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The role of accelerated hyperfractionated radiotherapy in the treatment of inoperable non-small cell lung cancer: a controlled clinical trial

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Introduction. Radiotherapy remains the basic form of treatment in cases of non-small cell lung cancer (NSCLC) but there still exist controversies concerning optimal radiotherapy regimen and in particular, the total dose and fractionation schedules.
Purpose. To prove whether the question: if using an unconventional dose fractionation regimen (accelerated hyperfractionation) could improve the results of palliative teleradiotherapy patients with NSCLC.
Material and methods. Between 1997 and 2000 in the Cancer Centre in Kraków (COOK) a controlled clinical trial was conducted in a group of 150 patients with locally advanced (III°) inoperable and unsuitable for radical radiotherapy NSCLC, with no major symptoms of the disease. In 76 patients conventionally fractionated radiotherapy was performed – 50 Gy in 25 fractions during 5 weeks (CF). 74 patients were irradiated twice a day (AHF); the dose per fraction was 1.25 Gy and the minimum interval between fractions – 6 hours. The total dose was 50 Gy in 40 fractions during 26 days.
Results. The probability of 12 months survival was 47.4% in the CF arm and 45.9% in the AHF arm; the probability of 24 months survival was 16.2% and 15.8% respectivly. In all 76 patients in CF arm the treatment was carried out in prescribed time without breaks. Out of 74 patients in the AHF group 8 (10,8%) did not complete the treatment and 2 of them died in 3 rd and 4 th week of treatment.
Conclusion. The use of accelerated hyperfractionation does not improve the results of palliative teleradiotherapy in patients with locally advanced NSCLC without severe symptoms related to intrathoracic tumor. The treatment of choice in this group of patients is conventionally fractionated radiotherapy with a total dose of 50 Gy in 25 fractions in 5 weeks of treatment.

Ocena skuteczności teleradioterapii metodą przyspieszonej hiperfrakcjonacji w paliatywnym leczeniu chorych na nieoperacyjnego, niedrobnokomórkowego raka płuca: kontrolowane doświadczenie kliniczne

Wstęp. Podstawową metodą paliatywnego leczenia chorych na niedrobnokomórkowego raka płuca (NKRP) jest teleradioterapia; nadal jednak istnieją kontrowersje dotyczące wyboru optymalnych warunków napromieniania, a w szczególności dawki całkowitej i sposobu jej frakcjonowania.
Cel pracy. Odpowiedź na pytanie: czy zastosowanie niekonwencjonalnego sposobu frakcjonowania dawki promieniowania (przyspieszona hiperfrakcjonacja) może poprawić wyniki paliatywnej radioterapii chorych na NKRP.
Materiał. W latach 1997–2000 w krakowskim oddziale Centrum Onkologii (COOK) przeprowadzono kontrolowane doświadczenie kliniczne w grupie 150 chorych na miejscowo zaawansowanego (III°) NKRP, nie kwalifikujących się do radykalnego leczenia chirurgicznego lub napromienianiem, u których nie stwierdzono nasilonych objawów związanych z rozrostem nowotworu w terenie klatki piersiowej. 76 chorych napromieniano paliatywnie dawką 50 Gy w 25 frakcjach w czasie 5 tygodni (KF), 74 chorych napromieniano paliatywnie metodą „2 x dziennie" dawką frakcyjną 1,25 Gy z przerwą między frakcjami 6 godzin, dawką całkowitą 50 Gy w 40 frakcjach w całkowitym czasie leczenia 26 dni (PHF).

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Wyniki. Prawdopodobieństwo przeżycia 12 miesięcy wyniosło 47,4% w grupie chorych napromienianych KF, a 45,9% w grupie chorych napromienianych PHF; prawdopodobieństwo przeżycia 24 miesięcy wyniosło odpowiednio: 16,2% i 15,8%. U wszystkich 76 chorych napromienianych KF leczenie przeprowadzono w planowanym czasie bez przerw. Spośród 74 chorych napromienianych PHF, u 8 tzn. 10,8% nie dokończono napromieniania: 2 z tych chorych zmarło w 3 i 4-tym tygodniu leczenia.

Wnioski. Zastosowanie przyspieszonej hiperfrakcjonacji dawki nie poprawia wyników paliatywnej teleradioterapii chorych na miejscowo zaawansowanego NKRP, u których nie stwierdza się ciężkich objawów związanych z szerzeniem się nowotworu w terenie klatki piersiowej. Postępowaniem z wyboru w tej grupie chorych pozostaje napromienianie z zastosowaniem klasycznej frakcjonacji z podaniem dawki 50 Gy w 25 frakcjach w czasie 5 tygodni.

