Treatment of stage III non-small cell lung cancer and limited-disease small-cell lung cancer

Treatment of stage III non-small cell lung cancer and limited-disease small-cell lung cancer

Behandeling van stadium III niet-kleincellig longkanker en limited disease kleincellig longkanker

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor
aan de Universiteit Utrecht
op gezag van de rector magnificus, prof.dr. J.C. Stoof,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen
op maandag 8 juni 2009 des middags te 12.45 uur

door

Sherif Youssef El Sharouni

geboren op 19 augustus 1957 te Caïro, Egypte

Promotor: Prof. dr J.J. Battermann

Co-promotor: Dr ir H.B. Kal

For my parents.
For Anja and our children
Mary-Ann, Rose-Marie,
Mark and Pieter.

CONTENTS

Chapter 1

General introduction and outline of the thesis

Lung cancer is one of the main causes of cancer death in the world, accounting for 25-29% of all male deaths from neoplasia in the United States and Europe. The incidence in women is lower although it is rapidly increasing and, since 1987, it has overtaken breast cancer as the primary cause of death in the United States (Weir *et al.*, 1997) and since 2007 also in the Netherlands (CBS 1, 2). The 5-year survival of lung cancer patients worldwide is between 6 to 14% among males and 7 tot 18% among females (Youlden *et al.*, 2008).

Incidence

In the Netherlands, the incidence of lung cancer in men is decreasing. In the period 1989-2005 the incidence decreased from 7235 patients (13% of all cancer cases) to 6436 patients (8% of all cancer cases) (IKC). On the contrary, in women lung cancer incidence is increasing and it seems that the end of this increase in not yet in sight. Between 1989 and 2005 the incidence increased, from 1305 patients (2.3% of all cancer cases) to 3439 patients (4.2% of all cancer cases) (IKC). The decrease in incidence in men is a little bit more than the increase among women, and in this way the total lung cancer incidence in the Netherlands is slowing down. The changes in lung cancer incidence are the results of the changes in smoking behaviour that started some decades ago.

On the contrary to lung cancer in males, the second most prevalent cancer, prostate cancer, is increasing from 4201 patients (7.5% of all cancer cases) in 1989 to 8812 patients (10.8% of all cancer cases) in 2005 (IKC). In women, the incidence of breast carcinoma increased in the period 1989-2003, mostly due to the screening program, from 7707 (13.8% of all cancer cases) to 11791 (15.5% of all cancer cases). Afterwards, the incidence stabilized (IKC).

Mortality

The number of deaths among males in the Netherlands due to lung cancer was 7318 (20.7% of all cancer cases) in 1989 and decreased to 6359 (16.1% of all cancer cases) in 2005. The death due to prostate cancer remained stable; the numbers are 2079 (5.9% of all cancer cases) and 2370 (6.0% of all cancer cases), respectively (IKC).

In 1989 the number of death due to lung cancer in women was 1232 (3.5% of all cancer cases) and in 2005 it was 3055 (7.7% of all cancer cases). For breast carcinoma the numbers are 3365 (9.5% of all cancer cases) and 3301 (8.3%), respectively.

In 2006, the number of deaths among women due to lung cancer has increased 5 times since 1970 (CBS 2).

In 2007, the deaths among women due to breast cancer was 3180, and for the first time there were more deaths due to lung cancer, 3384 patients (CBS 3).

Non-small cell lung cancer

Of the two main types of lung cancer, non-small cell lung cancer (NSCLC) is the most frequent and represents about 83% of all lung cancer cases in the western world (Youlden *et al.*, 2008).

Only 20% of patients with NSCLC are candidates for surgery at presentation. The five-year survivals in surgical stages I, II and IIIA are 41-67%, 22-55% and 9-25%, respectively (Mountain *et al.*, 1997).

About one-third of the patients with NSCLC have stage III disease at presentation (Jemal *et al.*, 2007). Stage III NSCLC is a heterogeneous group of patients, ranging from patients with potentially resectable disease with chest wall invasion and hilar lymph node metastases (T3N1), patients with mediastinal invasion of the primary tumour into the mediastinum (T4), to patients with unresectable disease due to mediastinal lymph node metastases (N2 and N3), supraclavicular lymph node metastases or malignant pleural effusion. Most patients with supraclavicular lymph node metastases and all patients with malignant pleural effusion are incurable with a poor prognosis (Jemal *et al.*, 2007).

Regarding inoperable stage III NSCLC, the median survival time with radiotherapy alone varies between 9-11 months with a 2-year survival of 10-20% and a 3-year survival of 5-10% (Perez *et al.*, 1987). The Radiation Therapy Oncology Group (RTOG 7301) suggested a total dose of 60 Gy as the standard regimen for NSCLC (Perez *et al.*, 1987). However, in a randomised, prospective trial this curative radiation therapy was associated with a 5-year survival of only 3% (Johnson *et al.*, 1990). Others also reported poor survival at 5 years of 5 to 15% with traditional dose and fractionation schedules (Sibley *et al.*, 1998, Graham *et al.*, 1995).

The poor rates of local control with standard radiation therapy and the radiobiological considerations of circumventing repopulation of the surviving tumour cells by keeping the overall treatment time short, led to investigation of new fractionation schemes. Shortening of the overall treatment time by accelerated hyperfractionated radiation therapy showed some advantage in treatment results (Cox *et al.*, 1990, Saunders *et al.*, 1997, Saunders *et al.*, 1998, Koutaïssoff *et al.*, 1999, Mehta *et al.*, 1998). On the other

hand, interruptions in the regimen, resulting in longer overall treatment times, decreased long-term survival (Cox *et al.*, 1990, 1993).

Cisplatin-based multi-drug regimens (cisplatin with *e.g.* etoposide, ifosfamide, mitomycin or vindesine) for NSCLC emerged during the 1970's, improving the survival in comparison to best supportive care (Rapp *et al.*, 1988). The standard of care nowadays for this group of patients is a combination of chemotherapy and radiation, often referred to as combined modality treatment (Pfister *et al.*, 2004).

The combined modality treatment with cisplatin-based chemotherapy and radiotherapy is superior to radiotherapy alone in terms of survival in locally advanced unresectable NSCLC (Aupérin *et al.*, 2007, Bradley 2005, Socinski *et al.*, 2004, Tada *et al.*, 2004). The expected 5-year survival, however, is still 10 to 15% in patients with unresectable stage IIIB NSCLC (Jett *et al.*, 2003, Sirzén *et al.*, 2003).

The American Society of Clinical Oncology guidelines state that combined modality treatment should exist of two to four cycles of platinum-based chemotherapy and patients should receive no less than the biological equivalent of 60 Gy of radiation in 1.8–2 Gy fractions (Pfister *et al.*, 2004).

In one of our reports we advocated to treat stage III NSCLC in the Netherlands with high-dose concurrent chemoradiotherapy as the standard treatment for patients with good physical condition (El Sharouni *et al.*, 2008).

Small-cell lung cancer

Small-cell lung cancer (SCLC) accounts for 17% of all lung cancer cases (Youlden *et al.*, 2008). SCLC is the most aggressive form of lung cancer, having greater potential to metastasise than other types of lung cancer. Nearly all patients (>95%) diagnosed with SCLC are current or ex-smokers (Jackman *et al.*, 2005). Staging systems divide SCLC into limited disease (LD) and extensive disease. About one third of the SCLC patients have LD. LD is by definition confined to one side of the chest, and the remaining patients have extensive disease (Jackman *et al.*, 2005). SCLC is characterized by rapid tumour growth, early manifestation of metastases and an overall poor prognosis. Without treatment, tumour progression in LD SCLC is rapid, with a median survival time of only a few months (Agra *et al.*, 2003, Zelen, 1973).

The role of chemotherapy (CT) has been extensively tested. Long-term survival in these cases is <10% (Kelly *et al.*, 2000, Hoschek *et al.*, 2007). For palliative reasons, thoracic radiotherapy (RT) was given to CT patients

who did not respond completely to chemotherapy. Thoracic radiotherapy, given in addition to complete remission after chemotherapy, resulted in significantly improved survival rates when compared to those treated with CT only (Warde *et al.*, 1992, Pignon *et al.*, 1992). Furthermore, it was noted that prophylactic cranial irradiation (PCI) improved survival of SCLC patients who achieved complete response following primary therapy (Aupérin *et al.*, 1999, Kotalik *et al.*, 2001, Pugh *et al.*, 2007, Prophylactic Cranial Irradiation Overview Collaborative Group, 2000). Takada *et al.* (2002) reported results of a randomized multicenter trial and concluded that concurrent chemoradiotherapy (CCT-RT) is more effective than sequentially applied chemotherapy and radiotherapy (SCT-RT). The 5-years survival was 23.7% and 18.3%, respectively. Hence, the main treatment regimen for LD SCLC nowadays consists of a combination of chemotherapy, thoracic radiotherapy and PCI.

Outline of the thesis

In chapter 2 we described a systematic review on the clinical results of radiotherapy, combined or not with chemotherapy, for inoperable stage III non-small cell lung cancer (NSCLC), to be able to define the best sequence of radiotherapy and chemotherapy.

In chapter 3 we investigated the influence of the waiting time for radiotherapy, i.e. the interval between the end of induction chemotherapy and the start of radiotherapy, on the rate of tumour growth of patients with NSCLC stage III.

In chapter 4 we discussed the influence of the duration of the waiting time between the end of the induction chemotherapy and the start of the radiotherapy on tumour control probability.

In chapter 5 we investigated whether gemcitabine may cause radiosensitization in well-differentiated and undifferentiated tumours, and rat skin.

In chapter 6 we described the results of a phase II national multicentre study with weekly docetaxel/cisplatin and concurrent thoracic radiotherapy followed, whenever possible, by surgery in patients with stage III non-small cell lung cancer.

In chapter 7 we analysed the treatment results of our patients' population with limited-disease small-cell lung cancer. They were treated with chemotherapy only and chemotherapy combined with sequential or concurrent radiotherapy.

References

1. Agra Y, Pelayo M, Sacristan M, *et al.* Chemotherapy versus best supportive care for extensive small cell lung cancer. Cochrane Database Syst Rev 4: CD001990, 2003.
2. Aupérin A, Arriagada R, Pignon JP, *et al*. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. N Engl J Med 341: 476-484, 1999.
3. Aupérin A, Rolland E, Curran WJ, *et al*. Concomitant radio-chemotherapy (RT-CT) versus sequential RT-CT in locally advanced non-small cell lung cancer (NSCLC): a meta-analysis using individual patient data from randomised clinical trials. J Thorac Oncol 2: S310, 2007.
4. Bradley J. A review of radiation dose escalation trials for non-small cell lung cancer within the radiation therapy oncology group. Semin Oncol 32: S111-S113, 2005.
5. CBS 1: http://www.cbs.nl/nl-NL/menu/themas/gezondheid-welzijn/publi-caties/artikelen/archief/2008/2008-2571-wm.htm.
6. CBS 2: http://www.cbs.nl/nl-NL/menu/themas/bevolking/publicaties/ar-tikelen/archief/2007/2007-2199-wm.htm.
7. CBS 3: http://statline.cbs.nl/StatWeb/publication/?DM=SLNL&PA=7052_95 &D1=1,7,18,31,34,38,42,49,56,63,66,71,75,79&D2=0&D3=l&D4=29-38&HDR=G1,G3,G2&STB=T&VW=T.
8. Cox JD, Azarnia N, Byhardt RW, *et al.* A randomized phase I/II trial of hyperfractionated radiation therapy with total doses of 60.0 to 79.2 Gy: possible survival benefit with greater than or equal to 69.6 Gy in favorable patients with Radiation Therapy Oncology Group stage III non-small-cell lung carcinoma: report of Radiation Therapy Oncology Group 83–11. J Clin Oncol 8: 1543-1555, 1990.
9. Cox JD, Pajak TF, Asbell S, *et al*. Interruptions of high-dose radiation therapy decrease long-term survival of favorable patients with unresectable non-small cell carcinoma of the lung: analysis of 1244 cases from 3 Radiation Therapy Oncology Group (RTOG) trials. Int J Radiat Oncol Biol Phys 27: 493-498, 1993.
10. El Sharouni SY, Aerts JGJV, Senan S, *et al*. Behandeling van patiënten met niet-kleincellig longcarcinoom stadium III: gelijktijdig hooggedoseerde chemotherapie en radiotherapie, Ned Tijdschr Geneeskd 152: 2714-2717, 2008.
11. Graham PH, Gebski VJ, Langlands AO. Radical radiotherapy for early nonsmall cell lung cancer. Int J Radiat Oncol Biol Phys 31: 261-266, 1995.
12. Hoschek S, Hoschek-Risslegger U, Fiegl M, *et al*. Small cell lung cancer. Wien Klin Wochenschr 119: 697-710, 2007.
13. IKC: http://www.ikcnet.nl.

14. Jackman DM, Johnson BE. Small-cell lung cancer. Lancet 366: 1385-1396, 2005.
15. Jemal A, Siegel R, Ward E, *et al*. Cancer statistics. CA Cancer J Clin 57: 43–66, 2007.
16. Jett JR, Scott WJ, Rivera MP, *et al*. American College of Chest Physicians. Guidelines on treatment of stage IIIB non-small cell lung cancer. Chest 123: 221S-225S, 2003.
17. Johnson DH, Einhorn LH, Bartolucci A, *et al*. Thoracic radiotherapy does not prolong survival in patients with locally advanced, unresectable non-small cell lung cancer. Ann Intern Med 113: 33-38, 1990.
18. Kelly K. New chemotherapy agents for small cell lung cancer. Chest 117: 156S-162S, 2000.
19. Kotalik J, Yu E, Markman BR, Evans WK; Cancer Ontario Practice Guidelines Initiative Lung Cancer Disease Site Group. Practice guideline on prophylactic cranial irradiation in small-cell lung cancer. Int J Radiat Oncol Biol Phys 50: 309-316, 2001.
20. Koutaïssoff S, Wellmann D, Coucke P, *et al*. Hyperfractionated accelerated radiotherapy (HART) for inoperable, nonmetastatic non-small cell lung carcinoma of the lung (NSCLC): results of a phase II study for patients ineligible for combination radiochemotherapy. Int J Radiat Oncol Biol Phys 45: 1151-1156, 1999.
21. Mehta M, Tannehill, S, Adak, S, *et al*. Phase II trial of hyperfractionated accelerated radiation therapy for non-resectable non-small-cell lung cancer: Results of Eastern Cooperative Oncology Group 4593. J Clin Oncol 16: 518-523, 1998.
22. Mountain CF. Revisions in the International System for Staging Lung Cancer. Chest 111: 1710-1717, 1997.
23. Perez CA, Pajak TF, Rubin P, *et al*. Long-term observations of the patterns of failure in patients with unresectable non-oat cell carcinoma of the lung treated with definitive radiotherapy. Report by the Radiation Therapy Oncology Group. Cancer 59: 1874-1881, 1987.
24. Pfister DG, Johnson DH, Azzoli CG, *et al*. American Society of Clinical Oncology treatment of unresectable non-small-cell lung cancer guideline: update 2003. J Clin Oncol 22: 330–353, 2004.
25. Pignon JP, Arriagada R, Ihde DC, *et al*. A meta-analysis of thoracic radiotherapy for small-cell lung cancer. N Engl J Med 327: 1618-1624, 1992.
26. Prophylactic Cranial Irradiation Overview Collaborative Group. Cranial irradiation for preventing brain metastases of small cell lung cancer in patients in complete remission. Cochrane Database Syst Rev 4: CD002805, 2000.
27. Pugh TJ, Gaspar LE. Prophylactic cranial irradiation for patients with lung cancer. Clin Lung Cancer 8: 365-368, 2007.
28. Rapp E, Pater JL, Willan A, *et al*. Chemotherapy can prolong survival in

patients with advanced non-small-cell lung cancer - report of a Canadian multicenter randomized trial. J Clin Oncol 6: 633-641, 1988.

29. Saunders M, Dische S, Barrett A, *et al*. Continuous hyperfractionated accelerated radiotherapy (CHART) *versus* conventional radiotherapy in non-small-cell lung cancer: a randomised multicentre trial. CHART Steering Committee. Lancet 350: 161-165, 1997.

30. Saunders MI, Rojas A, Lyn BE, *et al*. Experience with dose escalation using CHARTWEL (continuous hyperfractionated accelerated radiotherapy weekend less) in non-small-cell lung cancer. Br J Cancer 78: 1323-1328, 1998.

31. Sibley GS, Jamieson TA, Marks LB, *et al*. Radiotherapy alone for medically inoperable stage I non-small-cell lung cancer: the Duke experience. Int J Radiat Oncol Biol Phys 40: 149-154, 1998.

32. Sirzén F, Kjellén E, Sörenson S, *et al*. A systematic overview of radiation therapy effects in non-small cell lung cancer. Acta Oncol 42: 493-515, 2003.

33. Socinski M A, Zhang C, Herndon II J E, *et al*. Combined modality trials of the Cancer and Leukemia Group B in stage III non-small-cell lung cancer: analysis of factors influencing survival and toxicity. Annals Oncol 15: 1033–1041, 2004.

34. Tada T, Minakuchi K, Matsui K, *et al*. A single institutional subset analysis of the WJLCG study comparing concurrent and sequential chemoradiotherapy for stage III non-small-cell lung cancer. Radiat Med 22: 163–167, 2004.

35. Takada M, Fukuoka M, Kawahara M, *et al*. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with cisplatin and etoposide for limited-stage small-cell lung cancer: results of the Japan Clinical Oncology Group Study 9104. J Clin Oncol 20: 3054-3060, 2002.

36. Warde P, Payne D. Does thoracic irradiation improve survival and local control in limited-stage small-cell carcinoma of the lung? A meta-analysis. J Clin Oncol 10: 890-895, 1992.

37. Weir HK, Thun MJ, Hankey BF, *et al*. Annual report to the nation on the status of cancer, 1975-2000, featuring the uses of surveillance data for cancer prevention and control. J Natl Cancer Inst 95: 1276-1299, 2003.

38. Youlden DR, Cramb SM, Baade PD. The international epidemiology of lung cancer: geographical distribution and secular trends. J Thorac Oncol 3: 819-31, 2008.

39. Zelen M. Keynote address on biostatistics and data retrieval. Cancer Chemother Rep 3: 31-42, 1973.

Chapter 2

Sequential versus concurrent chemo-radiotherapy in inoperable stage III non-small cell lung cancer

S.Y. El Sharouni
H.B. Kal
J.J. Battermann
F.M.N.H. Schramel

Abstract

Aim: To define the best sequence of radiotherapy and chemotherapy for inoperable stage III non-small cell lung (NSCL) tumours.

Materials and Methods: A systematic review was performed on the clinical results of radiotherapy, combined or not with chemotherapy, for inoperable NSCL cancer stage III. The mean median survival time (MST) and mean overall survival (OS) percentages were derived for radiotherapy only, for sequential and for concurrent chemo-radiotherapy.

Results: The mean median survival time ± standard deviation for radiotherapy only was 10.4±1.8 months. For sequential chemo- and radiotherapy it was increased to 13.0±1.2 months. When induction chemotherapy was followed by concurrent radio-chemotherapy, the mean median survival time was 15.8±2.6 months. For concurrent radio-chemotherapy it was further increased to 16.4±2.7 months. The mean 2- and 3-year overall survivals for radiotherapy alone, sequential and concurrent radio-chemotherapy were 17.1±4.6 and 10, 23.8±6.3 and 18.5±7.0, and 32.5±8.7 and 25.7±6.3%, respectively.

Conclusion: Concurrent chemo-radiotherapy demonstrated increased efficacy over radiotherapy alone and sequential chemo-radiotherapy and should be the treatment of choice. Further improvements may be obtained by optimising the conditions for concurrent chemo-radiotherapy.

Introduction

Lung cancer is one of the main causes of cancer death in the world, accounting for 25-29% of all male deaths from neoplasia in the United States and Europe. The incidence in women is lower although it is rapidly increasing and, since 1987, it has overtaken breast cancer as the primary cause of death in the United States (1).

Of the two main types of lung cancer, non-small cell lung cancer (NSCLC) is the most frequent and represents between 70 and 80% of the cases. The overall survival is poor, around 13%, and has not changed significantly in recent decades, because the majority of patients are diagnosed in advanced stages of the disease. Five-year survivals in surgical stages I, II and IIIA are 41-67%, 22-55% and 9-25%, respectively (2). Regarding inoperable stage III NSCLC, the median survival time with radiotherapy alone varies between 9-11 months with a 2-year survival of 10-20% and a 3-year survival of 5-10% (3). The Radiation Therapy Oncology Group (RTOG 7301) suggested a total dose of 60 Gy as the standard regimen for NSCLC (3). However, in a randomised, prospective trial this curative radiation therapy was associated with a 5-year survival of only 3% (4). Others also reported poor survival at 5 years of 5 to 15% with traditional dose and fractionation schedules (*e.g.* 5, 6).

