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Conformal radiotherapy for Non-Small Cell Lung Cancer (NSCLC) to the dose of 70-74 Gy with or without elective nodal irradiation (ENI). Results and patterns of failures

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Study aim: to evaluate the feasibility of radiation dose escalation≥70 Gy to the tumor using the 3-DCRT technique and to examine the patterns of failure as a function of dose and irradiated volume in patients with NSCLC.
Material and methods. Between 1997-2003 sixty patients with NSCLC were irradiated to the dose 70-74 Gy using conformal techniques. Stage distribution was: I° – 16, II° – 26, III° – 18. For 40 patients the limited elective nodal irradiation (ENI) to 54-56 Gy was performed. 20 pts. were irradiated with omission of the ENI. Toxicity was evaluated according to the RTOG/EORTC criteria. Overall survival was estimated for 53 pts. with a follow-up period of at least 12 months (alive). Localization of failures was evaluated as function of the administered dose.
Results. The planned dose was administered according to the protocol to all patients, except for 4, in case of whom the dose to the lung exceeded protocol constraints (mean dose to lung ≤20 Gy). We lost 1 patient due to toxic death (radiation pneumonitis) and observed 1 case of grade III acute followed by grade III late pulmonary toxicity. In both these patients the mean dose to the lung was >20 Gy. Estimated 3-year overall survival rate was 22%, with median survival of 21 months. The first site of failure was in 27 pts., volume receiving doses ≥70 Gy, in 6 pts. distant metastases without local failure. No patient treated without ENI presented with isolated mediastinal failure outside the irradiated volume.
Conclusions. Conformal radiotherapy with moderate dose escalation to 70-74 Gy is feasible, as long as one respects the dose constraints for the lung. This approach does not improve treatment results as compared to older techniques. Omission of the ENI appears to be an attractive treatment option.

Umiarkowana eskalacja dawki fizycznej w radioterapii chorych na niedrobnokomórkowego raka płuca. Wyniki i przyczyny niepowodzeń

Cel pracy. Ocena wyników i toksyczności napromieniania z eskalacją fizycznej dawki całkowitej do 70-74 Gy z zastosowaniem technik konformalnych u chorych na niedrobnokomórkowego raka płuca
Materiał i metody. W latach 1997-2003 napromieniano 60 chorych do dawki 70-74 Gy. Podział wg stopnia zaawansowania: I° – 16, II° – 26, III° – 18. Czterdziestu chorych było napromienionych na ograniczony obszar elektywny do dawki 54-56 Gy, następnie z podwyższeniem dawki na guz i powiększone węzły chłonne do dawki 70-74 Gy. Dwudziestu chorych (w stopniu zaawansowania I lub II) było napromienianych z ominięciem obszaru elektywnego do dawki 70-74 Gy. W tej grupie chorzy z guzem zlokalizowanym centralnie otrzymywali na obszar wnęki niezmienionej w badaniach obrazowych napromienianie do dawki 50-54 Gy. Zasady radioterapii konformalnej odnośnie jednorodności dawki i dawki tolerancji dla narządów krytycznych były zapisane w protokole. Oceniano objawy toksyczności wczesnej i późnej wg skali EORTC/RTOG w stosunku do płuc, przełyku, serca i rdzenia kręgowego. Przeżycie przy zastosowaniu metody Kaplana-Meiera oceniono dla 53 chorych z minimalnym okresem obserwacji 12 miesięcy dla żyjących chorych. Oceniono lokalizację wznów w stosunku do napromienianego obszaru.
Wyniki. Zaplanowaną dawkę podano u wszystkich chorych, spełniając kryteria jednorodności dawki. Dawki tolerancji dla narządów krytycznych zostały zachowane, z wyjątkiem płuc, gdzie przekroczono dawkę średnią na płuca (20 Gy wg protokołu) w 4 przypadkach (21-25 Gy). Całkowity czas leczenia wahał się od 7 do 9 tygodni (średnia: 52 dni). Toksyczność wczesna i późna była akceptowalna, z wyjątkiem 1 zgonu toksycznego z powodu popromiennego zapalenia płuc i 1 przypadku III° toksyczności wczesnej, przechodzącej w późną, o tym samym nasileniu ze strony płuc. Te 2 najcięższe przypadki toksyczności