Key words: non-small cell lung cancer, palliative radiotherapy
Słowa kluczowe: niedrobnokomórkowy rak płuca, radioterapia paliatywna

Introduction

Between 1992 and 1996 in the Cancer Centre in Kraków a controlled clinical trial (KBN grant no 4 S402 111 06) was conducted in a group of 216 patients with locally advanced, inoperable and unsuitable for radical radiotherapy NSCLC, with no major symptoms of the disease [1, 2]. In the study group the irradiated patients have longer overall survival and better quality of life in comparison with the patients on supportive care only. Of the two compared fractionation regimens (hypofractionation versus conventional fractionation), the conventional fractionation (total dose 50 Gy, 2 Gy per fraction, 5 days per week, in 5weeks of treatment) appeared superior. Nevertheless the results were disappointing: one-year survival did not exceed 32%, 2 years – 14%, mean survival was 11 months.

In this situation, from 1.01.1997 till 30.03.2000 in COOK another controlled clinical trial was carried out, to find out if using an unconventional dose fractionation regimen (accelerated hyperfractionation) could improve the results of palliative teleradiotherapy in this group of patients.

The aim of this paper is the analysis of to analyse of this 3 years study comprising 150 patients accrued to the trial.

Material and methods

Before the trial began we obtained the approval of the Ethics Committee at COOK. Every patient enrolled into the trial gave signed informed consent.

1. The eligibility criteria were as follows:
(a) microscopically confirmed NSCLC, unsuitable for radical surgery or teleradiotherapy,
(b) age less than 70 years,
(c) stage III of the disease according to TNM UICC 1997 staging system with exception of patients with metastases to supraclavicular lymph nodes,
(d) performance status at least 50 according to Karnofsky scale,
(e) no prior anticancer treatment,
(f) no major symptoms of tumour spread in the chest which are classic indications for palliative radiotherapy (e.g. superior vena cava syndrome, marked effort dyspnoea due to main bronchus or carina infiltration, fully developed Pancoast syndrome, and massive haemoptisis).
2. Every patient had following examinations and tests carried out:
Bronchoscopy with biopsy of a sample for microscopic examination, chest X – ray (PA and lateral), brain CT (in patients with adenocarcinoma), spirometry, gasometry, abdomen ultrasound, blood test with differential white cell count, blood biochemistry (evaluating the function of parenchymal organs – transaminases, GGTP, bilirubin, creatinin, BUN, glucose, LDH, serum protein with electrophoresis).
The performance status was estimated according to Karnofsky scale.
3. The patients fulfilling the inclusion criteria were subsequently randomly assigned to one of the two groups:
(a) first group – „twice a day" regimen (AHF – accelerated hyperfractionation)
beam parameters: megavoltage X rays, beam energy 10MV,
technique: 1 Stage (up to 40 Gy): two opposed AP -PA portals encompassing the tumour with a 2 cm margin, unilateral hilum and mediastinum and in patients with N3 – contralateral hilum.
2 Stage (up to 50 Gy) three intersecting beams encompassing the tumour volume.
dose: two fractions daily, fraction dose 1.25 Gy, interfraction interval 6 hours; tumour dose: 50 Gy in 40 fractions during 20 days of irradiation in total treatment time of 26 days. (The treatment started on Monday and was carried out 5 days per week).
(b) second group: conventional fractionation regimen (CF)
Beam characteristics and radiotherapy technique as in the first group.
Dose: 50 Gy in 25 fractions during 5 weeks of treatment.
In both groups computer assisted treatment planning based on CT scans was used, the doses were estimated in ICRU reference points. All fields were treated daily.
Caution: the treatment was considered with palliative intent and therefore we used low fraction dose (1.25 Gy) in AHF arm and low total dose (50 Gy) in CF arm.
4. The assignment of a patient to one of the study groups was performed using the random number table method described by Peto et al. [3].
5. Follow up: all patients were controlled every two months with tests listed in paragraph 2 of the protocol except bronchoscopy. Thorax CT (if indicated) was repeated every 4-6 months.
6. The main endpoints were 12 and 24 months overall survival. The analysis of the quality of life was based on performance status estimation according to Karnofsky scale. To compare the efficacy of the two radiotherapy regimens in local control, the regression level of the tumour on X – ray films was evaluated 8 weeks after treatment completion.
7. Statistical analysis: the survival probability was estimated with Kaplan – Meier method [4] and in statistical differences analysis log – rank test (according to Peto et al.) was used [5].