The poor rates of local control with standard radiation therapy and the radiobiological considerations of circumventing repopulation of the surviving tumour cells by keeping the overall treatment time short, led to investigation of new fractionation schemes. Shortening of the overall treatment time by accelerated hyperfractionated radiation therapy showed some advantage in treatment results (7-11). On the other hand, interruptions in the hyperfractionation regimen, resulting in longer overall treatment times, decreased long-term survival (7, 12).

Cisplatin-based multidrug regimens (cisplatin with *e.g.* etoposide, ifosfamide, mitomycin or vindesine) for NSCLC emerged during the 1970's, improving the survival in comparison to best supportive care (13). The combined modality treatment with cisplatin-based chemotherapy and radiotherapy, either neoadjuvant with full-dose or concurrent with low-dose cisplatin-based therapy, is superior to radiotherapy alone in terms of survival in locally advanced unresectable NSCLC. The expected 5-year survival, however, is still 10 to 15% in patients with unresectable stage III NSCLC (14, 15).

We updated previous reviews on radiation therapy, combined or not

with chemotherapy, for inoperable stage III NSCLC, with the results of recently published randomised trials and other studies on concurrent chemo-radiotherapy.

Materials and Methods

Various recently published systematic reviews of the literature included studies up to 2000 or 2001. Therefore, the time-period chosen for our literature study was from 2000 to 2004. Searching Pubmed, Medscape and the Cochrane library identified reports on randomised trials. The key words used were: meta-analysis, carcinoma-non-small-cell-lung, randomised-controlled-trial, locally advanced and stage III. Articles discussing tri-modality therapy (chemo-, radiotherapy and surgery) were omitted from this review. From the reports, the mean median survival time (MST) and mean overall survival (OS) percentages were derived for radiotherapy alone, for sequential and for concurrent chemo-radiotherapy. The relative risks (RRs) of sequential chemo-radiotherapy *versus* radiotherapy alone and the RRs of concurrent *versus* sequential therapy were calculated per study for the 2-year overall survival end-point. This end-point was chosen because most randomised studies reported that value. Subsequently, we pooled the RRs. The relative risks, pooled RRs and 95% confidence intervals were calculated using STATA 8.0 and SPSS10. When a 95% confidence interval did not include the value 1, the RR was considered to be significantly different from 1.

Results

Summary of earlier meta-analyses and overviews. Three meta-analyses dealt with the value of chemotherapy in combination with radiotherapy for locally advanced NSCLC (16-18). The addition of chemotherapy to radiotherapy improved survival. However, the absolute benefit was relatively small, corresponding to a mean gain in median survival time of about 2 months and increase in overall survival at 2 years of 3 to 4%.
Sörenson *et al.* provided a systematic overview of chemotherapy effects in NSCLC (19). In stage III disease, the published data showed that induction cisplatin-based chemotherapy before radical radiotherapy modestly prolonged the long-term survival and lowered the incidence of distant

metastases compared with radiotherapy alone. Furthermore, published data showed that concurrent chemo- and radiotherapy with cisplatin or carboplatin might enhance local control and long-term survival (19).

Also in other reviews, comprising data up to 2001, strong evidence was noted that combined modality treatment with platinum-based chemotherapy and radiotherapy, either neoadjuvant or concurrent, was superior to radiotherapy alone in terms of survival in locally advanced unresectable NSCLC and should be the standard of care in patients with good performance status (14, 15, 20).

Overview of recent studies: radiotherapy alone, induction chemotherapy followed by radiotherapy with or without concurrent chemotherapy (Table I). Sause *et al.*, in a phase III clinical trial, tested whether chemotherapy followed by radiation therapy resulted in superior survival to either hyperfractionated radiation or standard radiation in surgically unresectable NSCLC (21). The patients were prospectively randomised to 2 months of cisplatin/vinblastine chemotherapy followed by 60 Gy at 2 Gy per fraction or 1.2 Gy per fraction delivered twice daily to a total dose of 69.6 Gy, or radiation therapy only with 2.0 Gy per fraction once daily to 60 Gy. Four hundred and ninety patients were registered of which 458 patients were eligible. The MSTs for standard radiotherapy, chemotherapy and radiotherapy, and for chemotherapy and hyperfractionated irradiation, were 11.4, 13.2 and 12 months, respectively. The respective 5-year survivals were 5, 8 and 6% (Table I). The log-ranked statistical comparison indicated that chemotherapy plus conventional irradiation resulted in a superior survival over radiotherapy only (*p*=0.04).

Kim *et al.* conducted a phase III randomised trial of combined chemo-radiotherapy *versus* radiotherapy alone in unresectable, locally advanced NSCLC (22). A total of 101 patients with unresectable stage IIIA or IIIB NSCLC were enrolled. Radiotherapy was administered in 1.8 Gy to 2.0 Gy fractions daily, 5 times weekly, for a total dose of 60 to 65 Gy. The combined group received induction with cisplatin, etoposide and vinblastine (CEV) chemotherapy followed by radiotherapy. The MST showed a tendency to be prolonged in the combined group (13.8 *vs.* 8.5 months). In patients with non-squamous histology, the MST was strikingly prolonged in the combined group as compared to the radiotherapy group (14 *vs.* 3.6 months, *p*=0.027). Kim *et al.* concluded that induction CEV chemotherapy plus radiotherapy is superior to radiotherapy alone in patients with unresectable locally advanced NSCLC (Table I).

Table I. Median survival time and overall survival after radiotherapy (RT) alone, and induction chemotherapy followed by radiotherapy, with or without concurrent chemotherapy.

First author	N	Induction chemo	RT (Gy) ± conc. chemo	Median survival time (months)	Overall survival (%)
Sause (21)	152		30x2	11.4	5y: 5
	154	C, V	30x2	13.2	5y: 8
	152	C, V	58x1.2	12	5y: 6
Kim (22)	46		60-65	8.5	
	43	C, V, E	60-65	13.8	
Metha (23)	59	Ca, pac	57.6; T=2.5 w	21	2y: 37; 3y: 20
	60	Ca, pac	32x2	12	2y: 28; 3y: 15
Vokes (24)	62	C, G	32x2 + CG	18.3	2y: 37; 3y: 28
	58	C, pac	32x2 + Cpac	14.8	2y: 29; 3y: 19
	55	C, vino	32x2 + Cvino	17.7	2y: 40; 3y: 23
Willner (25)	151	Ca, pac	60-66 + Pac	19.2	2y: 27
	151	Ca, pac	60-66	14.6	2y: 10
Brodin (26)	148	C, vind	56	11	2y: 21
	154		56	10.5	2y: 17
Crino (27)	33	C, etop	56	12	2y: 30, 6y: 0
	33		56	8.3	2y: 14, 6y: 0
Cullen (28)	223	mito, ifo, C	RT	11.7	2y: 24
	223		RT>40/15fr	9.7	2y: 16
Dillman (29)	78	C,V	30x2	13.7	1-7y: 54, 26, 24,19, 17, 13, 13
	77		30x2	9.6	1-7y: 40, 13, 10, 7, 6, 6, 6

| Study	N	Chemotherapy	RT	T	Survival
Gregor (30)	39	C, vind	50/20 fr	12	2y: 20
	39		50 /20 fr	12.2	2y: 20
Le Chevalier (31)	176	C, cyclo, vind, lomustine	60/2.5 Gy/fr	12	2y: 21
	177		60/2.5 Gy/fr	10	2y: 14
Kubota (32)	32	C, vind	50-60/2 Gy/fr	15.2	1-3y: 58, 36, 29
Sculier (33)	55	C, ifo, mito	30x2	12.4	2y: 22
Wolf (34)	37	ifo, vind	25x2/7w + C	13.7	2y: 24
Furuse (35)	158	C, vind, mito	56	13.3	2-5y: 27.4, 14.7, 10.1, 8.9
Curran (36)	200	C, V	60	14.6	4y: 12
Pierre (37)	104	C, vino	33x2	13.8	1y: 56; 2y: 23
Zatloukal (38)	50	C, vino	60	12.9	1-3y: 53, 14.3, 9.5
Choi (39)	32	E, C, ifo	60 + C	12.3	
Graham (40)	26	C, etop	65/5w + C	16.9	2y: 34
Saha (41)	57	Ca, pac	60	13.6	1y: 70; 2y: 28
Clamon (42)	137	C, V	60	13.5	2y: 26; 4y: 10
	146	C, V	60 + Ca	13.4	2y: 29; 4y: 13

N: number of patients; C: cisplatin; Ca: carboplatin; cyclo: cyclophosphamide; etop: etoposide; G: gemcitabine; ifo: iphosphamide; mito: mitomycin; pac: paclitaxel; V: vinblastine; vino: vinorelbine; vind: vindesine; RT: radiotherapy; T: overall treatment time radiotherapy; w: week; y: year; fr: fraction.

In a randomised phase III trial of the Eastern Cooperative Oncology Group (ECOG 2597), the efficacy of hyperfractionated accelerated radiotherapy (57.6 Gy over 2.5 weeks, 3 daily fractions given 4 h apart) was assessed in comparison to standard, once-daily fractionation (64 Gy, 2Gy/day), following 2 cycles of induction chemotherapy with carboplatin and paclitaxel in stage IIIA and IIIB NSCLC patients (23). With a MST of 21 *versus* 12 months, the efficacy of hyperfractionated accelerated radiation therapy appeared improved compared to that seen with the standard combined modality regimens (Table I).

Vokes *et al.* reported on a randomised phase II study comparing 4 cycles of cisplatin with either gemcitabine, paclitaxel or vinorelbine as induction chemotherapy followed by concurrent chemo-radiotherapy for stage IIIB NSCLC (24). Radiotherapy was administered in 33 fractions of 2 Gy. The 3-year survivals for the combination cisplatin/gemcitabine, cisplatin/paclitaxel and cisplatin/vinorelbine were 28, 19 and 23%, respectively. The MST values were 18.3, 14.8 and 17.7 months, respectively (Table I). The observed survival rates exceeded those of previous CALGB trials and may be attributable to the use of concurrent chemo-radiotherapy.

Willner *et al.* reported on a prospective randomised phase III trial of concurrent paclitaxel and radiotherapy *versus* radiotherapy alone, following induction chemotherapy with paclitaxel and carboplatin in stage III inoperable NSCLC (25). A total of 303 patients were included. The MST was 19.2 months for concurrent chemotherapy and radiotherapy *versus* 14.6 months for radiotherapy alone after induction chemotherapy. The authors concluded that concurrent radio-chemotherapy with paclitaxel is superior to radiotherapy alone following induction chemotherapy (Table I). In addition to these results of randomised trials, we summarized the MST and overall survival data for radiotherapy alone and sequential chemo-radiotherapy from the overview presented in Table 4 in the publication of Sirzén *et al.* (15, 26-34), and other recent sources (35-42) (Table I). From Sirzén *et al.*'s table, for radiotherapy alone, the mean MST was 10.4 ± 1.8 months and the mean 2- and 3-year OS values were 17.1 ± 4.6% and 10%, respectively (15). For sequential therapy with conventional radiotherapy (daily fractionation, overall treatment time 5 to 6 weeks), the mean MST was 13.0 ± 1.2 months and the mean 2- and 3-year OS were 23.8 ± 6.3% and 18.5 ± 7.0%, respectively. For induction chemotherapy followed by radiotherapy concurrent with chemotherapy, the mean MST was 15.8 ± 2.5 months and the mean 2-and 3-year OS were 31.3 ± 5.8% and 23.3 ± 4.5%, respectively (24, 25, 34, 39, 40, 42). These mean values for the MST
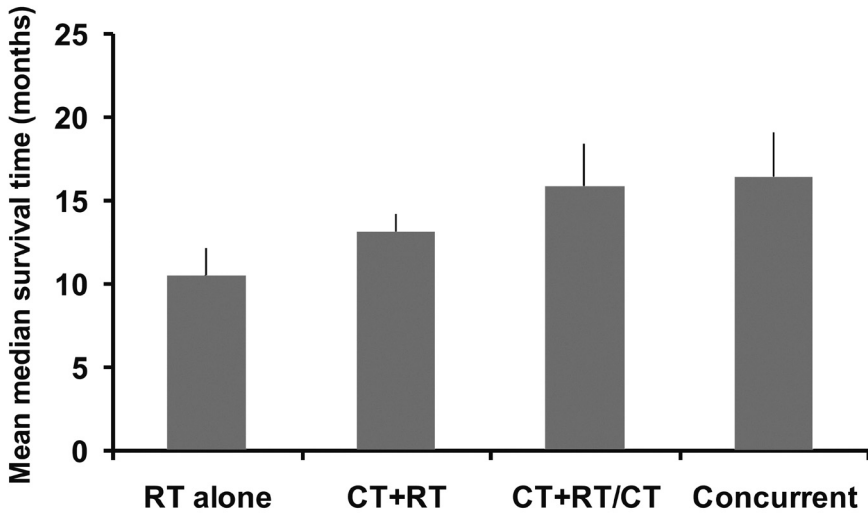
Figure 1. Mean median survival times of unresectable stage III non-small cell lung cancer for radiotherapy alone (RT alone), sequential chemo-radiotherapy (CT+RT), sequential therapy with concurrent chemo-radiotherapy (CT+RT/CT) and concurrent chemo-radiotherapy. The mean median survival times of CT+RT, CT+RT/CT and concurrent chemo-radiotherapy were significantly longer than that of RT only.

and OS at 2 and 3 years are shown in Figures 1 and 2, respectively.

In Table I, the results of 11 randomised trials are summarized (21-31). In Table II, the results of 6 of these trials (26-31), in which the 2-year OS for radiotherapy only and induction chemotherapy followed by radiotherapy (sequential regimen) were provided, are summarised and pooled. The RR of sequential therapy and radiotherapy alone for each trial and for the pooled results were determined. The mean OS for the pooled data for radiotherapy alone and for the sequential regimen are 15.6% and 22.9%, respectively. The OS was significantly higher for the sequential regimen (pooled RR=0.91; 95% confidence interval 0.87-0.96). This analysis also indicated that sequential therapy results in better OS than radiation only.

In conclusion, the results observed for stage III inoperable NSCLC indicate a small benefit in sequential chemo- and radiotherapy studies over radiotherapy alone. The gain in mean MST was a significant 2.6-month
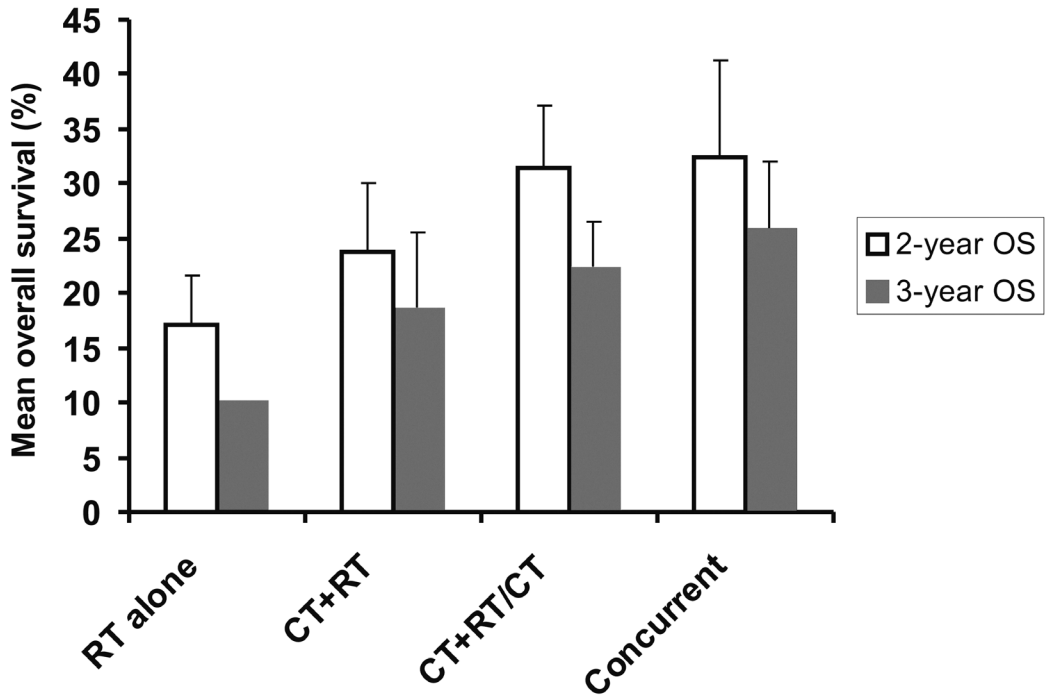
Figure 2. Mean 2- and 3-year overall survival of unresectable stage III non-small cell lung cancer for radiotherapy alone (RT alone), sequential chemo-radiotherapy (CT+RT), sequential therapy with concurrent chemo-radiotherapy (CT+RT/CT) and concurrent chemo-radiotherapy. The overall survivals of CT+RT/CT and concurrent chemo-radiotherapy were significantly different from that of RT only.

increase from 10.4 to 13.0 months ($p<0.05$), and a 6.2% point increase in 2-year OS, from 17.1 to 23.3% (ns). The pooled results of 6 randomised trials also indicated a significant increase in 2-year OS for sequential chemo-radiotherapy over radiotherapy alone. A further improvement in results was observed when, after induction chemotherapy, the subsequent radiotherapy was concurrently given with chemotherapy, (or when radiotherapy was given in a short overall time), the mean MST increased significantly ($p<0.05$) from 13 to 15.8 months and the mean 2-year OS increased significantly from 17.1 to 31.3% ($p<0.05$).

Table II. Two-year overall survival in 6 studies comparing radiotherapy (RT) only and induction chemotherapy followed by radiotherapy (Sequential CR); relative risk (RR) with 95% confidence interval (CI).

First author	Two-year Overall Survival						RR (95% CI)	Sig
	RT only			Sequential CR				
	N	Nsurv	Surv	N	Nsurv	Surv		
Brodin (26)	154	128	26	148	117	31	0.95 (0.85-1.06)	ns
Crino (27)	33	28	5	33	23	10	0.82 (0.63-1.07)	ns
Cullen (28)	223	187	36	223	169	54	0.90 (0.82-0.99)	s
Dillman (29)	77	67	10	78	58	20	0.85 (0.73-0.99)	s
Gregor (30)	39	31	8	39	31	8	1 (0.80-1.25)	ns
Le Chevalier (31)	177	152	25	176	139	37	0.92 (0.83-1.01)	ns
Pooled	703	593	110	697	537	160	0.91(0.87-0.96)	s
Mean OS		15.6%			22.9%			

N: number of patients; Nsurv: non-survivors; Surv: survivors; RR: relative risk; CI: confidence interval; Sig: significancy; s: significant (95%CI does not include the value 1); ns: non significant.

Concurrent versus sequential chemo-radiotherapy (Table III). In a Japanese randomised trial including 320 patients, chemotherapy concurrent with split-course daily radiotherapy was compared with induction chemotherapy followed by radiotherapy (35). The MST for concurrent versus sequential chemo-radiotherapy was 16.4 versus 13.3 months and the 2-year and 5-year survivals were 34.6 and 15.8% versus 27.4 and 8.9%, respectively (Tables I and III).

A long-term benefit was observed in the three-arm randomised phase III RTOG 9410 study with 600 patients for concurrent as compared to sequential chemo-radiotherapy (36). Two of the 3 arms compared the induction of vinblastine/cisplatin, followed by radiotherapy up to 60 Gy, with the same chemotherapy given concurrently with the same radiation dose. The third arm included radiotherapy twice daily up to 69.6 Gy, with concurrent chemotherapy consisting of cisplatin and oral etoposide.

Table III. Median survival time and overall survival after concurrent chemo-radiotherapy, and those of sequential chemo-radiotherapy as shown in Table I.

