Initial Tumor Size and Local Control in Stage III Non-Small Cell Lung Cancer Treated by Radio-Chemotherapy

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Key Words

Lung cancer
Cisplatin and irradiation
Vindesine and irradiation -Initial tumor size
Prognostic factors

Summary

In stage III non small cell lung cancer initial tumor size is a neglected prognostic factor. 22 patients with stage III disease have been treated with radio-chemotherapy (cisplatin/vindesine). A significant ($p < 0,001$) influence of initial tumor size on local control can be demonstrated. Future treatment strategies should include initial tumor size.

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Schlüsselwörter

Bronchialkarzinom
Cisplatin und Bestrahlung
Vindesin und Bestrahlung
Initiale Tumorgroße
Prognostische Faktoren
Zusammenfassung

Beim nicht kleinzelligen Bronchialkarzinom im Stadium III wird die initiale Tumorgroße als prognostischer Faktor gegenwärtig erheblich unterschätzt. An 22 Patienten, die mit Radiotherapie und gleichzeitiger Chemotherapie (Cisplatin/Vindesin) behandelt worden waren, wird der signifikante ($p < 0,001$) Einfluß der initialen Tumorgroße auf die lokale Kontrolle belegt. Zukünftige Behandlungsstrategien sollten die initiale Tumorgroße berücksichtigen.

Introduction

In addition to histogenesis and performance status, the size of the primary tumor is the most important predictor of response achieved by irradiation. The irradiation dose required to achieve a specified tumor control probability increases with tumor size. This has been shown for many solid tumors [1]. Regarding patients with locally advanced non-small cell lung cancer (NSCLC) treated by either radiotherapy or radiochemotherapy, initial tumor size is only rarely reported in current publications. We therefore analyzed our data to investigate the possible influence of initial tumor size on local control.

Patients and Methods

Twenty-two patients with NSCLC were entered into a study of chemotherapy with continuous cisplatin infusion plus bolus injection of vindesine with simultaneous standard fractionation radiotherapy [3]. Patients were classified retrospectively according to the TNM system

(UICC/AJC 1987). All patients received CT scans of the chest. Maximum tumor diameter was measured by CT. Direct extension of the primary tumor into the lymph nodes was classified as a single lesion. Besides endoscopic criteria, T4 was categorized if the tumor had reached or crossed the midline. Mediastinal lymph nodes larger than 2 cm were considered as positive. Overall survival was calculated from the first appearance of disease [2], defined as the date of X-ray diagnosis of lung cancer. Time to local progression was determined from the start of radio-chemotherapy until the date of first evidence of local or regional progression and estimated by Kaplan-Meier. The log rank test was used to compare the curves of local control.

Results

Twenty-two patients with stage III (UICC/AJC 1987) disease were identified. Patients had bidimensional measurable local or locoregional advanced disease. Patients were categorized as stage III for the following reasons: III A (8 patients) by T3 (bronchoscopy n = 2; CTn = 1) or N2 (mediastinoscopy n = 3; CT n = 2); III B (14 patients) by T4 (bronchoscopy and/or explorative thoracotomy n = 6; CTn = 5) or N3 (histologically proven neck nodes n = 2; mediastinoscopy n = 1). The minimum follow-up time of the surviving patients is 18 months. Based on the described CT findings, 2 subgroups were established (table 1).

When analyzing the time to local progression, 2 significantly ($p < 0.001$) different curves can be seen (fig. 1). Median sur-

Table 1. Characteristics of 22 patients with stage III NSCLC treated with radiochemotherapy

Subgroup 1 (< 6 cm)

Subgroup 2 (≥ 6 cm)

Median age, years (range)

55 (34

-67)

55 (41-66)

Sex Male Female

9

2

8 3

ECOG (median)

1(0-

2)

1 (0-2)

Histology

Squamous cell Large cell Adenocarcinoma

1

8 2 1

6 4 1

Stage III A III B

4 7

4 7

Radiotherapy dose,
median

58

58

Chemotherapy Cycles cisplatin, Cycles vindesine
median , median

3 4

3 4

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Probability of freedom from locoregional relapse

12 24 Months

Fig. 1. Time to local progression for the 2 subgroups of patients with stage III NSCLC ($p < 0.001$).