The survival was calculated from the date of randomisation to the date of a patient's death or his last visit in the COOK. The shortest follow – up was 6 months.

The survival was calculated in all patients.

From January 1997 to March 2000 150 patients with locally advanced, inoperable, unsuitable for radical radiotherapy NSCLC, without major chest symptoms were entered into the trial. According to the randomisation: in 74 patients accelerated hyperfractionation (”twice a day”) radiotherapy was carried out and 76 patients were conventionally irradiated. The population and clinical data of both compared patients groups are presented in Table I.

Tab. I. The population and clinical data of both compared patients groups

Population and clinical characteristics	AHF 74 patients		CF 76 patients	
	No	%	No	%
Sex:				
M	65	87.8	66	88.2
F	9	12.2	9	11.8
Age:				
Mean	59.2 years		59.1 years	
<50	10	13.6	10	13.2
50 – 60	32	43.2	34	44.7
>60	32	43.2	32	42.1
Histopathology:				
Squamous cell carcinoma	67	90.5	68	89.5
Adenocarcinoma	6	8.1	7	9.2
Large cell carcinoma	1	1.4	1	1.3
Clinical stage (UICC 1997):				
IIIA	26	35.1	26	34.2
IIIB	48	64.9	50	65.8
PS:				
Mean	71		70	
50 – 60	21	28.8	22	28.9
70 – 80	53	71.6	54	71.1

Table I shows that the analysed groups of patients did not differ in respect of population and clinical characteristics.

n all 76 patients in the CF arm the treatment was carried out in prescribed time, without breaks. At the end of radiotherapy and after completing the treatment in all these patients dysphagia was observed as a sequel of oesophagus irradiation; the severity of the reaction did not exceed EORTC grade 2 [6].

The tolerance of the treatment in the AHF group was markedly worse. Out of 74 patients 66 completed the treatment (89.2%); in 6 patients oesophagitis was of grade 3 according to EORTC classification. These patients required intensive anti-inflammatory treatment and 5-8 days breaks in radiotherapy. Out of 8 patients who did not complete the treatment 2 died in the 3rd and the 4th week of treatment (one of them because of pulmonary haemorrhage, the second one because of pneumonia with circulatory insufficiency); 6 patients went only trough the first part of treatment (40Gy) because of infection and lung inflammatory symptoms (4 patients) or circulatory insufficiency (2 patients).

In 1 patient in the CF and in 2 patients in the AHF group in 3rd and 4th month after radiotherapy broncho -oesophageal fistulas were diagnosed. These patients have died of uncontrolled local disease.

The evaluation of late complications is difficult because in majority of patients only a short term palliative effect was achieved.

The tolerance of the radiotherapy was worse and early complications more frequent in the AHF group.

The results

The probability of 24 months survival in the groups is presented in Fig.1.

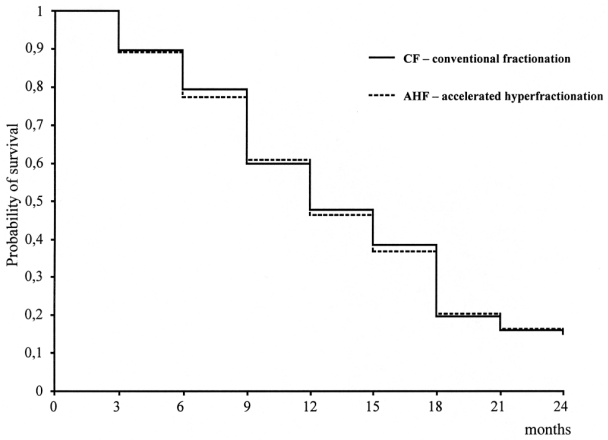

Fig. 1. The probability of 24 months survival in the groups

The probability of 12 months survival was 47.4% in the CF arm and 45.9% in the AHF arm; the probability of 24 months survival was 16.2% and 15.8%, respectively.

The differences are not statistically significant (log rank test, p>0.05). The mean survival was 10.8 and 10.6 months, respectively.

Table II presents the comparison of local control with two methods of palliative radiotherapy in patients with locally advanced, inoperable NSCLC.

Tab. II. The level of radiological regression of the tumour in two groups of patients irradiated with two different regimens of dose fractionation

X – ray regression of the tumour	AHF		CF	
	No	%	No	%
CR	5	6.6	5	6.8
> 50%	28	36.8	28	37.8
< 50% or progression	43	56.5	41	55.4
Total	76	100.0	74	100.0

Local control in the two compared fractionation regimens was very similar, the observed differences are statistically insignificant (log rank test, p(0.05).