First author	N	Chemo-therapy	RT (Gy)	Median survival time (months)	Overall survival (%)
Furuse (35)	156	C, vind, mito	56Gy/8w	16.5	2-5y: 34.6, 22.3, 16.9, 15.8
		sequential:		13.3	2-5y: 27.4, 14.7, 10.1, 8.9
Curran (36)	~200	C, V	60	17	4y: 21
	~200	C, etop	69.6/1.2 Gy/fr 2 fr/day	15.2	4y: 17
		sequential:		14.6	4y: 12
Pierre (37)	103	C, etop	33x2	15	1y: 56, 2y: 35
		sequential:		13.8	1y : 56 ; 2y : 23
Zatloukal (38)	52	vino, C	60	16.6	1-3y: 69.2, 34.2, 18.6
		sequential:		12.9	1-3y: 53, 14.3, 9.5
Choi (39)	42	C	30x2	14	
		sequential:		12.3	
Graham (40)	31	C, etop	65/5w	22.3	2y: 48
		sequential:		16.9	2y: 34
Saha (41)	55	pac, Ca	60	14.8	1y: 74.5; 2y: 31
	55	pac, Ca	60/Ca, pac	16.1	1y: 78.2; 2y: 31
		sequential:		13.6	1y : 70; 2y: 28
Jeremic (43)	98	Ca, etop	69.6/1.2 Gy/fr 2 fr/day	20	5y: 20
	97	Idem + weekend	69.6/1.2 Gy/fr 2 fr/day	22	5y: 23

Study	N	Chemo	RT		Survival
Ichinose (44)	70	UFT, C	30x2	16.5	1y: 67; 2y: 33
Ball (45)	41	Ca	30x2/6w	17	1y: 63; 2y: 29; 5y: 8
	42		30x2/6w	13.8	1y: 60; 2y: 26; 5y: 10
	41	Ca	30x2/3w	15	1y: 59; 2y: 20; 5y: 5
	36		30x2/3w	14.4	1y: 61; 2y: 28; 5y: 13
Blackstock (46)	41	G	60-74	18.8	
Dediu (47)	24	vino, C	15x2 + 15x2 T: 8w	12	
Kim (48)	108	pac, Ca	RT	18.4	2y: 38.5; 4y: 16.3, 6y: 10.1
Maguire (49)	62	C	52.5 - 55 fr 2.625-2.75		1-3y: 74, 35, 32
Park (50)	52	etop, C	63/1.8Gy/fr	15.3	1-3y: 62, 40, 30; 5y: 16
Ryu (51)	144	pac, C	39x1.8; T: 8w	14.1	
Rusu (52)	30	navelbine, C	30x2	13	1y: 55
Takayama (53)	63	pac, Ca	60-65/1.8-2/fr		1y: 54
Kaplanova (54)	45	pac, Ca	60		1-2y: 44, 13
Zajusz (55)	22	G	60	15.5	5y: 13

N: number of patients; C: cisplatin; Ca: carboplatin; etop: etoposide; G: gemcitabine; mito: mitomycin; pac: paclitaxel; UFT: uracil/tegafur; vino: vinorelbine; vind: vindesine; V: vinblastine; RT: radiotherapy; T: overall treatment time radiotherapy; w: week; fr: fraction.

In the sequential arm with vinblastine and cisplatin, the MST reached 14.6 months and the 4-year survival 12% (Table I), compared with 17 months and 21%, respectively, for concurrent vinblastine, cisplatin and radiotherapy (Table III). The twice-daily radiotherapy and concurrent etoposide and cisplatin had a MST of 15.2 months and 4-year survival of 17%.

A French co-operative group performed a phase III randomised trial of sequential *versus* concurrent chemo-radiotherapy in unresectable IIIA/IIIB patients (37). The chemotherapy consisted of cisplatin and vinorelbine for 3 cycles, followed by radiotherapy of 33 fractions of 2 Gy (Table I), or concurrent cisplatin/etoposide with radiotherapy followed by cisplatin and vinorelbine. For sequential therapy, the MST was 13.8 months and 1- and 2-year survivals 56% and 23%, respectively. With concurrent therapy, the MST was 15 months and the 1- and 2-year survival rates 56% and 35%, respectively, indicating a trend in favour of concurrent therapy (Table III).

Zatloukal *et al.* reported, in a randomised phase II study, on concurrent *versus* sequential radio-chemotherapy with vinorelbine plus cisplatin in locally advanced NSCLC (38). One hundred and two patients were enrolled. The chemotherapy consisted of 4 cycles of cisplatin and vinorelbine, repeated every 4 weeks. Radiotherapy was administered in 30 fractions of 2 Gy in 6 weeks. The MST for sequential therapy was 12.9 months and for concurrent therapy 16.6 months (p=0.023, log-rank test) (Tables I and III). The results confirmed the superiority of concurrent over sequential chemo-radiotherapy in terms of response rate and OS. The associated higher toxicities of concurrent radiotherapy appeared acceptable.

In a randomised trial in stage III NSCLC, the efficacy of hyperfractionated radiation therapy and concurrent low-dose, daily carboplatin/etoposide, with or without weekend carboplatin/etoposide chemotherapy, was determined (43). No statistically significant difference was found regarding MST and 5-year survival rates, 20 *versus* 22 months and 20 *versus* 23%, respectively (Table III). Thus, the addition of weekend carboplatin/etoposide did not significantly improve the results over those obtained with hyperfractionated radiotherapy and concurrent low-dose, daily carboplatin/etoposide, but it led to a higher incidence of acute high-grade haematological toxicity.

In a multi-institutional phase II trial, uracil/tegafur plus cisplatin with concurrent radiotherapy was considered to be a feasible and effective

treatment (44). The median survival time was 16.5 months and the 1- and 2-year survival rates were 67 and 33%, respectively (Table III).

Ball *et al.* however, reported on a 4-armed randomised phase III study of standard fraction radiotherapy or accelerated radiotherapy (30 x 2 Gy in 6 *vs* 3 weeks), with or without concurrent carboplatin, in 204 patients with inoperable NSCLC (45). Their study failed to show a significant survival advantage for any of the treatment arms or factors. Halving the overall treatment time resulted in significantly greater oesophageal toxicity with no survival advantage. It is probable that the number of patients per arm was too small for significant differences to be found. The results of this study are shown in Table III.

Additional MST and OS data for concurrent chemo-radiotherapy were derived from the abstracts of the 10th World Conference on Lung Cancer (39-41, 46-55), Table III. From Table III, the mean MST for concurrent chemo-radiotherapy was 16.4 ± 2.7 months and the mean 2- and 3-year OS rates were 32.5 ± 8.7% and 25.7 ± 6.3%, respectively. The mean values of the MST and OS are shown in Figures 1 and 2, respectively.

In only 3 randomised studies were 2-year OS for sequential and concurrent chemo-radiotherapy provided (35, 38, 41). They are listed in Table IV. We determined the RR of concurrent therapy and sequential therapy for each trial and for the pooled results. The mean OS for the pooled data for the sequential and concurrent treatments were 24.9 and 33.8%, respectively. The OS was significantly higher for the concurrent regimen (pooled RR=0.88; 95% confidence interval 0.79-0.98). This analysis also indicates that concurrent therapy results in better OS than sequential therapy.

In conclusion, the results observed for stage III inoperable NSCLC indicate a significant benefit for concurrent chemo-radiotherapy over sequential chemo-radiotherapy. For all studies together, the gain was a significant 3.4-month increase in mean MST, from 13.0 to 16.4 months ($p<0.05$), and OS at 2 and 3 years from 23.8 to 32.5 and 18.5 to 25.7%, respectively (not significantly, too few data points). Also the pooled results of 3 randomised studies comparing sequential and concurrent chemo-radiotherapy showed a significant increase in 2-year OS for the concurrent regimen (Table IV).

Survival curves. For radiotherapy alone, sequential chemo-radiotherapy, induction chemotherapy followed by concurrent chemo-radiotherapy and concurrent chemo-radiotherapy, the mean MST values, and the

Table IV. Two-year overall survival in 3 studies comparing sequential and concurrent chemo-radiotherapy, relative risks and pooled relative risk with 95% confidence interval.

First author	Two-year Overall Survival						RR (95% CI)	Sig
	Sequential			Concurrent				
	N	Nsurv	Surv	N	Nsurv	Surv		
Furuse (35)	158	115	43	156	102	54	0.90 (0.77-1.04)	ns
Zatloukal (38)	50	43	7	52	34	18	0.76 (0.61-0.95)	s
Saha (41)	57	41	16	55	38	17	0.96 (0.76-1.22)	ns
Pooled	265	199	66	263	174	89	0.88 (0.79-0.98)	s
Mean OS	24.9%			33.8%				

N: number of patients; Nsurv: non-survivors; Surv: survivors; RR: relative risk; CI: confidence interval; OS: overall survival.

mean OS rates at 1 to 6 years were calculated. The data points are shown in Figure 3. The curves through the data points are fitted by a power function $y=ax^{-b}$. The survival curves illustrate the benefits of concurrent therapy over radiotherapy alone: an increase in MST from 10.4 months (0.9 year) to 16.4 months (1.4 year) and with 5-year OS values from about 7 to 15%, respectively. The data points obtained for induction chemotherapy followed by concurrent chemo-radiotherapy (crosses) are close to the data points of the concurrent chemo-radiotherapy regimens. This indicates that the sequential treatment in which the radiotherapy part was combined with chemotherapy is approximately as effective as the shorter concurrent treatment.

Overall treatment time of sequential chemo-radiotherapy. Earlier, we reported on the influence of the waiting time between induction chemotherapy and the start of radiotherapy in stage III NCSLC (56). We described that, in the waiting period for potentially curative radiotherapy, which lasted from 29 to 141 days, 9 out of 22 lung cancer patients became incurable. The growth rate of lung tumours after induction chemotherapy was about twice that of non-treated tumours. This indicates that additional therapy deals with a rapidly proliferating tumour and that, for sequential chemo-radiotherapy, the delay in starting radiotherapy should be as short as reasonably achievable.
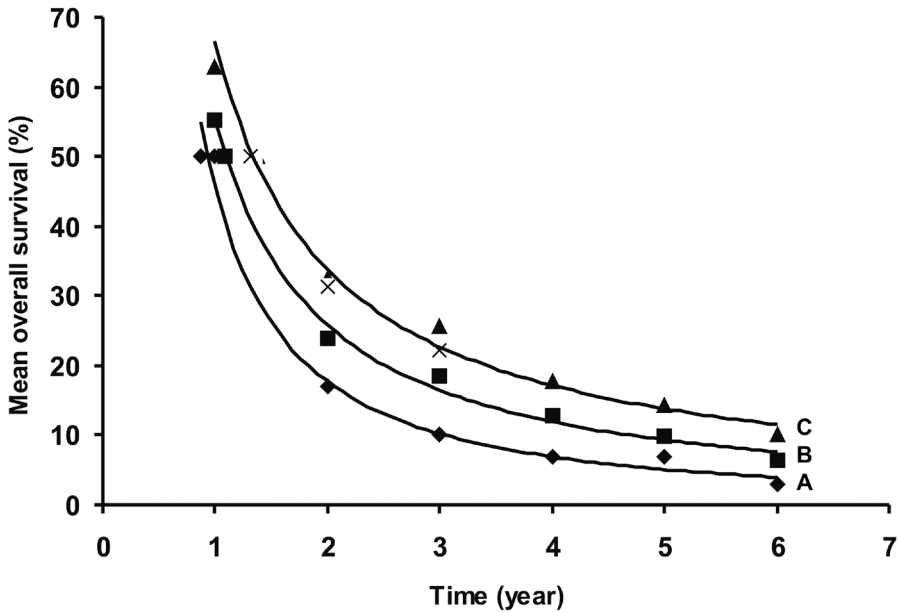
Figure 3. Mean overall survival of unresectable stage III non-small cell lung cancer with radiotherapy alone (curve A, diamonds), sequential chemo-radiotherapy (curve B, squares), concurrent chemo-radiotherapy (curve C, triangles) and sequential therapy with concurrent chemo-radiotherapy (crosses). The data points are fitted with a power function $y = ax^{-b}$. The data points are mean values of the figures in Tables I and III.

The influence of the waiting time between induction chemotherapy and radiotherapy on tumour control probability was also studied. For conventional radiotherapy, *e.g.* 33 fractions of 2 Gy in an overall treatment time of 45 days, the biologically effective dose in a previously untreated tumour is larger than in a tumour pre-treated with induction chemotherapy. That is because, in a previously untreated tumour, accelerated repopulation of the surviving tumour cells starts approximately in the third or fourth week of the radiotherapy (57), while in the pre-treated tumour (with induction chemotherapy) this repopulation is already present on the first day of the radiotherapy. The estimated dose to circumvent accelerated repopulation in lung tumours is about 0.45 to 0.6 Gy/day (57, 58). It is reasonable to assume that, due to induction chemotherapy, resting tumour cells are triggered to become proliferating cells. Thus, after induction chemotherapy, relatively

more tumour cells are cycling. Because of the smaller fraction of non-cycling cells, repair of potentially lethal damage is less, resulting in a more radiosensitive tumour after induction chemotherapy. Induction chemotherapy will, in general, also result in a smaller tumour volume and, hence, in a smaller number of tumour cells. This enhanced radiosensitivity and smaller number of cells will counteract the loss in the biologically effective dose of the subsequent radiotherapy. Indeed, the results of sequential chemo-radiotherapy show more benefit than radiation alone, as mentioned before. With the tumour control probability (TCP) model of Webb and Nahum (59), calculations can be made for the TCP for radiotherapy of a previously untreated tumour and of a tumour after induction chemotherapy. The assumptions are that the mean intrinsic radiosensitivity is 0.30 Gy^{-1} for an untreated tumour and 0.32 Gy^{-1} for a tumour after chemotherapy, that the clonogen density is $10^7 cm^{-3}$ (60) and that the tumour volume has decreased after induction chemotherapy, from *e.g.* 100 to 25 cm^3. Due to volume reduction and increased radiosensitivity, although a less biologically effective dose, the calculated TCP increased from about 4% for a previously untreated tumour to 20% for a pre-treated tumour. However, if the waiting period after induction chemotherapy is relatively long, the tumour volume will increase rapidly, because of the increased growth rate after chemotherapy, and the expected gain in TCP will be lowered, as shown in our earlier report (56). As a consequence, the interval between induction chemotherapy and radiotherapy should be as short as possible, as well as the overall treatment time of the radiotherapy following induction chemotherapy. This is clearly illustrated in the study by Metha *et al.* where accelerated radiotherapy improved the treatment results compared to the results after conventional fractionation (23).

Discussion and conclusion

From the above overview, it can be concluded that for patients with stage III unresectable NSCLC, progress has been made in the past decade. The 5-year survival has increased from about 7% for radiotherapy alone to 10% for sequential and about 15% for concurrent chemo-radiotherapy. However, the concurrent chemo-radiotherapy schedules were associated with higher toxicity as compared to sequential therapy with the same drug doses: acute oesophagitis, neutropenia and anaemia were significantly increased (*e.g.* 38, 44). For the clinician, it is a challenge to optimise the treatment, *e.g.* acute oesophagitis may be dealt with using

three-dimensional radiotherapy planning techniques. The suggestion that amifostine may protect the oesophagus was not confirmed in a large RTOG randomised trial (61). Other cytoprotectants have not been evaluated, though it would seem logical to do so in future trials (62).

For optimisation, high-precision radiotherapy must be applied to deliver a large radiation dose to the target area (63, 64), keeping the dose to surrounding tissues as low as possible; thus schemes for drug delivery have to be optimised. Further improvements may be obtained with consolidation chemotherapy after concurrent chemo-radiotherapy (65-67).

Although the predominant cause of death in NSCLC is believed to be distant metastases, local recurrence is still a major cause of failure. Animal experiments and clinical data in lung, prostate and mammary cancers indicated that improvements in local control would decrease distant metastases, since part of the distant metastases was derived from local recurrences of the cancer (68-71). Therefore, a further increase of local control for NSCLC could lead to improvement in survival.

References

1. Weir HK, Thun MJ, Hankey BF, *et al*: Annual report to the nation on the status of cancer, 1975-2000, featuring the uses of surveillance data for cancer prevention and control. J Natl Cancer Inst 95: 1276-1299, 2003.
2. Mountain CF: Revisions in the International System for Staging Lung Cancer. Chest 111: 1710-1717, 1997.
3. Perez CA, Pajak TF, Rubin P, *et al*: Long-term observations of the patterns of failure in patients with unresectable non-oat cell carcinoma of the lung treated with definitive radiotherapy. Report by the Radiation Therapy Oncology Group. Cancer 59: 1874-1881, 1987.
4. Johnson DH, Einhorn LH, Bartolucci A, *et al*: Thoracic radiotherapy does not prolong survival in patients with locally advanced, unresectable non-small cell lung cancer. Ann Intern Med 113: 33-38, 1990.
5. Sibley GS, Jamieson TA, Marks LB, *et al*: Radiotherapy alone for medically inoperable stage I non-small-cell lung cancer: the Duke experience. Int J Radiat Oncol Biol Phys 40: 149-154, 1998.
6. Graham PH, Gebski VJ, Langlands AO: Radical radiotherapy for early nonsmall cell lung cancer. Int J Radiat Oncol Biol Phys 31: 261-266, 1995.
7. Cox JD, Azarnia N, Byhardt RW, *et al.* A randomized phase I/II trial of hyperfractionated radiation therapy with total doses of 60.0 to 79.2 Gy: possible survival benefit with greater than or equal to 69.6 Gy in favorable patients with Radiation Therapy Oncology Group stage III non-small-cell lung carcinoma: report of Radiation Therapy Oncology Group 83–11. J Clin Oncol 8: 1543-1555, 1990.
8. Saunders M, Dische S, Barrett A, *et al*: Continuous hyperfractionated accelerated radiotherapy (CHART) *versus* conventional radiotherapy in non-small-cell lung cancer: a randomised multicentre trial. CHART Steering Committee. Lancet 350: 161-165, 1997.
9. Saunders MI, Rojas A, Lyn BE, *et al*: Experience with dose escalation using CHARTWEL (continuous hyperfractionated accelerated radiotherapy weekend less) in non-small-cell lung cancer. Br J Cancer 78: 1323-1328, 1998.
10. Koutaïssoff S, Wellmann D, Coucke P, *et al*: Hyperfractionated accelerated radiotherapy (HART) for inoperable, nonmetastatic non-small cell lung carcinoma of the lung (NSCLC): results of a phase II study for patients ineligible for combination radiochemotherapy. Int J Radiat Oncol Biol Phys 45: 1151-1156, 1999.
11. Mehta M, Tannehill, S, Adak, S, *et al*: Phase II trial of hyperfractionated accelerated radiation therapy for non-resectable non-small-cell lung cancer: Results of Eastern Cooperative Oncology Group 4593. J Clin Oncol 16: 518-523, 1998.
12. Cox JD, Pajak TF, Asbell S, *et al*: Interruptions of high-dose radiation therapy

decrease long-term survival of favorable patients with unresectable non-small cell carcinoma of the lung: analysis of 1244 cases from 3 Radiation Therapy Oncology Group (RTOG) trials. Int J Radiat Oncol Biol Phys 27: 493-498, 1993.

13. Rapp E, Pater JL, Willan A, *et al*: Chemotherapy can prolong survival in patients with advanced non-small-cell lung cancer - report of a Canadian multicenter randomized trial. J Clin Oncol 6: 633-641, 1988.

14. Jett JR, Scott WJ, Rivera MP, *et al*: American College of Chest Physicians. Guidelines on treatment of stage IIIB non-small cell lung cancer. Chest 123 (1 Suppl): 221S-225S, 2003.

15. Sirzén F, Kjellén E, Sörenson S, *et al*: A systematic overview of radiation therapy effects in non-small cell lung cancer. Acta Oncol 42: 493-515, 2003.

16. Marino P, Preatoni A, Cantoni A: Randomized trials of radiotherapy alone *versus* combined chemotherapy and radiotherapy in stages IIIa and IIIb nonsmall cell lung cancer. A meta-analysis. Cancer 76: 593-601, 1995.

17. Pritchard RS, Anthony SP: Chemotherapy plus radiotherapy compared with radiotherapy alone in the treatment of locally advanced, unresectable, non-small cell lung cancer: a meta-analysis. Ann Intern Med 125: 723-729, 1996.

18. Non-small Cell Lung Cancer Collaborative Group: Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. BMJ 311: 899-909, 1995.

19. Sörenson S, Glimelius B, Nygren P; SBU-group. Swedish Council of Technology Assessment in Health Care: a systematic overview of chemotherapy effects in non-small cell lung cancer. Acta Oncol 40: 327-339, 2001.

20. Robinson LA, Wagner H Jr, Ruckdeschel JC; American College of Chest Physicians: Treatment of stage IIIA non-small cell lung cancer. Chest 123 (1 Suppl): 202S-220S, 2003.

21. Sause W, Kolesar P, Taylor S IV, *et al*: Final results of phase III trial in regionally advanced unresectable non-small cell lung cancer: Radiation Therapy Oncology Group, Eastern Cooperative Oncology Group, and Southwest Oncology Group. Chest 117: 358-364, 2000.

