five percent evaluable stage III patients relapsed during a short follow-up period. These results indicate that dose escalation using 3-DCRT is not more effective than conventional radiotherapy in the management of stage III of NSCLC. There are promising results of the use of combined radiation and chemotherapy or accelerated fractionation schedules in stage III. We suggest that 3-DCRT techniques should be used in these new approaches to the

management of stage III patients with favorable prognostic factors in clearly designed and carefully monitored clinical trials.

It may be concluded that the escalation of dose up to 70 Gy is feasible with acceptable acute toxicity. Maturation of follow-up data is necessary to the proper evaluation of survival and late toxicity. The necessity of applying elective nodal irradiation needs further investigations.

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