In both groups the most frequent cause of death were distant metastases (almost 70%), accompanied by locoregional failure (the patients were treated with palliative intent!).

Unfortunately, in the investigated group it was not possible to carry out detailed quality of life assessment (ECOG scale, QLQ – C30 questionnaire). Many patients came for follow up visits irregularly, many of them refused to fill the questionnaires. It was not possible to treat as in-patient in COOK all the patients with progressive disease, so they were admitted to pulmonological wards all over south -eastern part of Poland.

The comparison of the quality of life in both groups of patients based on Karnofsky performance status estimated during follow up visits did not show statistically significant differences between CF and AHF fractionation regimens.

Discussion

Nearly 70% of patients with NSCLC are not qualified for radical surgery or radical radiotherapy (65-75 Gy) because of advanced stage of the disease, poor performance status and respiratory or circulatory insufficiency [7-9]. All these patients are potential candidates for the most effective form of palliation which is teleradiotherapy (despite the continuing progress in chemotherapy) [1, 2, 10-15]. Regarding the usefulness of palliative radiotherapy these patients could be divided into three groups:

(a) patients with clinically evident metastatic disease or life threatening symptoms (brain metastases, weight bearing bones involvement, spinal cord compression and so on),

(b) patients with severe complaints caused by tumour progression in the chest, that is with superior vena cava syndrome, Pancoast syndrome, main bronchus or tracheal progressive obstruction – irrespective of presence or absence of distant metastases,

(c) patients with locally advanced cancer without distant metastases (III() and without major symptoms of the tumour.

The patients from the first two groups have indisputable indications for palliative radiotherapy and most authors in such cases prefer in this situation (especially in group „a") hypofractionation -short regimens using high fraction doses (30 Gy/10fr., 20 Gy/5fr., 10 Gy/1fr.) [9-11, 13, 14, 16].

The third group (patients with stage III lung cancer, unsuitable for radical surgery, or radical radiotherapy, without marked symptoms of the disease). These patients cover some 20-30% of all NSCLC patients. As we already mentioned in the introduction both our studies and literature data show unequivocally that this group of patients benefit from palliative radiotherapy [1, 2, 7, 9, 12--15] but still exist controversies concerning optimal radiotherapy regimen and in particular the total dose and fractionation schedules.

Literature data indicate that local tumour regression in patients with NSCLC has positive influence on survival and there exists correlation between the total dose and the level of tumour regression [13, 14, 15]. In radical radiotherapy of inoperable, locally advanced NSCLC high doses (65-75Gy conventionally fractionated) are delivered. In palliative treatment such high doses and prolonged treatment are not only pointless but even contraindicated.

When designing described study we accepted 50 Gy in 25 fractions in 5 weeks of treatment as the reference protocol because it was well tolerated in our previous study, which is one of important conditions of palliative treatment [1, 2]. To maintain this good tolerance of radiotherapy and at the same time to improve its efficacy we decided to investigate hyperfractionated accelerated radiotherapy regimen using „twice a day" irradiation and keeping the total dose of 50 Gy. Theoretical basis and potential benefits of accelerated hyperfractionation in the treatment of cancers of different localisation are widely reported in literature [13]; in patients with NSCLC accelerated hyperfractionation has been studied in numerous controlled and uncontrolled clinical trials [7, 13-15]. Most of these trials, however, deal with radical radiotherapy and high total doses. The papers assessing the role of accelerated hyperfractionation in palliative treatment are rather scarce [15, 17, 18].

The analysis of the results of the trial in patients with locally advanced NSCLC revealed that the efficacy of the conventional fractionation (50 Gy in 25 fractions in 5 weeks treatment time) was very similar to that of accelerated regimen (50 Gy in 40 fractions, twice a day 1.25 Gy for four weeks). The probability of 12 months survival was 47.4% in the CF group and 45% in the AHF group; mean survival was 10.8 and 10.6 months, respectively.

Tolerance of the treatment was better and early complications were less frequent in the CF arm. Therefore the use of AHF according to the protocol investigated in our trial as palliative treatment in patients with locally advanced NSCLC is not justified and CF with total dose 50 Gy in 25 fractions in 5 weeks remains here the treatment of choice.

Conclusion

1. The use of accelerated hyperfractionation does not improve the results of palliative teleradiotherapy in patients with locally advanced NSCLC without severe symptoms related to intrathoratic tumor.
2. The treatment of choice in this group of patients is conventionally fractionated radiotherapy with a total dose of 50Gy in 25 fractions in 5 weeks of treatment.

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Refereces

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