22. Kim TY, Yang SH, Lee SH, *et al*: A phase III randomized trial of combined chemoradiotherapy *versus* radiotherapy alone in locally advanced non-small-cell lung cancer. Am J Clin Oncol 25: 238-243, 2002.

23. Mehta MP, Wang W, Johnson D, *et al*: Induction chemotherapy followed by standard thoracic radiotherapy *vs.* hyperfractionated accelerated radiotherapy for patients with unresectable stage IIIA and B non-small cell lung cancer: phase III study of the Eastern Cooperative Oncology Group (ECOG 2597). Abstract. Int J Radiat Oncol Biol Phys 57: S141, 2003.

24. Vokes EE, Herndon JE 2nd, Crawford J, *et al*: Randomized phase II study of cisplatin with gemcitabine or paclitaxel or vinorelbine as induction

chemotherapy followed by concomitant chemoradiotherapy for stage IIIB non-small-cell lung cancer: Cancer and Leukemia Group B study 9431. J Clin Oncol 20: 4191-4198, 2002.

25. Willner J, Huber H, Poellinger B, *et al*: CTRT 99/97 a randomized trial of simultaneous paclitaxel and radiotherapy *vs* radiotherapy alone following induction chemotherapy in stage III inoperable NSCLC. Abstract. Int J Radiat Oncol Biol Phys 57: S140, 2003.

26. Brodin O, Nou E, Mercke C, *et al*: Comparison of induction chemotherapy before radiotherapy with radiotherapy only in patients with locally advanced squamous cell carcinoma of the lung. The Swedish Lung Cancer Study Group. Eur J Cancer 32A: 1893-1900, 1996.

27. Crino L, Latini P, Meacci M, *et al*: Induction chemotherapy plus high-dose radiotherapy *versus* radiotherapy alone in locally advanced unresectable non-small-cell lung cancer. Ann Oncol 4: 847-851, 1993.

28. Cullen MH, Billingham LJ, Woodroffe CM, *et al*: Mitomycin, ifosfamide, and cisplatin in unresectable non-small-cell lung cancer: effects on survival and quality of life. J Clin Oncol 17: 3188-3194, 1999.

29. Dillman RO, Herndon J, Seagren SL, *et al*: Improved survival in stage III non-small-cell lung cancer: seven-year follow-up of cancer and leukemia group B (CALGB) 8433 trial. J Natl Cancer Inst 88: 1210-1215, 1996.

30. Gregor A, Macbeth FR, Paul J, *et al*: Radical radiotherapy and chemotherapy in localized inoperable non-small-cell lung cancer: a randomized trial. J Natl Cancer Inst 85: 997-999, 1993.

31. Le Chevalier T, Arriagada R, Tarayre M, *et al*: Significant effect of adjuvant chemotherapy on survival in locally advanced non-small-cell lung carcinoma. J Natl Cancer Inst 84: 58, 1992.

32. Kubota K, Furuse K, Kawahara M, *et al*: Role of radiotherapy in combined modality treatment of locally advanced non-small-cell lung cancer. J Clin Oncol 12: 1547-1552, 1994.

33. Sculier JP, Paesmans M, Lafitte JJ, *et al*: A randomised phase III trial comparing consolidation treatment with further chemotherapy to chest irradiation in patients with initially unresectable locoregional non-small-cell lung cancer responding to induction chemotherapy. European Lung Cancer Working Party. Ann Oncol 10: 295-303, 1999.

34. Wolf M, Hans K, Becker H, *et al*: Radiotherapy alone *versus* chemotherapy with ifosfamide/vindesine followed by radiotherapy in unresectable locally advanced non-small cell lung cancer. Semin Oncol 21(3 Suppl 4): 42-47, 1994

35. Furuse K, Fukuoka M, Kawahara M, *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 17: 2692-2699, 1999.

36. Curran WJ, Scott CB, Langer CJ, *et al*: Long-term benefit is observed in a phase III comparison of sequential vs concurrent chemo-radiation for patients with

unresected stage III NSCLC: RTOG 9410. Am Soc Clin Oncol, abstract 2499, 2003.

37. Pierre F, Maurice P, Gilles R *et al*: A randomized phase III trial of sequential chemoradiotherapy in locally advanced non-small cell lung cancer. Abstract. Proc Am Soc Clin Oncol 20: 312a, 2001.

38. Zatloukal P, Petruzelka L, Zemanova M, *et al*: Concurrent *versus* sequential chemoradiotherapy with cisplatin and vinorelbine in locally advanced non-small cell lung cancer: a randomized study. Lung Cancer 246: 87-98, 2004.

39. Choi JH, Lim HY, Kim HC, *et al*: The addition of induction chemotherapy failed to improve therapeutic outcome of concurrent chemoradiotherapy in patients with locally advanced non-small cell lung cancer. Abstract. Lung Cancer 41, Suppl 2: S238, 2003.

40. Graham PH, Abell FL, Capp A, *et al*: Concurrent end-phase boost radiation therapy to 65 Gy in 5 weeks for non-small cell lung cancer with or without cisplatin chemotherapy. Abstract. Lung Cancer 41, Suppl 2: S243-245, 2003.

41. Saha S, Das Gupta P, Gangopadhaya S: Various chemoradiation modalities in inoperable non-small-cell lung cancer: an Indian experience. Abstract. Lung Cancer 45: S54-55, 2004.

42. Clamon G, Herndon J, Cooper R, Chang AY, Rosenman J, Green MR: Radiosensitization with carboplatin for patients with unresectable stage III non-small-cell lung cancer: a phase III trial of the Cancer and Leukemia Group B and the Eastern Cooperative Oncology Group. J Clin Oncol 17: 4-11, 1999.

43. Jeremic B, Shibamoto Y, Acimovic L, *et al*: Hyperfractionated radiation therapy and concurrent low-dose, daily carboplatin/etoposide with or without weekend carboplatin/etoposide chemotherapy in stage III non-small-cell lung cancer: a randomized trial. Int J Radiat Oncol Biol Phys 50: 19-25, 2001.

44. Ichinose Y, Nakai Y, Kudoh S, *et al*: Uracil/tegafur plus cisplatin with concurrent radiotherapy for locally advanced non-small-cell lung cancer: a multi-institutional phase II trial: Clin Cancer Res 10: 4369-4373, 2004.

45. Ball D, Bishop J, Smith J, *et al*: A randomised phase III study of accelerated or standard fraction radiotherapy with or without concurrent carboplatin in inoperable non-small cell lung cancer: final report of an Australian multi-centre trial. Radiother Oncol 52: 129-136, 1999.

46. Blackstock AW, Case LD, Ho C, *et al*: Gemcitabine and concurrent thoracic radiotherapy. A phase I/II study in patients with advanced non-small cell lung cancer. Abstract. Lung Cancer 41, Suppl 2: S243, 2003.

47. Dediu M, Tarlea A, Iorga P, *et al*: Split course radiation with concurrent vinorelbine (NVB) and cisplatin (CDDP) in locally advanced non-small cell lung cancer (NSCLC). A phase II study. Abstract. Lung Cancer 41, Suppl 2: S238, 2003.

48. Kim DW, Shyr Y, Akerley WL, *et al*: Tumor responsiveness to combined modality therapy is highly significant predictor of survival for patients with locally advanced non-small cell lung cancer. Abstract. Lung Cancer 41, Suppl 2: S239-240, 2003.

49. Maguire J, Page R, Kelly V, *et al*: Improved local control and survival in stage III NSCLC with concurrent cisplatinum and radical radiotherapy in four weeks. Abstract. Lung Cancer 41, Suppl 2: S245, 2003.

50. Park J, Ahn YC, Kim H, *et al*: A phase II trial of concurrent chemoradiation therapy followed by consolidation chemotherapy with oral etoposide and cisplatin for locally advanced inoperable non-small cell lung cancers. Lung Cancer 42, 227-235, 2003.

51. Ryu MH, Kim SW, Hwang CY, *et al*: Severe radiation pneumonitis after concurrent chemoradiation therapy in locally advanced non-small cell lung cancer: risk factors and the prognosis. Abstract. Lung Cancer 41, Suppl 2: S238-239, 2003.

52. Rusu P, Ciuleanu TE, Cernea D, *et al*: Concurrent chemoradiotherapy with navelbine and cisplatin for unresectable stage III NSCLC: a phase II study. Abstract. Lung Cancer 41, Suppl 2: S241, 2003.

53. Takayama K, Nakanishi Y, Kawasaki M, *et al*: Concurrent paclitaxel, carboplatin and radiation therapy for locally advanced non-small cell lung cancer. Abstract. Lung Cancer 41, Suppl 2: S243, 2003.

54. Kaplanova J, Spelda S, Skrickova J, *et al*: Concomitant chemotherapy with paclitaxel, carboplatin and radiotherapy in the tresatment of locoregionally advanced non-small-cell lung cancer. Abstract. Lung Cancer 45: S59, 2004.

55. Zajusz A, Nowicka E, Behrendt K, *et al*: The efficacy of concurrent thoracic radiotherapy and gemcitabine in locally advanced NSCLC patients (LA-NSCLC) – long-term results. Abstract. Lung Cancer 45: S59-60, 2004.

56. El Sharouni SY, Kal HB, Battermann JJ: Accelerated regrowth of non-small-cell lung tumours after induction chemotherapy. Br J Cancer 89: 2184-2189, 2003

57. Koukourakis M, Hlouverakis G, Kosma L, *et al*: The impact of overall treatment time on the results of radiotherapy for nonsmall cell lung carcinoma. Int J Radiat Oncol Biol Phys 34: 315-322, 1996.

58. Fowler JF, Chappell R: Non-small cell lung tumors repopulate rapidly during radiation therapy. Int J Radiat Oncol Biol Phys 46: 516-517, 2000.

59. Webb S, Nahum AE: A model for calculating tumour control probability in radiotherapy including the effects of inhomogeneous distributions of dose and clonogenic cell density. Phys Med Biol 38: 653-666, 1993.

60. Webb S: Optimum parameters in a model for tumour control probability including interpatient heterogeneity. Phys Med Biol 39: 1895-1914, 1994.

61. Werner-Wasik M, Scott C, Movas B, *et al*: Amifostine as mucosal protectant in patients with locally advanced non-small cell lung cancer (NSCLC)

receiving intense chemotherapy and thoracic radiotherapy (RT): results of the Radiation Therapy Oncology Group (RTOG) 98-01 study. Abstract. Int J Radiat Oncol Biol Phys 57 (Suppl 2): S216, 2003.

62. Xian CJ: Roles of growth factors in chemotherapy-induced intestinal mucosal damage repair. Curr Pharm Biotechnol 4: 260-269, 2003.

63. Senan S, De Ruysscher D, Girraud P, *et al*: Literature-based recommendations for treatment planning and execution in high-dose radiotherapy for lung cancer. Radiother Oncol 71: 139-146, 2004.

64. Socinski MA, Zhang C, Herndon JE II, *et al*: Combined modality trials of the Cancer and Leukemia Group B in stage III non-small-cell lung cancer: analysis of factors influencing survival and toxicity. Ann Oncol 15: 1033-1041, 2004.

65. Sakai H, Yoneda S, Kobayashi K, *et al*: Phase II study of bi-weekly docetaxel and carboplatin with concurrent thoracic radiation therapy followed by consolidation chemotherapy with docetaxel plus carboplatin for stage III unresectable non-small cell lung cancer. Lung Cancer 43: 195-201, 2004.

66. Gandara DR, Chansky K, Albain KS, *et al*: Consolidation docetaxel after concurrent chemoradiotherapy in stage IIIB non-small-cell lung cancer: phase II Southwest Oncology Group Study S9504. J Clin Oncol 21: 2004-2010, 2003.

67. Gaafar RM, Abdelbaki H, Safwat A, *et al*: Accelerated hyperfractionation radiotherapy and daily cisplatin followed by consolidation chemotherapy. A phase II trial for patients with inoperable stage III NSCLC. Abstract. Lung Cancer 45: S53-54, 2004.

68. Ramsay J, Suit HD, Sedlacek R: Experimental studies on the incidence of metastases after failure of radiation treatment and the effect of salvage surgery. Int J Radiat Oncol Biol Phys 14: 1165-1168, 1988.

69. Fu XL, Jiang GL, Wang LJ, *et al*: The value of local control in the radiation therapy for non-small cell lung cancer. Shanghai Med 19: 559-561, 1996.

70. Freiha FS, Bagshaw MA: Carcinoma of the prostate: results of post-irradiation biopsy. Prostate 5: 19-25, 1984.

71. Whelan TJ, Julian J, Wright J, *et al*: Does locoregional radiation therapy improve survival in breast cancer? A meta-analysis. J Clin Oncol 18: 1220-1229, 2000.

Chapter 3

Accelerated regrowth of non-small cell lung tumours after induction chemotherapy

S.Y. El Sharouni
H.B. Kal
J.J. Battermann

Summary

Induction chemotherapy of non-small cell lung cancer (NSCLC) stage III with gemcitabine and cisplatin for downstaging of the tumour with the aim for further treatment with ionising radiation is one of the treatments for lung cancer patients. The purpose of this study was to investigate the influence of the waiting time for radiotherapy, that is the interval between induction chemotherapy and radiotherapy, on the rate of tumour growth for patients with NSCLC.

Interval times between end of induction chemotherapy and date of diagnostic CT, planning CT and first day of radiotherapy were determined for 23 patients with NSCLC. Increase in gross tumour volume was measured for 18 patients by measuring the dimensions of the primary tumour and lymph node metastases on the diagnostic CT after induction chemotherapy and on the CT used for radiotherapy planning. For each patient the tumour volume doubling time was calculated from the time interval between the two CTs and ratio of the gross volumes on planning CT and diagnostic CT.

The mean time interval between end of chemotherapy and day of diagnostic CT was 15.8 days, and till first day of radiotherapy 80.3 (range 29 - 141) days. In all, 41% of potentially curable patients became incurable in the waiting period. The ratio of gross tumour volumes of the two CTs ranged from 1.1 to 81.8 and the tumour volume doubling times ranged from 8.3 to 171.4 days, with a mean value of 45.8 days and median value of 29.4 days. This is far less than the mean tumour volume doubling time of NSCLC in untreated patients found in literature.

This study shows that in the time interval between end of induction chemotherapy and start of radiotherapy rapid tumour progression occurs as result of accelerated tumour cell proliferation: mean tumour volume doubling times are much shorter than those in not treated tumours. As a consequence, the gain obtained with induction chemotherapy with regard to volume reduction was lost in the waiting time for radiotherapy. We recommend diminishing the time interval between chemo- and radiotherapy to as short as possible.

Introduction

Lung cancer is the leading cause of cancer death in both men (32%) and women (25%) (Perez and Brady, 1998). In the last decades, there was a sharp increase in the incidence of lung cancer (Storm *et al*, 1999; Teppo *et al*, 1999). About two-third of non-small cell lung cancer (NSCLC) patients are diagnosed with distant disease, which restricts the option of radically intended treatment to less than one-third of patients (Jensen *et al*, 2002). The results of radiotherapy alone for lung cancer patients are still disappointing. Overall, only 5% of patients survived more than five years; loco-regional control was about 20% after five years and more than 60% of patients developed distant metastases (Fietkau, 2001).

Shortening of the overall treatment time (OTT) improved local control and survival after radiotherapy of lung cancer patients (Fu *et al*, 1997; Bonner *et al*, 1998; Saunders *et al*, 1999) indicating the importance of cellular repopulation as a cause of failure in the radiotherapy of NSCLC (Saunders *et al*, 1997; Fowler and Chappell, 2000). Furthermore, tumour progression during the waiting time till the start of radiotherapy for lung cancer and head-and-neck tumours, respectively, was reported, indicating a possible negative influence on treatment results (O'Rourke and Edwards, 2000; Waaijer *et al*, 2003).

Owing to restaging procedure after induction chemotherapy and waiting times for radiotherapy, we were interested to know to what extent the waiting period between the end of induction chemotherapy and the start of radiotherapy might influence tumour behaviour. To our knowledge, such a study on behaviour of NSCLC after induction chemotherapy has not been reported yet. The purpose of this study was to investigate the influence of the waiting time on the rate of tumour growth in patients with NSCLC treated with induction chemotherapy.

Materials and Methods

In the period 1999-2000, 23 patients with stage III NSCLC received induction chemotherapy with cisplatin and gemcitabine in the University Medical Centre Utrecht and in 10 regional hospitals. Gemcitabine was administered at a dose of 1000-1250 mg/m^2 on days 1, 8, and in some regional hospitals also on day 15. Cisplatin was given at doses ranging from 80-100 mg/m^2 on day 1. The treatment was repeated every 3 - 4 weeks.

Table 1: Patient characteristics.

Gender	
Male	13
Female	10
Age (year)	
Mean	59.3
Range	41 - 73
Histology	
Squamous cell carcinoma	7
Adenocarcinoma	3
Large-cell carcinoma	9
Not defined	4
Referral to Radiotherapy Department	
Curative intent	22
Palliative intent	1
Radiotherapy	
Curative irradiation	13
Palliative irradiation	10

In general, the 23 patients received 3 - 4 cycles before re-evaluation with CT scan and 22 patients were referred to the Radiotherapy Department in Utrecht with curative intent for stages IIIA and downstaged IIIB NSCLC. Patient characteristics - gender, age and histology, curative or palliative intent - are shown in Table 1.

A retrospective study was performed to evaluate the duration of the waiting period between the end of induction chemotherapy and the start of radiotherapy, and to look at tumour volume increase in that waiting period. CT scans were made for re-evaluation of tumour response after induction chemotherapy (CTr) at the referring hospitals and for planning

purposes (CTp) at our Radiotherapy Department. Before CT planning, contrast infusion was given to all patients. Most of the diagnostic CT and all planning CT scans were spiral scans. The diagnostic scans were performed with breath-hold, the planning CT's during quiet respiration. Tumour movement as a consequence of both cardiac and respiratory activity may occur with the greatest average movement near 1 cm (Ross *et al,* 1990). However, for the present analysis of tumour volumes and subsequent tumour volume doubling times, changes in organ positions would not significantly affect the analyses of changes in apparent physical volume due to the state of breathing at the time of CT data acquisition (Balter *et al,* 1996). The gross tumour volumes, that is the sum of the volume of the primary tumour and that of a lymph node metastasis if present, *Vr* at restaging and *Vp* on planning CT, could be determined for 18 patients. The delineation of tumour volume on CTp scans was performed using PLATO IPS version 2.7 (Nucletron, The Netherlands). Tumour volume *V* was calculated by multiplying 0.5 times the maximum diameters in ventral/dorsal d_{vd} and lateral directions d_l and the number *n* of CT slices in craniocaudal direction on which the tumour was visible times slice thickness *t*: $V = 0.5d_{vd}d_lnt$. CTr scans had a slice thickness of 8-10 mm; CTp scans had a slice thickness of 5 mm. Measurements were performed by one observer (SYES) without involvement of a radiologist. Most of the restaging CT's were made in the regional hospitals and we were not able to use the digital formats of these CT's. Therefore, all CT's for restaging and planning purposes were analysed using the same method as described.

For each patient the gross tumour volumes *Vr* and *Vp* were calculated and with the time interval *T* between CTr and CTp, the tumour volume doubling time *Td* could be estimated: *Td* = Tln2/ln*(Vp/Vr)* (Hasegawa *et al,* 2000).

According to our protocol, patients with stage IIIB NSCLC receive palliative radiotherapy and with stage IIIA high-dose radiotherapy with curative intent. In case of downstaging from stage IIIB to IIIA or no upgrading from stage IIIA to IIIB high-dose loco regional radiotherapy was given. Otherwise, palliative radiotherapy was given.

The given dose for curative intended radiotherapy was 66 Gy in 33 fractions, 5 times/week, and for palliative radiotherapy it was 30 Gy in 10 fractions of 3 Gy in 4 fractions/week.

Results

After induction chemotherapy 23 patients were referred to the Radio-
therapy Department. One patient had complete response and 17 patients
had partial response, thus the response rate after chemotherapy was
78% (18 out of 23 patients). 22 Patients were referred for treatment with
curative intent. However, 9 out of these 22 patients (41%) had progression
of their disease in the waiting period to such extent (i.e. upgrading to stage
IIIB) that they became ineligible for high-dose radiotherapy. The mean
interval time between end of induction chemotherapy and CTr was 15.8
days (range -14 to 33 days; one patient had CTr during chemotherapy).
The mean interval time between CTr and CTp was 52.3 days (range 16-
99 days), and interval between end of chemotherapy and first day of
radiotherapy was 80.3 days (range 29-141 days). The overall treatment
time, from start of the chemotherapy till the end of radiotherapy varied
between 115 and 219 days, Table 2.