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ze strony płuc dotyczyły chorych z najwyższą dawką średnią i największą objętością PTV w całej grupie. Oszacowane 3-letnie przeżycie całkowite wyniosło 22%, z medianą przeżycia 21 miesięcy. Nie stwierdzono istotnego statystycznie wpływu na przeżycie stopnia zaawansowania, dawki, obszaru napromieniania, wieku, płci, utraty masy ciała. Pierwszym miejscem wznowy w 27 przypadkach był nawrót miejscowy w obszarze eskalacji dawki, w 6 przypadkach przerzuty odległe bez stwierdzenia wznowy miejscowej. W jednym przypadku stwierdzono wznowę w okolicy nadobojczykowej nie napromienianej zgodnie z protokołem ograniczonego napromieniania elektywnego. Żaden chory, u którego nie włączono do napromieniania obszaru elektywnego, nie miał w dotychczasowym okresie obserwacji izolowanego nawrotu w tym obszarze.
Wnioski. Napromienianie konformalne z umiarkowaną eskalacją dawki do 70-74 Gy jest wykonalne pod warunkiem nie przekraczania dawek tolerancji dla płuc. Nie prowadzi jednak do poprawy wyników w porównaniu do radioterapii z zastosowaniem starszych technik i niższych dawek. Przekraczanie całkowitego czasu leczenia powyżej 7 tygodni mogło być jedną z ważnych przyczyn pogorszenia wyników. Zgodnie z sugestiami innych autorów, należy nie przedłużać całkowitego czasu leczenia u chorych na raka płuca powyżej 7 tygodni.

Key words: non-small cell lung cancer, conformal radiotherapy, dose escalation, elective nodal irradiation
Słowa kluczowe: niedrobnokomórkowy rak płuca, radioterapia konformalna, eskalacja całkowitej dawki, napromienianie elektywne

Introduction

Radiotherapy accounts for a disappointingly low rate of local control in patients with Non-Small Cell Lung Cancer (NSCLC) [1]. There exists some suggestions that higher doses of radiation to the tumor may result in improved local control in inoperable NSCLC [2-4]. This led us, like many other authors during the nineties [5-8], to perform a study on the results of physical dose escalation in such patients. The purpose of the study was to evaluate the feasibility of radiation dose escalation ≥70 Gy to the tumor using 3-dimensional conformal radiation therapy (3-DCRT) techniques. Patterns of failure as a function of dose and irradiated volume were examined.

Material and methods

Between November 1997 and April 2003 60 patients (47 men, 13 women; mean age 67 yrs, range: 50-80 yrs) entered the study. 23 pts. (38%) were over 70 years of age. Histologically we found squamous cell carcinoma in 40 pts., adenocarcinoma in 4 pts., large cell carcinoma in 2 pts. and 14 cases of NSCC without further specification. Tumour stage according to the TNM UICC classification was I in 16 cases, II in 26 cases, IIIA in 12 cases and IIIB in 6 cases; 47 pts. (78%) had Karnofsky performance status (KPS) >70, 13 (22%) had KPS of 70, due, mainly, to co-morbidity; 10 pts. (17%) reported pre-treatment weight loss of over 10% of the initial value. Patients in stage I and II were found to be inoperable because of medical problems. Pre-treatment evaluation included physical examination, complete blood count, serum chemistry, chest X-ray, bronchoscopy, CT scan of the chest and upper abdomen, bone scan and CT or MRI of the brain for patients with clinical suspicion of metastases.

A 3-D treatment planning system (TMS-Helax or Cadplan) was used for all patients after computed tomography, including the entire lung volume. CT scans were performed at 1 cm intervals through regions outside the predicted irradiation field and at 5 mm intervals within the predicted PTV. Forty patients underwent limited elective nodal irradiation (ENI) to the dose of 54-56 Gy with subsequent irradiation of the gross tumor volume (GTV) with margins to the dose of at least 70 Gy. Twenty patients were irradiated exclusively to GTV with margins. Omission of ENI concerned patients with poor respiratory functions and lower (I/II) stages of the disease. For patients with ENI two different clinical target volumes were contoured. The first (CTV1) included macroscopic (GTV) and microscopic (ENI plus margins around GTV) tumor volume. The second – CTV2 included only – GTV with 5 mm margins. GTV was defined as tumor visible in CT and bronchoscopy plus the lymph nodes which, on CT scans, had a diameter equal or larger than 1.0 cm in the short axis. In CTV1 the region of subclinical disease (uninvolved ipsilateral hilar – group 10, subcarinal – group 7, lower paratracheal – group 4L for tumors of left side, aortico-pulmonary window – group 5 and right lower paratracheal – 4R irrespectively of tumor site, according to the classification of AJCC and ATS), beyond CTV2 was included. PTV1 consisted of CTV1 with 1-2 cm margins, PTV2 included CTV2 with 1-2 cm margins. The size of the margins depended on tumor mobility. The dose prescribed to the PTV1 was 54-56 Gy; PTV2 received 70-74 Gy. For patients without ENI only one CTV was contoured and consisted of GTV with 5 mm margins. Margins of 1-2 cm were added for creating PTV1. For centrally located tumors the ipsilateral hilar region was included in PTV1, irradiated to the dose of 54 Gy. PTV2 (receiving doses 70-74 Gy) consisted of CTV with minimal (0.5- 1.5 cm) margins, depending on tumor motion. Specific dose constraints for critical structures were observed. The dose to the spinal cord did not exceed 50 Gy. At least 50% of the total lung volume received less than 20 Gy and the mean dose for the lung was below 20 Gy. The length of the esophagus receiving over 60 Gy did not exceed 10 cm. The entire heart volume received less than 40 Gy. The critical structure tolerance was inferred from the DVH analysis. The dose distribution among PTV2 ranged from 95% to 107%. 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 dose homogeneity and deliver the maximum achievable dose to PTV2. Custom blocks and MLC were used to minimize the dose delivered to healthy adjacent tissues. The dose per fraction was 2 Gy, delivered once a day, five times per week. High energy photons (4, 6, 15 MV) were used.