Overall survival time for all patients is 15 months with a 2-year overall survival of 25%. No statistically significant difference was observed concerning overall survival of the 2 subgroups.

Discussion

Though the results of a retrospective analysis based on a small selected subgroup of patients should be interpreted with caution, our findings focus attention on initial tumor size. This neglect is probably due to the TNM system for lung cancer, which is based mainly on the anatomic extent of disease and only to a minor degree on tumor size. In most of the patients with NSCLC, CT scanning allows an estimation of maximum tumor diameter. Our data demonstrate a significant influence of initial tumor size on local relapse. This finding is important for those patients who are treated with curative intent and not with a palliative or prophylactic-palliative aim. In contrast to published data [5], our findings are based on CT scanning. Results from a large randomized study (Radiation Treatment Oncology Group) suggest that intrathoracic recurrences were correlated not only with the dose of irradiation, but also with tumor size measured on plain X-rays [5]. Local failure after irradiation with 60 Gy was 0% (1–3 cm), 35% (4–6 cm), and 46% (> 6 cm). We believe that plain radiography alone is not sufficient to determine local control; computed tomography and endoscopy should provide additional important information.

Tannock critically reviewed combined modality treatment with radiotherapy and chemotherapy (either sequential or simultaneous) and concluded that in NSCLC without distant meta-stases the limited activity of drugs for NSCLC makes it unlikely that the combined use of radiation and chemotherapy would lead to substantial therapeutic gain [6]; however, he acknowledges the preliminary data of the Cancer and Leukemia Group B which compares, in a prospective

randomized study, neoadjuvant chemotherapy of short duration (2 cycles cisplatin/velban) followed by radiotherapy (60 Gy; starting day 50) to radiotherapy alone. Median survival is 13.6 months (combined arm) vs. 9.7 months (radiotherapy alone; $p = 0.002$ log rank test; R.

Dillmann, personal communication) in stage III disease.

Our current treatment policy for patients with inoperable or unresectable stage III (especially III B) NSCLC is based on the following criteria for eligibility: (1) Karnofsky Index $\geq 70\%$, (2) maximum tumor diameter as measured by computed tomography < 6 cm, (3) reasonable size of the irradiation portals in relation to the irradiated lung tissue, (4) age < 70 years, and (5) weight loss $< 5\%$. In these patients radio-chemotherapy with curative intent is planned, whereas patients beyond these criteria are not treated with combined modality. Other factors influencing decisions on how to manage a patient with stage III NSCLC will not be discussed here. In these patients 2 cycles of cisplatin (week 1 and 5; each cycle: $20\text{mg/m}^2/\text{day} \times 4$ given as a 1-h infusion) and 2 injections of vindesine (week 3 and 7; each injection 3 mg/m^2) are administered simultaneously with external beam irradiation (single dose $1.7\text{--}1.8\text{ Gy}$; total dose $60\text{--}65\text{ Gy}$). We thus modified our original regimen [3], increasing the irradiation dose to improve local control and reducing the total dose of cytostatic substances to circumvent hematologic toxicity. Infusional cisplatin [3] is replaced by fractionated cisplatin given as a 1-h infusion. The data reported by a French group [4] underline the concept of radio-chemotherapy, since the evaluation of 75 patients with fiberoptic bronchoscopy resulted in a response rate lower than expected from plain X-rays. In selected patients we consider additional afterloading (high dose rate) treatment. In an effort to give this subgroup of patients the opportunity for cure, one must first obtain a complete remission with no diagnosable disease after the completion of radio-chemotherapy. On the basis of several prospective randomized trials as well as numerous retrospective studies, the results of our small but well-defined group of patients are of major importance for future trials, as authors in general agree [1] on the importance of tumor size in local control.

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