Table 2: Mean duration of treatments and interval times with range (day).

Induction chemotherapy	59.6 (37 - 98)
Interval end of chemotherapy - CTr	15.8 (-14* - 33)
Interval CTr - CTp	52.3 (16 - 99)
Interval end of chemotherapy - 1st consultation radiotherapist	46.0 (1 -80)
Interval 1st consultation - CTp	15.7 (11 - 40)
Interval CTp -1st irradiation	14.1 (6 -20)
Interval end of chemotherapy - 1st irradiation	80.3 (29 – 141)
Radiotherapy	
Curative intent	44.3 (30 - 50)
Palliative intent	11.1 (8 – 15)
Total treatment time	169.8 (115-219)

* One patient had CT for restaging 2 weeks before end of induction chemo-
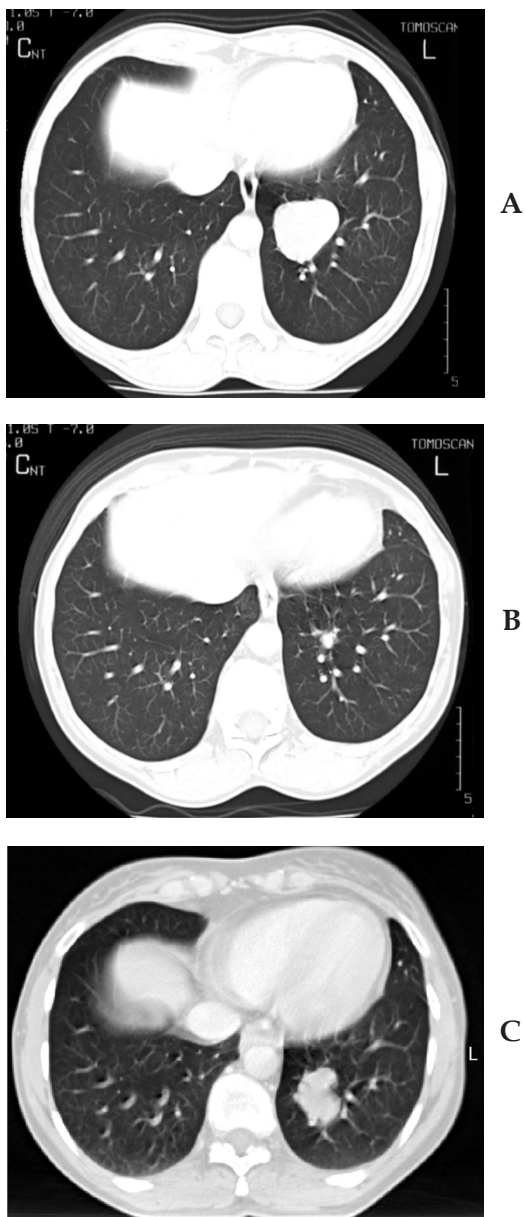therapy

Based on CTr and CTp scans, all patients had tumour volume increase. Gross tumour volumes at CTr varied between 1 and 367 cm^3, at the moment of CTp they varied between 45 and 793 cm^3, Table 3. For the patient with complete response, the volume at CTr could not be determined, the volume was assumed to be 1 cm^3. In Figure 1 the CTs of a patient made 78 days before the induction chemotherapy, 55 days after the start of chemotherapy and 72 days after the end of chemotherapy for planning purposes, are shown. It illustrates the efficacy of the induction chemotherapy and the fast regrowth of the tumour after chemotherapy.

The ratios of gross tumour volumes at CTp and at CTr are shown in Table 3. It varies from 1.1 to 81.8. The Td values are shown in Table 3. Td values ranged from 8.3 to 171.4 days with a mean of 45.8 days and a median value of 29.4 days. The number of tumour volume doubling times in the waiting period between the end of induction chemotherapy and start of radiotherapy was calculated by dividing waiting time by tumour volume doubling time, Table 3. The number of Td's as a function of the waiting period is also presented in Figure 2.

Although the correlation coefficient is rather low, it demonstrates that the number of Td's increases for longer waiting periods. The number of Td's in the waiting period ranges from 0.3 to 10, the mean is 3.3 and the median value is 2.7.
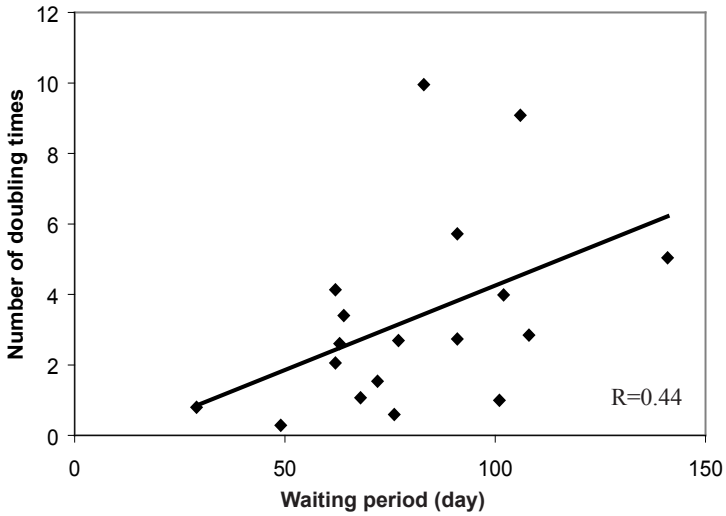
The tumour doubling times as a function of the volume as determined with CTr (starting volume) are shown in Figure 3. It illustrates that the tumours with the smallest starting volumes after chemotherapy had the fastest Td, indicating fast proliferating of the tumour cells surviving the induction chemotherapy.

Table 3: The interval between CTr and CTp, gross tumour volumes at CTr and CTp, tumour volume doubling time Td, number of Tds in waiting period (i.e. the end of chemotherapy, the start of radiotherapy) and ratio of gross tumour volumes.

Patient no.	Interval CTr-CTp (days)	Gros tumour volume at CTr (cm³)	Gros tumour volume at CTp (cm³)	Td (days)	Waiting period (days)	Number of Td in waiting period	Volume at CTp/ volume at CTr
4	68	14	793.5	11.7	106	9.1	56.7
5	88	62	112.9	101.7	101	1	1.8
6	49	26.3	99.2	25.6	102	4	3.8
7	38	9.9	57.2	15	62	4.1	5.8
8	99	51.7	600.7	28	141	5	11.6
9	53	1	81.8	8.3	83	10	81.8
10	48	25.5	51.8	46.9	72	1.5	2
12	44	9.6	48.5	18.8	64	3.4	5.1
13	16	242.4	258.6	171.4	49	0.3	1.1
14	42	85	223	30.2	62	2.1	2.6
15	71	48	104.1	63.6	68	1.1	2.2
16	36	25.2	60.3	28.6	77	2.7	2.4
17	27	36	60.1	36.5	29	0.8	1.7
18	25	367.4	752	24.2	63	2.6	2
20	57	91	298.5	33.3	91	2.7	3.3
21	85	160	253.9	127.6	76	0.6	1.6
22	48	18.8	45.2	37.9	108	2.8	2.4
23	48	15.75	127.2	15.9	91	5.7	8.1
Mean		71.6	223.8	45.8		3.3	10.9
Median		31.2	108.5	29.4		2.7	2.5

Figure 1. (**A**): CT scan of a NSCLC 78 days before induction chemotherapy; (**B**): CT scan made 55 days after start of induction chemotherapy with gemcitabine and cisplatin; and (**C**): CT scan of the same tumour 72 days after induction chemotherapy.

Figure 2. The number of doubling times in the waiting period between the end of induction chemotherapy and start of radiotherapy as a function of waiting period.
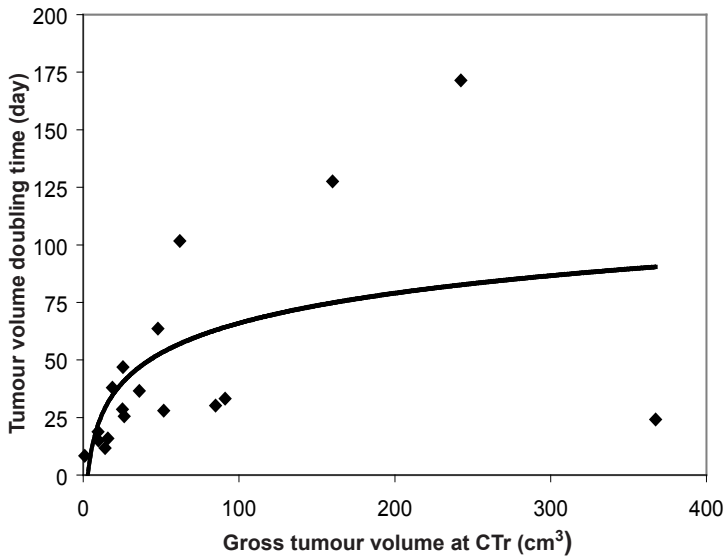
Figure 3. Tumour volume doubling time as function of gross tumour volume at CT for restaging (CTr).

Discussion

Waiting time

In the last years delays in starting radiotherapy is becoming an increasing problem. Apart from the psychological distress for the patients the question is whether waiting times and delays have any bearing on prognosis and treatment. Specifically, the hypothesis is raised that longer delays are associated with poorer survival or more advanced stage disease. A strong independent association between tumour volume and survival in patients with NSCLC was reported (Etiz *et al*, 2002, Bradley *et al,* 2002; Willner *et al*, 2002). It was recommended that waiting times for radiotherapy should be as short as reasonably achievable (ASARA) (Mackillop *et al*, 1996). Delay in treatment increases the risk that metastases will develop before treatment is started. Treatment delay may also lead to increased complication rate. As tumours increase in size, larger volumes of normal tissue have to be irradiated to encompass them, and the probability of radiation complications increases as a function of the volume irradiated. O'Rourke and Edwards (2000) described that in the waiting period for potentially curative radiotherapy that lasted from 35 to 187 days, 6 of their 29 lung cancer patients (21%) became incurable. An even larger percentage of patients in our study became incurable, nine of 22 potentially curable patients (41%) were treated with palliative intent after a waiting period ranging from 29 to 141 days. These nine patients had progression of their tumour to stage IIIB at the time of planning CT and became ineligible for high-dose radiotherapy.

Waaijer *et al* (2003) investigated tumour growth of oropharyngeal tumours in the waiting time for radiotherapy and estimated an average control loss of 16-19% for these tumours during the waiting time.

Fortin *et al* (2002) concluded that delaying radiotherapy had a deleterious effect on patients with early head-and-neck squamous cell carcinomas. Radiotherapy should be started as soon as possible, preferably within 20-30 days after evaluation by a radiation oncologist.

Among patients with an upper aerodigestive tract cancer, professional delays of more than 1 month contributed to an increased risk for being diagnosed with late-stage disease (Allison *et al*, 1998). However, no significant correlation between waiting time and the outcome of early-stage laryngeal and nasopharyngeal cancers was found (Barton *et al*, 1997; Brouha *et al*, 2000). Lee *et al* (1993) however, have shown that advanced stage of head-and-neck tumours have a clear negative effect on treatment results.

From the above reports, we conclude that long waiting times and delays may lead to important deterioration in local control rates.

In the present study, we observed a large variety in waiting times for radiotherapy after induction chemotherapy varying from 29 to 141 days and an increase in tumour volume in all patients. Pulmonologists and radiotherapists made the decision for combined chemo/radiotherapy for NSCLC patients in our region; however, patients were referred only after postchemotherapy evaluation to the department of radiotherapy. The causes of the long waiting times, therefore, are the restaging procedure after the induction chemotherapy, the time to overcome possible side effects of the chemotherapy, the time till referring patients as well as the waiting time from referring the patient till the start of radiotherapy (waiting time for the first visit, for performing the planning CT and for the start of radiotherapy). In that waiting period, we observed an increase in the gross tumour volume with a factor of more than 3. This volume increase, however, is faster after induction chemotherapy than in untreated tumours.

Repopulation and tumour doubling time

There are many publications on experimental tumours that have shown rates of repopulation after radiotherapy that are equal to or often faster than the rates of cell repopulation in tumours without radiotherapy (Hermens and Barendsen, 1967; Suit and Urano, 1969; Abe *et al*, 1991; Begg *et al*, 1991; Milas *et al*, 1994). Intervals between chemotherapy doses are needed to allow repopulation of normal tissues. During these intervals, however, the surviving tumour cells can proliferate and repopulate (Stephens and Peacock, 1977; Rosenblum *et al*, 1976; 1983; Milas *et al*, 1994).

Data on tumour volume doubling time (Td) for human lung tumours are reported by Hasegawa *et al* (2000), Steel (1977), Usuda *et al* (1994), Fujimura *et al* (1979), Filderman *et al* (1986) and Geddes (1979). The data are summarised in Table 4. They indicate that for untreated NSCL tumours the mean Td is in excess of 93 days.

O'Rourke and Edwards (2000) reported that the delay between diagnostic CT scan and planning CT amounted 18-131 days with a median of 54 days. Tumour growth in terms of percentage change in tumour cross-sectional area ranged from 0 to 373% with a median increase of 19%. If this value of 19% is used for the median interval of 54 days, a Td of 68 days can be derived, and for an interval of 113 days, the Td is 143 days.

Table 4: Mean tumour volume doubling times (Td's) as reported in literature and mean Td of the present study.

Reference	Tumour type	Mean Td (d)	Overall mean Td (d)
Hasegawa *et al* (2000)	adenoca	533	
	squamous cell ca	129	
			452
Steel (1977)	adenoca	148	
	squamous cell ca	85	
	undiffer. tumours	79	
			104
Usada *et al* (1994)	adenoca	163	
	squamous cell ca	80	
	large cell ca	67	
			103
Fujimura *et al* (1979)	adenoca	116	
	large cell ca	71	
			93
Filderman *et al* (1986)	adenoca	180	
	large cell ca	100	
			140
Geddes (1979)	adenoca	161	
	squamous cell ca	88	
	large cell ca	86	
			102
Present results			46

In the present study we observed after induction chemotherapy a clear progression in tumour volume with Td's varying from 8.3 to 171.4 days with a mean and median value of 45.8 and 29.4 days, respectively, Table 3. This latter Td value is far less than Td's found for untreated NSCLC, Table 4. It indicates accelerated repopulation of cells surviving the induction chemotherapy course. Our findings are in line with those of others who observed a rapid regrowth after irradiation of pulmonary metastases (Battermann *et al*, 1981), and after surgery in head-and-neck cancer (Trotti *et al,* 1998; Ang *et al,* 2001; Awwad *et al,* 2002). In their review, Davis and Tannock (2000) reported on repopulation of tumour cells between cycles of chemotherapy as a neglected factor. We can conclude that fast regrowth of remaining tumour cells occurs after induction chemotherapy, radiotherapy and surgery.

As illustrated in Figure 2 and Table 3, the number of Td's in the waiting period ranges from 0.3 to 10. The mean number is 3.3. In the waiting period the mean tumour volume increases with a factor of more than 3.

As shown in Figure 3, the small tumours have the shortest Td. For instance, tumours with a volume up to 40 cm^3 have a mean Td of 24.5 days (range 8.3 to 46.9 days). To our knowledge such a short mean Td value for lung tumours has not been reported earlier. Hasegawa *et al* (2000) determined growth rate of small lung cancers detected on mass CT screening. The shortest Td they found was 52 days. From the CT scans inserted in figure 1 in the paper by O'Rourke and Edwards (2000), a Td of 18.3 days can be derived. This value is for a patient receiving prior chemotherapy (O'Rourke, personal communication, 2003) and confirms our findings that after induction chemotherapy fast regrowth occurs. In our study the shortest Td was 8.3 days.

In conclusion, we present evidence that after induction chemotherapy fast regrowth of NSCLC occurs and that accelerated repopulation of surviving tumour cells is responsible for the fast regrowth. It is clear that the beneficial result of induction chemotherapy, that is tumour volume regression, has faded away. The Td is far shorter than that of untreated lung tumours. This influences the treatment results significantly. It is tragically that interval times up to more than 3 months are found whereas radiotherapy can be started within one month after induction chemotherapy as observed here. In all, 41% of potentially curable patients became incurable in that waiting period. We recommend that radiotherapy should start as soon as possible, preferably within 2 - 3 weeks, after the last

chemotherapy cycle. Owing to the accelerated cell proliferation observed, accelerated radiotherapy should be given serious consideration to keep overall treatment time short. In further studies, concurrent chemo-radiotherapy treatment should be considered since a growing body of data shows that concurrent chemo-radiotherapy improves survival in selected patients in stage III NSCLC (Schaake-Koning *et al*, 1994; Furuse *et al*, 1999; Curran *et al*, 2003).

References

1. Abe Y, Urano M, Kenton LA, Kahn J, Willet CG (1991) The accelerated repopulation of a murine fibrosarcoma, FSA-II, during the fractionated irradiation and the linear-quadratic model. Int J Radiat Oncol Biol Phys 21: 1529-1534

2. Allison P, Franco E, Black M, Feine J (1998) The role of professional diagnostic delays in the prognosis of upper aerodigestive tract carcinoma. Oral Oncol 34: 147-153

3. Ang KK, Trotti A, Brown BW, Garden AS, Foote RL, Morrison WH, Geara FB, Klotch DW, Goepfert H, Peters LJ (2001) Randomized trial addressing risk features and time factors of surgery plus radiotherapy in advanced head-and-neck cancer. Int J Radiat Oncol Biol Phys 51: 571-578

4. Awwad HK, Lotayef M, Shouman T, Begg AC, Wilson G, Bentzen SM, Abd El-Moneim H, Eissa S (2002) Accelerated hyperfractionation (AHF) compared to conventional fractionation (CF) in the postoperative radiotherapy of locally advanced head and neck cancer: influence of proliferation. Br J Cancer 86: 517-523

5. Balter JM, Ten Haken RK, Lawrence TS, Lam KL, Robertson JM (1996) Uncertainties in CT-based radiation therapy treatment planning associated with patient breathing. Int J Radiat Oncol Biol Phys 36:167-174

6. Barton MB, Morgan G, Smee R, Tiver KW, Hamilton C, Gebski V (1997) Does waiting time affect the outcome of larynx cancer treated by radiotherapy? Radiother Oncol 44: 137-141

7. Battermann JJ, Breur K, Hart GA, van Peperzeel HA (1981) Observations on pulmonary metastases in patients after single doses and multiple fractions of fast neutrons and cobalt-60 gamma rays. Eur J Cancer 17: 539-548

8. Begg AC, Hofland I, Kummermehr J (1991) Tumour cell repopulation during fractionated radiotherapy: correlation between flow cytometric and radiobiological data in three murine tumours. Eur J Cancer 27: 537-543

9. Bonner JA, McGinnis WL, Stella PJ, Marschke RF Jr, Sloan JA, Shaw EG, Mailliard JA, Creagan ET, Ahuja RK, Johnson PA (1998) The possible advantage of hyperfractionated thoracic radiotherapy in the treatment of locally advanced non-small cell lung carcinoma: results of a North Central Cancer Treatment Group Phase III Study. Cancer 82: 1037-1048

10. Bradley JD, Ieumwananonthachai N, Purdy JA, Wasserman TH, Lockett MA, Graham MV, Perez CA (2002) Gross tumor volume, critical prognostic factor in patients treated with three-dimensional conformal radiation therapy for non-small-cell lung carcinoma. Int J Radiat Oncol Biol Phys 52:49-57

11. Brouha XD, Op de Coul B, Terhaard CH, Hordijk GJ (2000) Does waiting time for radiotherapy affect local control of T1N0M0 glottic laryngeal carcinoma? Clin Otolaryngol 25: 215-218

12. Curran WJ, Scott CB, Langer CJ, Komaki R, Lee JS, Hauser S, Movsas B, Wasserman T, Sause W, Cox JD (2003) Long-term benefit is observed in a phase III comparison of sequential vs concurrent chemo-radiation for patients with unresected stage III non-small cell lung cancer: RTOG 9410. Annual meeting Am Soc Clin Oncol , May 31-June 3, Chicago, abstract no 2499

13. Davis AJ, Tannock JF (2000) Repopulation of tumour cells between cycles of chemotherapy: a neglected factor. Lancet Oncol 1: 86-93

14. Etiz D, Marks LB, Zhou SM, Bentel GC, Clough R, Hernando ML, Lind PA (2002) Influence of tumor volume on survival in patients irradiated for non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 53: 835-846