All patients were evaluated once a week during treatment. During the follow-up, patients were seen initially 6 weeks after treatment, and then every 3 months. CT of the chest 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 [9]. Overall survival and progression-free survival was estimated according to the Kaplan-Meier method. Each progression within the thorax was evaluated in relation to the irradiated volume and received dose.

Results

Acute toxicity was analysed for all 60 patients. Late toxicity was assessed for patients surviving for at least 6 months without disease progression. Fifty-three patients included in the study before November 2002, with a minimum follow-up of 12 months for alive patients were taken into account for survival and patterns of failure analysis.

Treatment protocol compliance

Doses from 70 to 74 Gy (74 Gy – 25 pts., 72 Gy – 10 pts., 70 Gy – 25 pts.) were delivered. Overall treatment time ranged from 7 to 9 weeks (mean: 52 days). A level of mean dose to lung fixed at/or below 20 Gy was exceeded in 4 cases (21-25 Gy). These 4 pts. had stage III disease and in three of them the tumor located in the lower lobe. The mean volumes of PTV1 and PTV2 for these pts. were 600 cc and 250 cc, respectively, whilst in the group with mean dose to both lungs below 20 Gy were 400 cc for PTV1 and 160 for PTV2. The mean dose to lung tended to increase with increased irradiated volumes. Dose constraints for heart, esophagus and spinal cord were observed for all patients. Dose homogeneity criteria were fulfilled for all patients.

Toxicity evaluation

Acute esophageal toxicity was mild, with 9 (15%) cases of grade I, 4 (7%) of grade II and 1 (1.5%) of grade III toxicity according to the RTOG/ EORTC score. No case of such toxicity occurred among patients without ENI. To date we have not observed any late toxic effects from the esophagus. Acute pulmonary toxicity was assessed in 56 patients. Four were excluded from analysis (2 because of rapid tumor progression, 2 because of death from intercurrent disease). Of the evaluable patients 10 (17%) experienced radiation pneumonitis. Eight (13%) were scored as grade II, 1 (1.5%) as grade III RTOG/EORTC toxicity. In 1 (1.5%) patient radiation pneumonitis led to toxic death (grade V). All cases of radiation pneumonitis occurred in the group irradiated with ENI. To date evaluation of the late pulmonary toxicity was performed in 34 patients who met two conditions – follow-up longer than 6 months and no local disease progression before this time. In 16 (53%) patients moderate fibrosis of grade II RTOG/EORTC score has been found, with none or minor clinical symptoms. One patient with grade III acute pulmonary toxicity subsequently developed grade III late toxicity. There was no correlation between pulmonary toxicity and mean dose to lung or pulmonary volume received dose superior to 20 Gy when grade II toxic effects had been analysed. However, both the death and the sole case of III grade acute/late pulmonary toxicity occurred in patients with the highest mean dose to lungs (25 and 23 Gy, respectively). Both these patients had tumours in the lower lobe and the largest volumes of PTV. To date neither radiation-related cardiotoxicity nor radiation-related myelopathy have been observed.

Treatment responses, survival and pattern of failures

Response to radiotherapy was assessed by chest X-ray taken at 1.5, 3 and 6 months and by CT taken at 3 and 6 months after treatment. Of the 60 patients 56 were evaluated for response. There were 19 cases (34%) of CR, 23 cases (41%) of PR, 9 cases (16%) of stabilization and 5 cases (9%) of progression within the first 6 months. Among complete responders 6 cases (32%) were confirmed in bronchoscopy. In 6 pts. the evaluation of the response to treatment was hampered by the appearance of radiation-related lung condensations within the treated volume erroneously suggesting tumor growth occurring within the first 6 months. These abnormalities remained stable for the next 6 months or more and, finally, these patients were considered as partial responders.