15. Fietkau R (2001) Concomitant radiochemotherapy of advanced non-small-cell lung cancer. Lung Cancer 33: Suppl 1:S65-76

16. Filderman AE, Shaw C, Matthay RA (1986) Lung cancer. Part I: Etiology, pathology, natural history, manifestations, and diagnostic techniques. Invest Radiol. 21: 80-90

17. Fortin A, Bairati I, Albert M, Moore L, Allard J, Couture C (2002) Effect of treatment delay on outcome of patients with early-stage head-and-neck carcinoma receiving radical radiotherapy. Int J Radiat Oncol Biol Phys 52: 929-936

18. Fowler JF, Chappell R (2000). Non-small cell lung tumors repopulate rapidly during radiation therapy. Int J Radiat Oncol Biol Phys 46:516-517

19. Fu XL, Jiang GL, Wang LJ, Qian H, Fu S, Yie M, Kong FM, Zhao S, He SQ, Liu TF (1997) Hyperfractionated accelerated radiation therapy for non-small cell lung cancer: clinical phase I/II trial. Int J Radiat Oncol Biol Phys 39: 545-552

20. Fujimura S, Suda S, Yamauchi A, Sato H, Sohara Y, Kondo T (1979) Tumor doubling time and PPD skin test reactivity in resectable lung cancer. J Jpn Lung Cancer Soc 19: 135-142

21. Furuse K, Fukuoka M, Kawahara M, Nishikawa H, Takada Y, Kudoh S, Katagami N, Ariyoshi Y (1999) 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 17: 2692-2699

22. Geddes DM (1979) The natural history of lung cancer: a review based on rates of tumour growth. Br J Dis Chest 73: 1-17

23. Hasegawa M, Sone S, Takashima S, Li F, Yang ZG, Maruyama Y, Watanabe T (2000) Growth rate of small lung cancers detected on mass CT screening. Br J Radiol 73: 1252-1259

24. Hermens AF, Barendsen GW (1967) Cellular proliferation patterns in an experimental rhabdomyosarcoma in the rat. Eur J Cancer 3: 361-369

25. Jensen AR, Mainz J, Overgaard J (2002) Impact of delay on diagnosis and treatment of primary lung cancer. Acta Oncol 41: 147-152

26. Lee WR, Mancuso AA, Saleh EM, Mendenhall WM, Parsons JT, Million RR (1993) Can pretreatment computed tomography findings predict local control in T3 squamous cell carcinoma of the glottic larynx treated with radiotherapy alone? Int J Radiat Oncol Biol Phys 25: 683-687

27. Mackillop WJ, Bates JH, O'Sullivan B, Withers HR (1996) The effect of delay in treatment on local control by radiotherapy. Int J Radiat Oncol Biol Phys 34: 243-250

28. Milas L, Nakayama T, Hunter N, Jones S, Lin TM, Yamada S, Thames H, Peters L (1994) Dynamics of tumor cell clonogen repopulation in a murine sarcoma treated with cyclophosphamide. Radiother Oncol 30: 247-253

29. O'Rourke N, and Edwards R (2000) Lung cancer treatment waiting times and tumour growth. Clin Oncol (R Coll Radiol) 12: 141-144

30. Perez CA, Brady LW (1998) Principles and practice of radiation oncology. Third edition, ISBN 0 397 58416 4

31. Rosenblum ML, Gerosa MA, Dougherty DV, Wilson CB (1983) Improved treatment of a brain-tumor model. Part 1: Advantages of single- over multiple-dose BCNU schedules. J Neurosurg 58: 177-182

32. Rosenblum ML, Knebel KD, Vasquez DA, Wilson CB (1976) In vivo clonogenic tumor cell kinetics following 1,3-bis(2-chloroethyl)-1-nitrosourea brain tumor therapy. Cancer Res 36: 3718-3725

33. Ross CS, Hussey DH, Pennington EC, Stanford W, Doornbos JF (1990) Analysis of movement of intrathoracic neoplasms using ultrafast computerized tomography. Int J Radiat Oncol Biol Phys 18:671-677

34. Saunders M, Dische S, Barrett A, Harvey A, Gibson D, Parmar M (1997) Continuous hyperfractionated accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small-cell lung cancer: a randomised multicentre trial. CHART Steering Committee. Lancet 350: 161-165

35. Saunders M, Dische S, Barrett A, Harvey A, Griffiths G, Palmar M (1999) Continuous, hyperfractionated, accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small cell lung cancer: mature data from the randomised multicentre trial. CHART Steering committee. Radiother Oncol 52: 137-148

36. Schaake-Koning C, van den Bogaert W, Dalesio O, Festen J, Hoogenhout J, van Houtte P, Kirkpatrick A, Koolen M, Maat B, Nijs A, Renaud A, Rodrigus R, Schuster-Uitterhoeve L, Sculier J, van Zandwijk N, Bartelink H (1994) Radiosensitization by cytotoxic drugs. The EORTC experience by the Radiotherapy and Lung Cancer Cooperative Groups. Lung Cancer 10, Suppl 1:S263-270

37. Steel GG (1977) The growth kinetics of tumours. Oxford University Press, Oxford

38. Stephens TC, Peacock JH (1977) Tumour volume response, initial cell kill and cellular repopulation in B16 melanoma treated with cyclophosphamide and 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea. Br J Cancer 36: 313-321

39. Storm HH, Dickman PW, Engeland A, Haldorsen T, Hakulinen T (1999) Do morphology and stage explain the inferior lung cancer survival in Denmark? Eur Respir J 13: 430-435

40. Suit H, Urano M (1969) Repair of sublethal radiation injury in hypoxic cells of a C3H mouse mammary carcinoma. Radiat Res 37: 423-434

41. Teppo L, Dickman PW, Hakulinen T, Luostarinen T, Pukkala E, Sankila R, Soderman B (1999) Cancer patient survival--patterns, comparisons, trends--a population-based Cancer Registry study in Finland. Acta Oncol 38: 283-294

42. Trotti A, Klotch D, Endicott J, Ridley M, Cantor A (1998) Postoperative accelerated radiotherapy in high-risk squamous cell carcinoma of the head and neck: long-term results of a prospective trial. Head Neck 20:119-123

43. Usuda K, Saito Y, Sagawa M, Sato M, Kanma K, Takahashi S, Endo C, Chen Y, Sakurada A, Fujimura S (1994) Tumor doubling time and prognostic assessment of patients with primary lung cancer. Cancer 74: 2239-2244

44. Waaijer A, Terhaard CH, Dehnad H, Hordijk GJ, van Leeuwen MS, Raaymakers CP, Lagendijk JJ (2003) Waiting times for radiotherapy: consequences of volume increase for the TCP in oropharyngeal carcinoma. Radiother Oncol 66: 271-276

45. Willner J, Baier K, Caragiani E, Tschammler A, Flentje M (2002) Dose, volume, and tumor control prediction in primary radiotherapy of non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 52: 382-389

Chapter 4

Tumour control probability of stage III inoperable non-small cell lung tumours after sequential chemo-radiotherapy

S.Y. El Sharouni
H.B. Kal
J.J. Battermann

Abstract

Background: The aim of this study was to investigate the influence of the duration of the waiting time between end of induction chemotherapy and start of radiotherapy on tumour control probability (TCP).

Patients and methods: Twenty-three patients with inoperable stage III non-small cell lung cancer (NSCLC) received induction chemotherapy followed by radiotherapy. The mean waiting period between end of induction chemotherapy and start of radiotherapy was 80.3 days; in this period the median tumour volume increased with a factor of about 6. The Poisson model for TCP and the linear-quadratic model were used to calculate changes in TCP in the waiting time.

Results: The 2-year survival of patients treated with curative intent was 8%, lower than the mean value of 26% derived from other studies. Assuming that radiotherapy started at day of restaging or at first day of radiotherapy (RT1), the calculated mean TCP at restaging was 13.3% and at RT1 was 0.5% for patients treated with curative intent.

Conclusions: The calculated TCP decreased in the waiting period from 13.3 to less than 1%. Hence, the relatively long interval time between chemo- and radiotherapy had a deleterious effect on local control. We recommend the waiting time to be as short as possible.

Introduction

Of the two main types of lung cancer, small cell lung cancer and non-small cell lung cancer (NSCLC), the latter is the most frequent and represents between 70 and 80% of cases. Overall survival is around 13%, and has not changed significantly in recent decades. The reason is that the majority of patients are diagnosed in advanced stages of the disease. Five-year survivals in surgical stages I, II and IIIA are 41-67%, 22-55% and 9-25%, respectively (1).

Among the treatments for inoperable stage III NSCLC, induction chemotherapy with gemcitabine and cisplatin for downstaging the tumours with the aim of further treatment with ionising radiation or surgery. If no stringent arrangements are made, the waiting time between induction chemotherapy and irradiation may be considerable. In general, waiting times for radiotherapy are a cause for concern in many radiotherapy departments. Fortin *et al.* (2) analysed the impact of delaying treatment on the outcome of 623 patients with early head-and-neck (H&N) squamous cell carcinomas and concluded that delaying radiotherapy had a deleterious effect. Waaijer and colleagues (3) investigated tumour growth of oropharyngeal tumours in the waiting time for radiotherapy. They estimated an average control loss of 16-19% for these tumours during the mean waiting period of 56 days. The risk of death increased by 2% for each day of waiting for radiotherapy for rapidly growing grade III/IV gliomas (4). In a theoretical study Wyatt *et al.* (5) calculated that slow growing tumours, such as prostate carcinomas are likely to be affected only to a small extent by delays in treatment, about 0.1% reduction in tumour control probability (TCP) per week of delay. Rapidly growing tumours, such as mammary tumours post-surgery and squamous cell carcinoma H&N tumours are affected to a much larger extent, up to about 7% reduction for each week's delay for mammary tumours, and 1% reduction per week for H&N tumours. Advanced stage of H&N tumours has a clear negative effect on treatment results (6). In only a few clinical studies on early stage laryngeal and nasopharyngeal cancers, was the negative effect of waiting times on treatment outcome not convincing (7, 8).

We previously found that growth of NSCLC after induction chemotherapy was faster than that of untreated tumours (9). In the waiting period between end of induction chemotherapy and start of radiotherapy 41% of the tumours became stage IIIB and were treated with palliative intent (9).

We applied a TCP model on our patient data, calculated tumour control

rate loss in the waiting period between the end of induction chemotherapy and start of radiotherapy and compared the results with the actual treatment outcome and results found in the literature.

Patients and Methods

Patients characteristics. As previously reported, in the period 1999-2000 13 males and 10 females with inoperable stage IIIA and B NSCLC received induction chemotherapy with cisplatin and gemcitabine at the University Medical Centre Utrecht and in 10 regional hospitals (9). The mean age of the patients was 59.3 years (range 41-73). Gemcitabine was administered at a dose of 1000-1250 mg/m² on days 1 and 8, and in some regional hospitals also on day 15. Cisplatin was given at doses ranging from 80-100 mg/m² on day 1. When gemcitabine was administered on days 1 and 8, the next cycle started on day 22. With administration on days 1, 8 and 15, the next cycle started on day 29. In general, patients received 3-4 cycles before re-evaluation with a CT- restaging and then were referred to the Radiotherapy Department in Utrecht for treatment with curative intent for stages IIIA NSCLC. We also reported that the mean interval time between end of chemotherapy and CT-restaging was 16.1 days, between CT-restaging and CT-planning 50.1 days and between CT-planning and first day of radiotherapy (RT1) 14.1 days (9). Hence, the mean total waiting period between the end of induction chemotherapy and the start of radiotherapy was 80.3 days (range 29-141 days). The gross tumour volumes at the CT-restaging varied between 1 and 367 cm³ and at the moment of the CT-planning they varied between 45 and 793 cm³. The tumour volume doubling time *Td* ranged from 8.3 to 171.4 days with a mean of 45.8 days and a median value of 29.4
The given dose for curatively intended radiotherapy was 66 Gy in 33 fractions, 5 times/week in 45 days, and for palliative radiotherapy it was 30 Gy in 10 fractions, 4 times/week in 15 days. The median survival duration and 2-year survival were calculated from the patients' records.

Tumour control probability analysis. The Poisson model for tumour control probability (TCP), an exponential function of tumour volume increase, and the linear-quadratic model of cell kill with a factor quantifying accelerated repopulation, were used to calculate changes in TCP in the waiting time (5, 10-12). TCP is given by

$$TCP = \exp(-VN) \tag{1}$$

where V is the tumour volume and N is the number of clonogens per cm^3. The number of clonogens per cm^3 surviving radiotherapy can be estimated by

$$N = N_0 \exp[-(\alpha D(1+d/(\alpha/\beta))+\gamma(To-Tdel)] \tag{2}$$

where N_0 is the number of clonogens per cm^3 before radiation treatment, D is the total dose, d is the fraction dose, α and β are the parameters which determine the initial slope and degree of curvature of the underlying cell-survival curve, To is the overall treatment time of the radiation treatment, $Tdel$ is the delay time to onset of accelerated proliferation and γ is the time factor for accelerated repopulation. For the factor γ we used 0.693/$Tpot$ where $Tpot$ is the potential doubling time (5). For NSCLC we applied a $Tpot$ value of 5 days, the same value as was previously used for H&N cancers (13).

For our analysis we used a clonogen density $N_0 = 10^7$ cm^{-3}, according to Webb (14) who found that value as the best fit to clinical data for squamous cell carcinoma of the upper respiratory and digestive tract.

The volume at first day of radiotherapy $V(RT1)$ was calculated:

$$V(RT1) = V1*2^{t/Td} \tag{3}$$

where $V1$ is the volume on the CT-restaging, t is the time interval between restaging and start of radiotherapy and Td is the tumour volume doubling time. Td can be derived as follows:

$$Td = 0.693t_{rp}/\ln(Vp/V1) \tag{4}$$

where Vp is the tumour volume at CT-planning and t_{rp} the time interval between CT-restaging and CT-planning.

The TCP was analysed according to $\alpha = 0.30$ Gy^{-1} with a spread $\sigma = 0.02$ Gy^{-1} as approximation for the whole population (3), and $Tdel = 14$ days, assuming that accelerated repopulation in a previous untreated tumour started in the third week after start of radiotherapy (15, 16). Furthermore, for tumours after induction chemotherapy, we assigned $Tdel = 0$ days, assuming that in that tumour accelerated repopulation was still present at the first day of radiotherapy and that the clonogen density was returned

to the pre-treatment level (17, 18). The parameters used in the TCP analysis are represented in Table I. In addition, due to a smaller fraction of quiescent cells implying less repair of potentially lethal damage (19), an increase in overall radiosensitivity was assumed. As a consequence, the value of the parameter α was increased.

Statistics. Kaplan-Meier survival analysis was performed using SPSS10.1 by scoring the survival time after the start of radiotherapy as an event.

Table I. Parameters and values used in the TCP analysis.

Parameter	Value
N	10^7 cells/cm^3
α	0.30 +/- 0.02 resp. 0.32 +/- 0.02 Gy^{-1}
α/β	15 Gy
Tpot	5 d
To	45 d
Tdel	14 d resp. 0 d
D	66 Gy (33 x 2 Gy)

Results

Survival. After induction chemotherapy, 23 patients were referred to the radiotherapy department of whom 22 for curative intent. However, 9 out of these 22 patients (41%) had progression of their disease in the waiting period to such extent that they could not receive the planned curatively intended radiotherapy. These patients were diagnosed at CT-planning as stage IIIB, and were treated according to our protocol with a total dose of 30 Gy, mainly to prevent severe complications due to tumour extension. The 2-year survival of the 23 patients was 13% (3 out of 23), however, two of the three patients had a recurrent tumour and intrapulmonary metastases and only one patient is tumour-free after second-line chemotherapy and surgery but with severe normal tissue morbidity. The two-year survival of patients treated with curative intent was 8% (1 out of 13). However, this patient developed local recurrence.

Survival as function of time after start of curatively intended radiotherapy for stage IIIA (total dose 66 Gy) is represented in Figure 1, curve A, and palliative radiotherapy for stage IIIB (total dose 30 Gy), in curve B of the same figure. Median survival duration for patients receiving curatively intended radiotherapy was 12.6 +/- 2.8 months, and 6.4 +/- 1.2 months for palliative-treated patients.
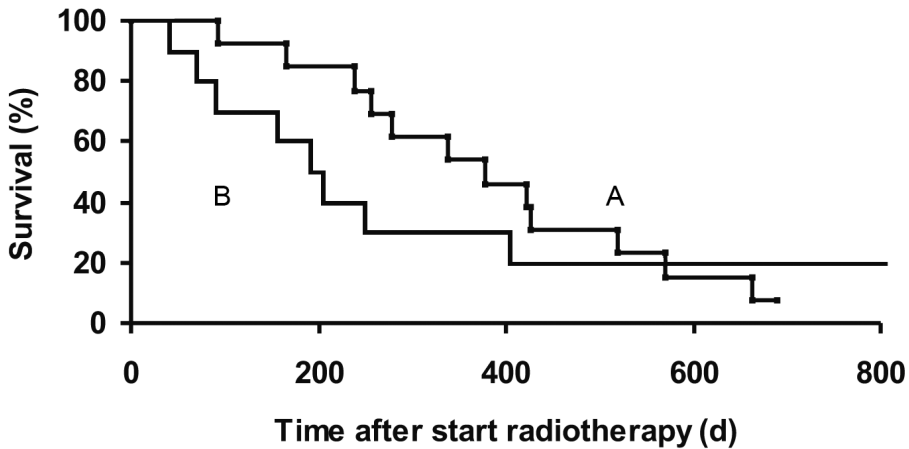
Figure 1. Overall survival as a function of time after start of curatively intended radiotherapy (radiation dose of 66 Gy), curve A, and palliative radiotherapy (dose of 30 Gy), curve B.

Tumour control probability, radiation only. TCP was modelled for radiotherapy only (no induction chemotherapy) and it was assumed that accelerated repopulation started at day 14 after start of radiotherapy (15, 16). For $N = 10^7/cm^3$, $\alpha = 0.30 +/- 0.02\,Gy^{-1}$ and a tumour volume of 75 cm^3 (i.e. a diameter of about 5.3 cm), a reasonable TCP value was found according to clinical experience, i.e. for a TCP of about 5% (20). The relationship between *TCP* and tumour volume for *Tdel* = 14 days, α = 0.30, 0.28 and 0.32 Gy^{-1}, and for the *TCP* as a mean for a population with different sensitivities

$$TCP = [TCP(\alpha = 0.28\ Gy^{-1}) + TCP(\alpha = 0.32\ Gy^{-1})]/2,$$

is given in Figure 2. For the population average (Figure 2, diamonds) the *TCP* at 75 cm^3 is 5%. For volumes in excess of 100 cm^3, *TCP* is less than 2.5%.

TCP, repopulation and radiosensitivity. After induction chemotherapy, *Tdel* was assumed = 0 d, thus accelerated repopulation was still present when radiotherapy started. The dose to compensate for the repopulation after induction chemotherapy Dr can be derived from equation (2).

For α = 0.30 Gy $^{-1}$, *To* = 45 d, *Tdel* = 0 d and *Tdel* = 14 d, γ = 0.693/*Tpot* d^{-1}, *Tpot* = 5 d, *d* = 2 Gy, *D* = 66 Gy, α/β = 15 Gy:

N(after radiation treatment, *Tdel* = 14 d, *D*) = *N*(after radiation treatment following induction chemotherapy, *Tdel* = 0 d, *D* + *Dr*).

N_0exp[-0.30x66x[1+2/15] + 0.693x(45-14)/5] = N_0exp[-0.30x(66 + *Dr*)x[1+2/15] + 0.693x(45-0)/5].

This results in a *Dr* of 5.7 Gy. Thus, to compensate for accelerated repopulation, the dose after induction chemotherapy should be enhanced from 66 Gy to 71.7 Gy in order to keep the TCP equal to that of a tumour treated with radiotherapy only. In clinical practice however, the radiation dose after induction chemotherapy is generally not increased. Nevertheless, in general, a higher local control was observed for sequential chemo-radiotherapy (20). This can be attributed to a reduced tumour volume after induction chemotherapy, e.g. from 75 to 30 cm^3. The mean *TCP* calculated for α = 0.30+/- 0.02 Gy^{-1}, *Tdel* = 0 d and V = 30 cm^3, however was less than 0.1% (Figure 3, triangles). Hence, a smaller tumour volume did not compensate the loss of a calculated dose of 5.7 Gy. It was therefore assumed that after chemotherapy the repopulating tumour had a higher radiosensitivity due to a smaller fraction of resting cells (hence, a larger fraction of proliferating cells) and as a consequence less repair of potentially lethal damage (19). Therefore, the radiosensitivity parameter α was increased. For a tumour volume of 30 cm^3, *Tdel* = 0 d and α = 0.32 +/-0.02 Gy^{-1} (population with different sensitivities), a TCP value of 12% (Figure 3, diamonds) was calculated. This increase in radiosensitivity was sufficient to obtain the increased TCP values for combined modality treatment in the range of clinical values observed (20). TCP curves for α = 0.34 and 0.32 Gy^{-1} are also depicted in Figure 3.
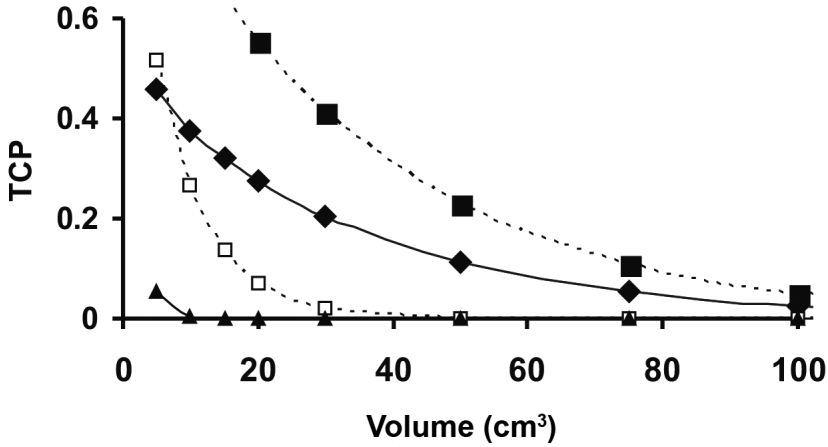
Figure 2. Tumour control probability (TCP) after radiotherapy only as function of tumour volume of previously untreated tumours. *TCP* was calculated for α = 0.32 Gy^{-1} (large squares), α = 0.30 Gy^{-1} (open squares), α = 0.28 Gy^{-1} (triangles), and the average of the TCPs for α = 0.32 Gy^{-1} and α = 0.28 Gy^{-1} (diamonds); D = 66 Gy, N_0 = 10^7/cm³, α/β = 15 Gy, *Tdel* = 14 days.
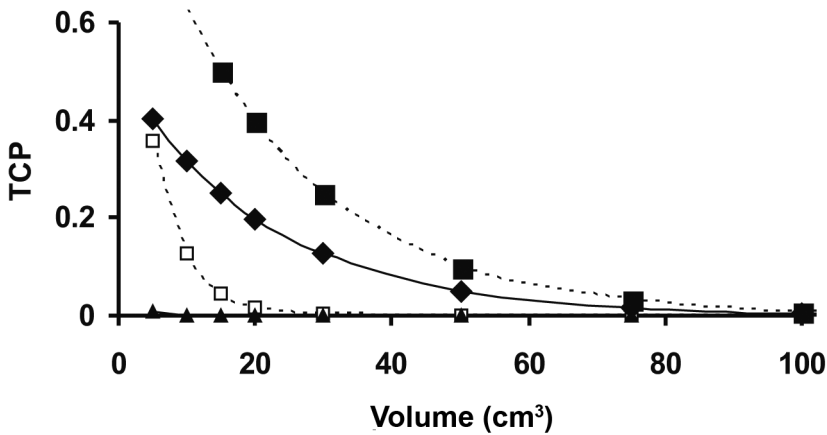
Figure 3. Tumour control probability (TCP) as function of tumour volume after sequential chemo-radiotherapy assuming accelerated repopulation. TCP was calculated for α = 0.34 Gy^{-1} (large squares), α = 0.30 Gy^{-1} (open squares), average of TCPs for α = 0.32 Gy^{-1} and α = 0.28 Gy^{-1} (triangles), and average of TCPs for α = 0.34 Gy^{-1} and α = 0.30 Gy^{-1} (diamonds); D = 66 Gy, N_0 = 10^7/cm³, α/β = 15 Gy, *Tdel* = 0 days.

Table II. Tumour volumes of individual patients (n = 18) at CT-restaging, CT-planning and at first day of radiotherapy (RT1), as well as mean and median values.

Patient nr	Volume (cm^3) CT-restaging	Volume (cm^3) CT-planning	Volume (cm^3) RT1
4	14	793	1277
5	62	113	118
6*	26	99	162
7*	10	57	131
8	52	601	871
9	1	82	204
10*	25	52	64
12	10	48	75
13*	242	259	280
14*	85	223	315
15	48	104	112
16*	25	60	98
17*	36	60	81
18	367	752	1031
20	91	298	434
21*	160	254	275
22*	19	45	65
23*	16	127	234
Mean	72	224	324
Median	31	108	183

*10 Patients treated with curative intent (D = 66 Gy)

TCP for clinical data. Using the gross tumour volumes (i.e. the sum of the volume of the primary tumour and that of a lymph node metastasis if present), at day of CT-restaging and of CT-planning and the interval times between CT-restaging and start of radiotherapy, the volumes of 18 evaluable patients at start of radiotherapy (RT1) were calculated (Table II).

For these 18 patients the mean tumour volume at CT-restaging was 72 cm^3 and the median volume 31 cm^3. At time of CT-planning and RT1 the mean (and median) tumour volumes were 224 (108) and 324 (183) cm^3, respectively.

For the 10 patients treated with curative intent (Table II), the mean TCP with standard deviation, calculated with α = 0.32 +/- 0.02 Gy^{-1}, at CT-restaging is 13.3% +/- 10.8%. The mean TCP at RT1 was 0.5 +/- 0.7%. Thus, due the mean waiting period of 73 d for these 10 patients, the mean TCP of 13.3% with a median tumour volume of 25 cm^3 was reduced to less than 1% with a median tumour volume of 146 cm^3.

Discussion

Tumour volume and local control. The importance of tumour volume on local control is evident (e.g. 21-25). Dubben and colleagues (26) concluded that tumour volume is the most precise and most relevant predictor of radiotherapy outcome. For NSCLC tumours with a volume larger than 100 cm^3, doses up to 80 Gy did not improve local control, whereas for tumours smaller than 100 cm^3, 3-year local control rates of more than 40% were reached (25). Martel *et al.* (27) observed a similar effect, and found an influence of dose larger than 73 Gy on local control only in tumours smaller than 200 cm^3. This indicates that for tumours larger than 100-200 cm^3 doses in excess of about 80 Gy are required for long-term control. A strong correlation of survival time with tumour size was also reported by others (28-34). Using the TCP concept as described here, it is quite clear that for tumours in excess of 100 cm^3 the TCP is almost zero (Figure 2). Also in our patients' population two years after treatment, only one out of 13 patients treated with curative intent was still alive, albeit with tumour.

Median survival duration and 2-year survival. From studies in which results of chemotherapy followed by radiotherapy were compared to those of radiation alone median survival duration and 2-year survival were derived, Table III (29, 35-52). The mean of the median survival durations was 13.6 +/- 2.2 months and the mean of the 2-year local survival was 26.0 +/- 6.9%. In our study, the median survival duration of the patients treated with curative intent was 12.6 +/- 2.8 months, within the range found in above-mentioned studies. However, survival at 2 years was only 8% (1 out of 13 patients treated with curative intent). The low survival percentage is due to the relatively long waiting time and hence increased tumour volume in our study as will be discussed below.

Waiting time. Waiting times for radiotherapy are a cause for concern in many radiotherapy departments. In the waiting period, tumour volume increase may lead to a higher stage with negative consequences for local control. A strong independent association between tumour volume and survival was reported (25, 53-55). O'Rourke and Edwards (55) reported that in the waiting period for potentially curative radiotherapy that lasted from 35 to 187 days, 6 of their 29 lung cancer patients (21%) became incurable. An even larger percentage of patients in our study got progression and

Table III. Two-year overall survival (OS) and median survival duration (MSD) of sequential chemo- radiotherapy on stage III NSCLC.

References	2-year OS (%)	MSD (month)
Graham *et al* (29)	34	16.9
Brodin *et al* (35)	21	11
Choi *et al* (36)		12.3
Crino *et al* (37)	30	12
Cullen *et al* (38)	24	11.7
Curran *et al* (39)		14.6
Dillman *et al* (40)	26	13.7
Furuse *et al* (41)	27.4	13.3
Gregor *et al* (42)	20	12
Kim *et al* (43)		13.8
Kubota *et al* (44)	36	15.2
Le Chevalier *et al* (45)	21	12
Metha *et al* (46)	28	12
	37	21
Pierre *et al* (47)	23	13.8
Sause *et al* (48)	32	13.2
Sculier *et al* (49)	22	12.4
Wolff *et al* (50)	24	13.7
Willner *et al* (51)	10	14.6
Zemanova *et al* (52)		13
Mean +/- SD	26.0 +/-6.9	13.6+/-2.2
Present study	8%	12.6+/-2.8 month

the planned curatively intended radiotherapy could not be given. Nine of the 22 patients (41%) were treated with palliative intent after a waiting period in our study ranging from 29 to 141 days. The higher stage (from IIIA to IIIB) is correlated with tumour volumes in excess of 100 cm^3. The TCP analysis revealed that for tumours of that size, local cure is almost impossible with the doses usually applied in radiotherapy.

Partial response. Response rate after induction chemotherapy in our patients was 78% (9). Assume that the volume was reduced to 30% of the volume just before chemotherapy. For a tumour volume of 100 cm^3 treated with radiotherapy only (D = 66 Gy), the TCP is about 2.5% (Figure 2). The calculated TCP of a volume of 30 cm^3 after induction chemotherapy with accelerated repopulation and a higher radiosensitivity, is 12%. Hence, due to the double advantage of volume reduction and higher radiosensitivity as a result of induction chemotherapy, TCP is 5-fold enhanced, provided that radiotherapy is started as soon as possible after induction chemotherapy. For a delay in treatment of 80 days (i.e. the mean waiting period in our study, almost 3 doubling times), the median volume of about 30 cm^3 was increased to about 180 cm^3 for which the TCP is less than 1%. This is further evidence of the deleterious effect of a waiting period on tumour control probability.

Conclusions

In the mean waiting period of 80 days between end of induction chemotherapy and start of radiotherapy, the median tumour volume in our patients increased with a factor of about 6. As a consequence, the observed two-year survival of patients treated with curatively intended radiotherapy is only 8%, while from other studies a mean two-year survival value of about 26% was found for sequential chemo-radiotherapy. This is also reflected in the calculated TCP for the curatively intended treated patients; the TCP decreased in the waiting period from 13.3% to less than 1%. We conclude from our material that the interval time between chemo- and radiotherapy should be as short as possible. In further studies simultaneous chemo-radiotherapy treatment should be considered.

References

1. Mountain CF: Revisions in the International System for Staging Lung Cancer. Chest 111: 1710-1717, 1997.
2. Fortin A, Bairati I, Albert M, Moore L, Allard J, Couture C: Effect of treatment delay on outcome of patients with early-stage head-and-neck carcinoma receiving radical radiotherapy. Int J Radiat Oncol Biol Phys 52: 929-236, 2002.
3. Waaijer A, Terhaard CH, Dehnad H, Hordijk GJ, van Leeuwen MS: Waiting times for radiotherapy: consequences of volume increase for the TCP in oropharyngeal carcinoma. Radiother Oncol 66: 271-276, 2003.
4. Do V, Gebski V, Barton MB: The effect of waiting for radiotherapy for grade III/IV gliomas. Radiother Oncol 57: 131-136, 2000.
5. Wyatt RM, Beddoe AH, Dale RG: The effects of delays in radiotherapy treatment on tumour control. Phys Med Biol 48: 139-155, 2003.
6. Lee WR, Mancuso AA, Saleh EM, Mendenhall WM, Parsons JT, Million RR: Can pretreatment computed tomography findings predict local control in T3 squamous cell carcinoma of the glottic larynx treated with radiotherapy alone? Int J Radiat Oncol Biol Phys 25: 683-687, 1993.
7. Barton MB, Morgan G, Smee R, Tiver KW, Hamilton C, Gebski V: Does waiting time affect the outcome of larynx cancer treated by radiotherapy? Radiother Oncol 44: 137-141, 1997.
8. Brouha XD, Op De Coul B, Terhaard CH, Hordijk GJ: Does waiting time for radiotherapy affect local control of T1N0M0 glottic laryngeal carcinoma? Clin Otolaryngol 25: 215-218, 2000.
9. El Sharouni SY, Kal HB, Battermann JJ: Accelerated regrowth of non-small cell lung tumours after induction chemotherapy. Br J Cancer 89: 2184-2189, 2003.
10. Barendsen GW: Dose fractionation, dose rate and iso-effect relationships for normal tissue responses. Int J Radiat Oncol Biol Phys 8: 1981-1997, 1982.
11. Jones B, Dale RG: Mathematical models of tumour and normal tissue response. Acta Oncol 38: 883-893, 1999.
12. Porter EH: The statistics of dose/cure relationships for irradiated tumours. Part I. Br J Radiol 53: 210-227, 1980.
13. Bourhis J, Dendale R, Hill C, et al: Potential doubling time and clinical outcome in head and neck squamous cell carcinoma treated with 70 Gy in 7 weeks. Int J Radiat Oncol Biol Phys 35: 471-476, 1996.
14. Webb S: Optimum parameters in a model for tumour-control probability including interpatient heterogeneity. Phys Med Biol 39:1895-1914, 1994.
15. Tarnawski R, Fowler J, Skladowski K, et al: How fast is repopulation of tumor cells during the treatment gap? Int J Radiat Oncol Biol Phys 54, 229-236, 2002.
16. Terhaard CHJ, Kal HB, Hordijk GJ: Why to start the concomitant boost in

accelerated radiotherapy for advanced laryngeal cancer in week 3. Int J Radiat Oncol Biol Phys 61: 62-69, 2005.

17. Hermens AF, Barendsen GW: Changes of cell proliferation characteristics in a rat rhabdomyosarcoma before and after X-irradiation. Eur J Cancer 5: 173-189, 1969.

18. Stephens TC, Currie GA, Peacock JH: Repopulation of gamma-irradiated Lewis lung carcinoma by malignant cells and host macrophage progenitors. Br J Cancer 38: 573-582, 1978.

19. Barendsen GW, Van Bree C, Franken NA: Importance of cell proliferative state and potentially lethal damage repair on radiation effectiveness: implications for combined tumor treatments. Int J Oncol 19: 247-256, 2001.

20. Sirzén F, Kjellen E, Sorenson S, Cavallin-Stahl E. A systematic overview of radiation therapy effects in non-small cell lung cancer. Acta Oncol 42: 493-515, 2003.

21. Bentzen SM, Thames HD: Tumor volume and local control probability: clinical data and radiobiological interpretations. Int J Radiat Oncol Biol Phys 36: 247-251, 1996.

22. Brenner DJ. Dose, volume, and tumor-control predictions in radiotherapy. Int J Radiat Oncol Biol Phys 26: 171-179, 1993.

23. Doweck I, Denys D, Robbins KT: Tumor volume predicts outcome for advanced head and neck cancer treated with targeted chemoradiotherapy. Laryngoscope 112: 1742-1749, 2002.

24. Kurek R, Kalogera-Fountzila A, Muskalla K, *et al*: Usefulness of tumor volumetry as a prognostic factor of survival in head and neck cancer. Strahlenther Onkol 179: 292-297, 2003.

25. Willner J, Baier K, Caragiani E, Tschammler A, Flentje M. Dose, volume, and tumor control prediction in primary radiotherapy of non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 52: 382-389, 2002.

26. Dubben HH, Thames HD, Beck-Bornholdt HP: Tumor volume: a basic and specific response predictor in radiotherapy. Radiother Oncol 47: 167-174, 1998.

27. Martel MK, Strawderman M, Hazuka MB, Turrisi AT, Fraass BA, Lichter AS. Volume and dose parameters for survival of non-small cell lung cancer patients. Radiother Oncol 44: 23-29, 1997.

28. Dosoretz DE, Katin MJ, Blitzer PH, *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 24: 3-9, 1992.

29. Graham PH, Abell FL, Capp A, *et al*: Concurrent end-phase boost radiation therapy to 65 Gy in 5 weeks for non-small cell lung cancer with or without cisplatin chemotherapy. Lung Cancer 41: Suppl 2, 243-245, 2003.

30. Karstens JH, Andreopoulos D, Ammon J: Initial tumor size and local control in stage III non-small cell lung cancer treated by radio-chemotherapy. Onkologie 13: 144-145, 1990.

31. Krol AD, Aussems P, Noordijk EM, Hermans J, Leer JW: Local irradiation alone for peripheral stage I lung cancer: could we omit the elective regional nodal irradiation? Int J Radiat Oncol Biol Phys 34: 297-302, 1996.
32. Noordijk EM, vd Poest Clement E, Hermans J, Wever AM, Leer JW. Radiotherapy as an alternative to surgery in elderly patients with resectable lung cancer. Radiother Oncol 13: 83-89, 1988.
33. Oehler W, Eichhorn HJ: Primary tumor volume and prognosis in bronchial carcinoma. Strahlenther Onkol 168: 73-78, 1992.
34. Sandler HM, Curran WJ Jr, Turrisi AT 3rd. The influence of tumor size and pre-treatment staging on outcome following radiation therapy alone for stage I non-small cell lung cancer. Int J Radiat Oncol Biol Phys 19: 9-13, 1990.
35. Brodin O, Nou E, Mercke C, *et al*: Comparison of induction chemotherapy before radiotherapy with radiotherapy only in patients with locally advanced squamous cell carcinoma of the lung. The Swedish Lung Cancer Study Group. Eur J Cancer 32A: 1893-1900, 1996.
36. Choi JH, Lim HY, Kim HC, *et al*: The addition of induction chemotherapy failed to improve therapeutic outcome of concurrent chemoradiotherapy in patients with locally advanced non-small cell lung cancer. Lung Cancer 41: Suppl 2, S238, 2003.
37. Crino L, Latini P, Meacci M, *et al*: Induction chemotherapy plus high-dose radiotherapy versus radiotherapy alone in locally advanced unresectable non-small-cell lung cancer. Ann Oncol 4: 847-851, 1993.
38. Cullen MH, Billingham LJ, Woodroffe CM, *et al*: Mitomycin, ifosfamide, and cisplatin in unresectable non-small-cell lung cancer: effects on survival and quality of life. J Clin Oncol 17: 3188-3194, 1999.
39. Curran WJ, Scott CB, Langer CJ, *et al*: Long-term benefit is observed in a phase III comparison of sequential vs concurrent chemo-radiation for patients with unresected stage III NSCLC: RTOG 9410. Ann Meeting Am Soc Clin Oncol, May 31-June 3, Chicago (abstract 2499), 2003.
40. Dillman RO, Herndon J, Seagren SL, Eaton WL Jr, Green MR: Improved survival in stage III non-small-cell lung cancer: seven-year follow-up of cancer and leukemia group B (CALGB) 8433 trial. J Natl Cancer Inst 88: 1210-1215, 1996.
41. Furuse K, Fukuoka M, Kawahara M, *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 17: 2692-2699, 1999.
42. Gregor A, Macbeth FR, Paul J, Cram L, Hansen HH: Radical radiotherapy and chemotherapy in localized inoperable non-small-cell lung cancer: a randomized trial. J Natl Cancer Inst 85: 997-999, 1993.
43. Kim TY, Yang SH, Lee SH, *et al*: A phase III randomized trial of combined chemoradiotherapy versus radiotherapy alone in locally advanced non-small-cell lung cancer. Am J Clin Oncol 25: 238-243, 2002.