The estimated actuarial 1-, 2- and 3-year overall survival rates (Kaplan-Meier) for the entire group were 79%, 40%, and 22%, respectively, with a median survival of 21 months. The actuarial 1-, 2-, and 3-year progression free survival rates were 61%, 37% and 17%. Five pts. (9%) died from cancer or reasons unrelated to treatment (2 – cardiac infarct, 2 – cerebral vascular incidents and 1 – decompensation of pretreatment major cardiac insufficiency). Three of these patients had stage I disease, i.e. deaths from intercurrent diseases occurred in 19% of stage I patients. Actuarial cause-specific at 1-, 2- and 3-year survivals were 82%, 49% and 27%, respectively. The potential influence of stage of the disease, age, weight loss, KPS, type of irradiation (with vs. without ENI), dose (70 Gy vs. 72-74 Gy) and gender on the overall survival were estimated in univariate analysis (log-rank test). No examined variable had statistically significant influence on survival. Three-year overall survival rates for stage I, II, and III were 34%, 20%, and 16%, respectively.

To date we have observed 27 local recurrences, all of them within the previous dose escalation area. One patient treated with limited ENI relapsed in non-treated homolateral supraclavicular area. None of the 20 pts. treated without ENI recurred within non-treated "elective areas" as the first site of failure. The 2 regional progressions observed in this group were subsequent to the local disease progression. Six pts. developed distant metastases without thoracic progression assessed by radiological means.

Discussion

3-DCRT techniques allow for safe moderate dose escalation in the management of NSCLC, under the condition of respecting dose constraints, especially for the lung. Two cases of major lung toxicity (1 –V gr. and 1 – III gr.) occurred in pts. with the highest mean dose to the lung. In both these cases the tumour was located in the lower lobe and they had the largest irradiation volume

(PTV1 and PTV2). Other authors have also stressed the correlation of PTV volume, lung mean dose and tumour location with pulmonary toxicity [10, 11].

Despite acceptable toxicity the presented results are not promising when compared with those obtained with older radiotherapy techniques. The high level of local failures in the region of moderate dose escalation shows the limits of such an approach in the improvement of local control in NSCLC. We assume that the prolongation of overall treatment time beyond 7 weeks resulted in loss of local control. Other data also relate poorer survival with the prolongation of the overall treatment time [12]. More recent dose escalation trials keep overall treatment time constant – 5 weeks in the Mehta et al. [13] trial or 6 weeks in the Dutch trial [14]. Some authors suggest the necessity of a new approach to dose escalation in NSCLC by use of conformal techniques in dose-per-fraction escalation in view of the shortening of treatment time [13].

The presented poor results of conventionally fractionated 3-DCRT radiotherapy for early stages of NSCLC are in agreement with other series [15]. The dominant site of failure for these patients was local, indicating that moderate dose escalation with the extension of treatment time to and beyond 7 weeks is an inappropriate approach. Intercurrent deaths of 19% of I stage patients reflect significant co-morbid disease while their advanced age renders them unfit for thoracic surgery. Sibley et al. [16] found a 33% rate of intercurrent deaths in a group of 156 patients with stage I NSCLC treated with radiotherapy alone. These results suggest that shorter hypofractionated regimens, such as 48 Gy in 12 fractions with careful treatment planning, could be more appropriate for this population of patients [17].

Our preliminary results agree with other data suggesting the possibility of omitting ENI in pts. with clinical T1 and T2 N0 disease [16, 18, 19]. Nevertheless in such cases careful long-term monitoring of the pattern of failures is necessary. It is also possible that a real percentage of regional failures is underestimated due to predominant clinical problems caused by local failures. In any case, as long as the problem of improving local disease eradication is not solved by current approaches it is not necessary to worry about all possible sites of failures which do not significantly contribute to patient death. ENI is, additionally, the main source of pulmonary toxicity, as was also shown in the current study. No patient irradiated without ENI experienced any grade of radiation pneumonitis.

We continue this scheme of irradiation giving a dose of 70 Gy and omitting ENI (except irradiation of hilar and subcarinal regions for centrally located tumors) in some patients with stage I and II disease unfit for, or refusing, surgery. All attention is paid not to exceed the overall treatment time beyond 7 weeks. For patients with early stages of the disease but with major health problems and/or KPS not exceeding 70 we apply the hypofractionated regime, omitting ENI conformal radiation schedules (12 x 4 Gy) as described by Cheung et al. [17]. Patients with stage III disease are included in dose-per-fraction escalation protocols. Limited ENI (as described in this study) is performed in stage III patients.

Conclusions

Moderate dose escalation is feasible using 3-DCRT techniques, however it does not improve treatment results when compared to conventional treatment techniques and doses. It incites authors to look for other treatment strategies, such as dose-per-fraction escalation using conformal techniques for advanced stages, irradiation to 70 Gy without elective nodal irradiation and keeping overall treatment below 7 weeks for some early stages. For early stages with significant comorbidity or advanced age hypofractionated regimens with careful treatment planning are advisable.

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