44. Kubota K, Furuse K, Kawahara M, *et al*: Role of radiotherapy in combined modality treatment of locally advanced non-small-cell lung cancer. J Clin Oncol 12: 1547-1552, 1994.
45. Le Chevalier T, Arriagada R, Tarayre M, *et al*: Significant effect of adjuvant chemotherapy on survival in locally advanced non-small-cell lung carcinoma. J Natl Cancer Inst 84: 58, 1992.
46. Mehta MP, Wang W, Johnson D, *et al*: Induction chemotherapy followed by standard thoracic radiotherapy vs. hyperfractionated accelerated radiotherapy for patients with unresectable stage IIIA and B non-small cell lung cancer: phase III study of the eastern cooperative oncology group (ECOG 2597). Int J Radiat Oncol Biol Phys 57: S141, 2003.
47. Pierre F, Maurice P, Gilles R, *et al*: A randomized phase III trial of sequential chemoradiotherapy in locally advanced non-small cell lung cancer [abstract]. Proc Amer Soc Clin Oncol 20: 312a, 2001.
48. Sause W, Kolesar P, Taylor S IV, *et al*: Final results of phase III trial in regionally advanced unresectable non-small cell lung cancer: Radiation Therapy Oncology Group, Eastern Cooperative Oncology Group, and Southwest Oncology Group. Chest 117: 358-364, 2000.
49. Sculier JP, Paesmans M, Lafitte JJ, *et al*: A randomised phase III trial comparing consolidation treatment with further chemotherapy to chest irradiation in patients with initially unresectable locoregional non-small-cell lung cancer responding to induction chemotherapy. European Lung Cancer Working Party. Ann Oncol 10: 295-303, 1999.
50. Wolf M, Hans K, Becker H, *et al*: Radiotherapy alone versus chemotherapy with ifosfamide/vindesine followed by radiotherapy in unresectable locally advanced non-small cell lung cancer. Semin Oncol 21: 42-47, 1994.
51. Willner J, Huber R, Poellinger B, *et al*. CTRT 99/97 a randomized trial of simultaneous paclitaxel and radiotherapy vs radiotherapy alone following induction chemotherapy in stage III inoperable NSCLC. Int J Radiat Oncol Biol Phys 57: S140, 2003.
52. Zemanova M, Petruzelka L, Zemanova M, *et al*: Concurrent versus sequential radiochemotherapy with vinorelbine plus cisplatin (V-P) in locally advanced non-small cell lung cancer. A randomized phase II study (Abstract 1159). Proc Am Soc Clin Oncol (ASCO) 290a, 2002.
53. Etiz D, Marks LB, Zhou SM, *et al*: Influence of tumor volume on survival in patients irradiated for non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 53: 835-846, 2002.
54. Jensen AR, Mainz J, Overgaard J: Impact of delay on diagnosis and treatment of primary lung cancer. Acta Oncol 41: 147-152, 2002.
55. O'Rourke N, Edwards R: Lung cancer treatment waiting times and tumour growth. Clin Oncol (R Coll Radiol) 12: 141-144, 2000.

Chapter 5

Gemcitabine as a radiosensitizer in undifferentiated tumors

H.B. Kal
S.Y. El Sharouni
A.D. Barten-van Rijbroek

Abstract

Background: Gemcitabine (dFdC) may cause radiosensitization by specific interference with homologous recombination-mediated DNA double-strand break repair. The radiosensitizing effect of dFdC might be less in normal healthy tissue and more restricted to undifferentiated tumor cells, making it a tumor-selective radiosensitizer. Whether dFdC acted as radiosensitizer in undifferentiated and well-differentiated rat tumors and on rat foot skin was tested.

Materials and Methods: Undifferentiated L44 lung tumors in BN rats, MLL prostate tumors in Copenhagen rats, and well-differentiated L42 lung tumors in WAG/Rij rats were used. The tumors were treated with a single X-ray dose, combined or not with dFdC (30 mg/kg) administered 24 h earlier. Tumor volume growth delay was the end-point used. In addition, rat foot skin was treated with a single dose of 22.5 Gy with or without dFdC. The degree of skin damage was determined according to a scoring system.

Results: For tumor growth delay, dose-enhancement ratios were 1.37 and 1.23-1.36 for the L44 and MLL tumors, respectively. No radiosensitization was observed for the well-differentiated L42 tumors and foot skin.

Conclusion: Radiosensitization by gemcitabine was observed in the undifferentiated tumors, but not in the well-differentiated tumors and skin. Our data support further trials to evaluate the usefulness of dFdC as radiosensitizer in undifferentiated tumors.

Introduction

Gemcitabine (2′,2′-difluoro-2′-deoxycytidine, Gemzar, dFdC) is a deoxy-cytadine analogue well known for its antitumor activity in different tumor types (1-8). It has been shown that dFdC enhanced radiation-induced chromosomal aberrations (9), which suggests interference with repair of DNA damage, particularly the repair of double strand breaks (DSBs). It was found that homologous recombination (HR) was involved in the synergistic interaction between dFdC and cisplatin (10) and that dFdC causes radiosensitization by specific interference with HR (11). Increased radiosensitivity was observed in HR-deficient irs1 and irs1SF hamster cell lines and in HR-deficient Drosophila melanogaster (12). Adult mice deficient in HR, however, did not show hypersensitivity to radiation, and the impact of HR deficiency only became apparent in a non-homologous end joining (NHEJ)-deficient background (13, 14). From these, it was concluded that HR plays a minor role in the repair of double strand breaks in matured, differentiated cells (11). In undifferentiated cells, HR may contribute to DSB repair and hence to cellular radiosensitivity. It was speculated that the radiosensitizing effect of dFdC in patients might be less in normal tissues and more restricted to undifferentiated tumors (11). The radiosensitizing effect of dFdC was reported for several experimental tumors, most of them undifferentiated to poorly-/moderately-differentiated (1-8). In the present study, rats were used to test whether dFdC-mediated radiosensitization occurs in undifferentiated lung and prostate tumors and in a well-differentiated lung tumors. In addition, responses of skin as a well-differentiated tissue were scored.

Materials and Methods

Animal strains and tumors. The L44 is a radiation- (external chest irradiation) induced undifferentiated carcinoma, originally diagnosed as an adenosquamous lung carcinoma, which grows in female BN (Orl) Ico rats (Charles River, Maastricht, the Netherlands) with a tumor volume doubling-time of about 4 days (15-17). The R3327-MATLyLu prostate tumors (MLL) in male Copenhagen rats (Cop/Hsd, Harlan World Head Quarters, Indianapolis, Indiana, USA) is a fast growing anaplastic and metastasizing tumor (18, 19) with a tumor volume doubling-time of about 2 days. The L42 is a radiation- (I-125) induced well-differentiated squamous cell

carcinoma and grows in female WAG/Rij rats (Charles River, Maastricht, the Netherlands) with a tumor volume doubling-time of about 4 days (15-17).

Female BN and WAG/Rij rats and male Copenhagen rats were inoculated in the flank under isoflurane anesthesia with tumor pieces of about 2 mm^3.

Treatment. DFdC (Eli Lilly, Nieuwegein, the Netherlands) was reconstituted in physiological saline and stored at –30° C. The drug was injected i.p. into rats at room temperature using single doses ranging from 10 to 90 mg/kg in a volume of about 2 to 3 ml. The weight of the animals at the start of the treatments was about 170 gram (BN and WAG/Rij rats) and 220 gram (Copenhagen rats).

X-ray doses (200 kV, 20 mA, 0.5 mm Cu, dose rate 4 Gy/min, Philips Orthovolt RT250) were administered locally under hypnorm/dormicum anesthesia. When combined with dFdC at a concentration of 30 mg/kg, irradiation was performed 24 h after dFdC administration. The time interval of 24 h was chosen based on data in the literature (2, 3).

Tumors were treated at a volume of about 0.5 - 1 cm^3. L44 tumors were treated with a single dose of 10 Gy, MLL tumors with single doses of 20 and 30 Gy, and L42 tumors with a single dose of 15 Gy with or without dFdC. Tumors were measured twice per week with calipers. The tumor volume was based on 2 orthogonal cross-sectional diameter measurements ($V=0.5a^2b$ with a the smallest diameter). The volumes were then expressed as a percentage of the pretreatment volume on day 1, which was designated as 100%.

Skin. Early skin responses of a hind foot following irradiation with a single dose of 22.5 Gy with or without dFdC, were scored over a period of 5 weeks. The degree of damage as a function of time after treatment was determined according to the scoring system shown in Table I.

Table I. Scoring system of acute skin reactions of rat foot after radiation treatment.

Symptom	Score
Slight reddening, dry desquamation, or moist desquamation of < 25% of sole area	0.5
Reddening, or moist desquamation > 25% of sole area	1
Two toes attached	2
Three toes attached	3
Four toes attached	4
Club-foot	5

Score can be higher by combination of symptoms

End-points. Excess growth delay (EGD) is the time interval for the tumor to reach four times its pre-treatment volume (T4t) minus the time for a control tumor (with the same volume as the pre-treatment volume of the treated tumor) to reach four times that volume (T4): EGD = T4t-T4. Specific growth delay (SGD) was calculated for each treated tumor: SGD = EGD/T4. Using SGD, differences in the growth rate of tumors differing in starting volume at day 0 and between experiments can be dealt with. For skin the mean value and standard error of the maximal skin scores of animals at risk per experimental group were determined. The enhancement ratio is defined as the SGD (radiation+dFdC)/SGD (radiation).

Statistics. The Kaplan-Meier analysis was performed using SPSS10.1 by scoring an event as EGD, SGD or maximum skin score.

Approval. The Animal Experiments Ethical Committee of the University Medical Center Utrecht, the Netherlands, approved the animal experiments.

Results

Toxicity of dFdC. Single doses of dFdC ranging from 10 to 90 mg/kg were administered i.p. to tumor-bearing animals. The weight of the animals and tumor volumes were recorded. The maximal mean weight loss of BN rats for dFdC doses from 10 to 90 mg/kg was 0.6 to 4.3 gram (0.9 to 2.5%), for Copenhagen rats for dFdC doses from 15 to 90 mg/kg, this value was in the range of 2.5 to 9.7 gram (1.1 to 4.4%); for Wag/Rij rats it was 1.3 gram (0.8%) for a dose of 30 mg/kg, Figure 1.
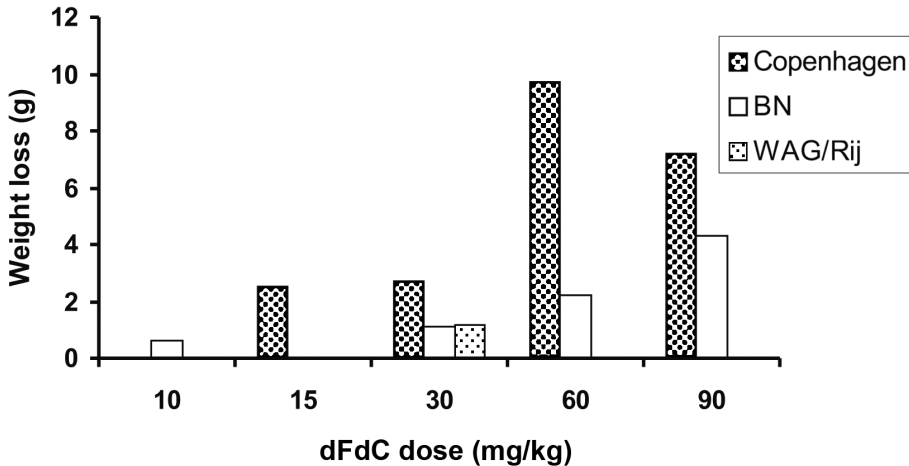
Figure 1. Maximum weight loss of Copenhagen, BN and WAG/Rij rats after administration of a single dose of dFdC.

DFdC, tumors. For a dFdC dose of 30 mg/kg, the mean and standard error (SE) of the EGD and mean and SE of the SGD for L44 tumors in BN rats were 1.6 ± 0.4 d and 0.24 ± 0.06, respectively. For MLL tumors in Copenhagen rats, these values were 1.1 ± 0.7 d and 0.3 ± 0.2 respectively, and for L42 tumors in Wag/Rij rats were 10.4 ± 2.7 d and 0.78 ± 0.21, respectively. For the experiments to determine whether dFdC would interact with radiation, the dose of 30 mg/kg dFdC was selected, i.e. a dose with a small effect on weight loss and on tumor growth delay.

DFdC and radiation, tumors. L44 tumors were treated with a single dose of 10 Gy, this resulted in a mean SGD of 1.53 (95% confidence interval: 1.19-1.87). For the combined treatment of dFdC (30 mg/kg) and a dose of 10 Gy, the SGD = 2.09 (95% confidence interval: 1.86-2.33). The enhancement ratio (ER) was 2.09/1.53 = 1.37 ± 0.23, Table II. MLL tumors were treated with single doses of 20 and 30 Gy, and the results are shown in Table II. The ERs were 1.36 ± 0.34 and 1.23 ± 0.22 for the combinations dFdC + 20 Gy and dFdC + 30 Gy, respectively. L42 tumors were treated with single doses of 15 Gy. The results are shown in Table II. The ER was 1.0 ± 0.1. Although L42 tumors were more affected by the dFdC dose than the 2 other tumors (SGD=0.78 versus 0.24 and 0.32), the combined effect of dFdC and radiation did not show any radiosensitization by DFdC at all. Examples of growth curves of the 3 tumors and responses to treatments are shown in Figure 2.

Table II. Specific growth delay (SGD) for three rat tumors with 95% confidence interval (95% CI) for dFdC, single radiation doses, and combined treatments, with enhancement ratio (ER) ± standard error (SE); N, number of tumors tested.

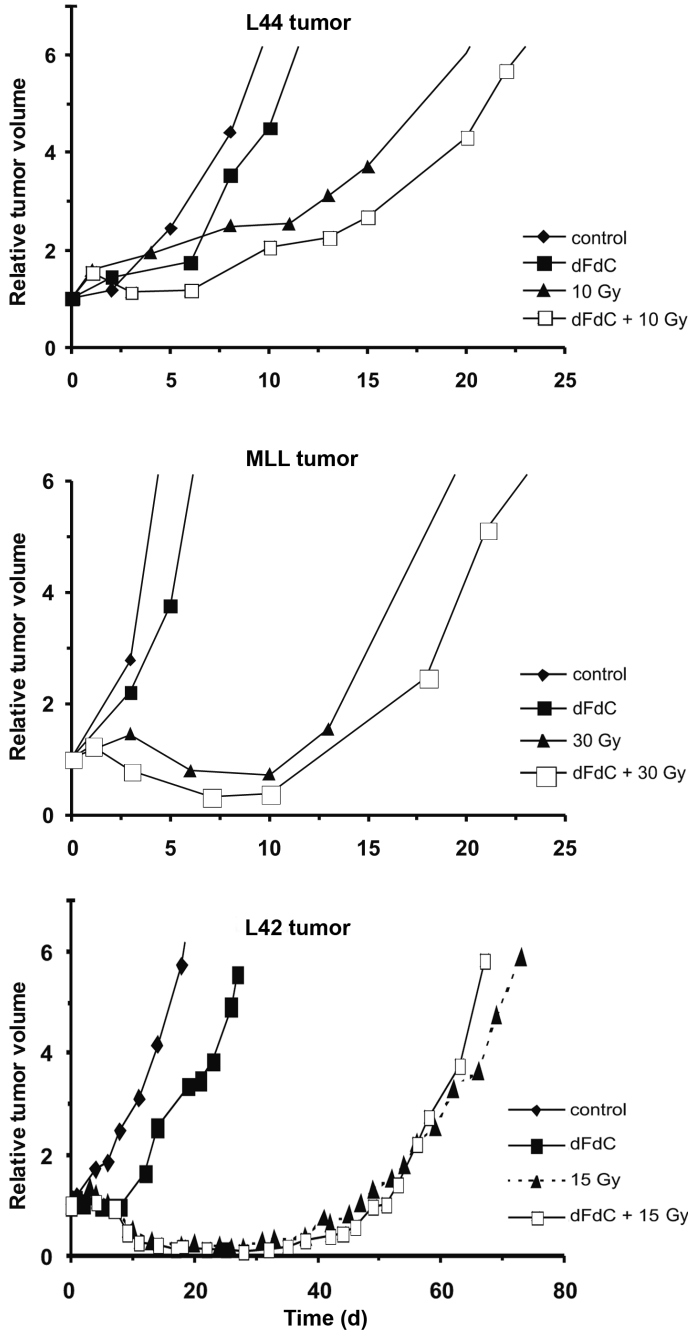| Tumors	Treatment	N	SGD (95% CI)	ER ± SE
L44	dFdC (30 mg/kg)	11	0.24 (0.13-0.35)	
	10 Gy	15	1.53 (1.19-1.87)	
	dFdC + 10 Gy	15	2.09 (1.86-2.33)	1.37 ± 0.23
MLL	dFdC (30 mg/kg)	10	0.32 (0-0.69)	
	20 Gy	5	2.91 (1.87-3.95)	
	dFdC + 20 Gy	5	3.97 (3.43-4.51)	1.36 ± 0.34
	30 Gy	10	3.55 (3.17-3.94)	
	dFdC + 30 Gy	8	4.37 (3.33-5.40)	1.23 ± 0.22
L42	dFdC (30 mg/kg)	14	0.78 (0.37-1.19)	
	15 Gy	13	3.73 (3.30-4.17)	
	dFdC + 15 Gy	19	3.73 (3.45-4.01)	1.0 ± 0.1

dFdC = gemcitabine

Figure 2. Growth curves of control L44, MLL and L42 tumors, and curves after start of treatment with dFdC, a single dose of X-rays and combined treatments.

DFdC and radiation, skin. For BN rats at the dose of 22.5 Gy, the mean skin score was 2.9 ± 0.7, and for the combination of dFdC (30 mg/kg) and 22.5 Gy, the mean score was 2.5 ± 0.7. For Copenhagen rats the mean scores were 4.5 ± 0.7 and 3.7 ± 0.7 and for WAG/Rij rats were 2.9 ± 0.9 and 2.75 ± 0.3, respectively. Surprisingly, the mean scores after the combination treatment are less than after radiation only, indicating radioprotection by dFdC. However, these differences are not statistically significant. The mean maximum skin scores and 95% confidence intervals for the 3 rat strains are summarized in Table III.

Table III. Mean scores with standard errors (SE) and 95% confidence intervals (CI) of foot skin reactions of 3 rat strains after treatments with a single dose of 22.5 Gy, and a dose of 22.5 Gy 24 h after administration of dFdC (30 mg/kg) (dFdC+ 24 h + 22.5 Gy).

		Mean skin score				
		22.5 Gy			dFdC + 24 h + 22.5 Gy	
Rat strain	N	Mean ± SE	95% CI	N	Mean ± SE	95%CI
BN	17	2.9 ± 0.7	(1.5 – 4.2)	15	2.5 ± 0.7	(1.2 – 3.8)
Cop/Hsd	16	4.5 ± 0.7	(3.2 – 5.8)	15	3.7 ± 0.7	(2.4 – 5.1)
WAG/Rij	5	2.9 ± 0.9	(1.3 – 4.4)	4	2.7 ± 0.3	(2.3 – 3.2)

dFdC = gemcitabine

Discussion

In our experiments, it was found that dFdC enhanced the radiation response in 2 undifferentiated rat tumors, but not in the well-differentiated L42 tumor or rat skin. This is in accord with the expectation that a radio-sensitizing effect of dFdC might be present in undifferentiated tumors. Evidence suggests that the radiosensitization effect of dFdC is associated with redistribution of cells into the S-phase with a simultaneous depletion of dATP pools (20-22). Others reported that dFdC is an effective inhibitor of DNA synthesis (23-25) and inhibits the repair of radiation-induced chromosome damage in vitro (26). Experiments have also addressed the possibility that reoxygenation of hypoxic cells is an additional mechanism by which dFdC enhances tumor radioresponse (2). In addition, the elimination of the S-phase cells from the tumor population by dFdC and the redistribution of surviving cells into a more radiosensitive compartment of the cell cycle may play a part (2). The target for radiosensitization induced by dFdC was found to be homologous recombination (HR) of DNA double-strand breaks (11) rather than the non-homologous end-joining pathway (27). As was demonstrated by Essers *et al*. (14), HR-deficient mice are hypersensitive to ionizing radiation at the embryonic, but not at the adult stage. Thus, a defect in HR may affect the radiosensitivity of undifferentiated embryonic stem cells (13) and cultured cell lines (28-37) and its impact on the radiosensitivity of differentiated adult cells in vivo might be limited or even absent (11). Wachters *et al*. (11) speculated that the radiosensitizing effect of dFdC in patients might be less in normal healthy tissue and more restricted to (undifferentiated) tumor cells, making it a tumor-selective radiosensitizer. Therefore, it was of interest to study the responses of un- and well-differentiated experimental tumors to dFdC and ionizing radiation as well as the response of the skin. Our results do indicate that the expectation of Wachters *et al*. might be true.

Radioenhancement in experimental tumors

Several authors (1-8) reported the enhancement of radiosensitivity by dFdC in experimental tumors. We expected that radioenhancement primarily occurs in undifferentiated and poorly-differentiated tumors. The tumor models showing radioenhancement are detailed in Table IV. The human squamous carcinoma FaDu (1) and pancreatic tumors MiaPaCa-2 (8, 38), the mouse Sa-NH sarcoma (2, 3, personal communication) and SCC

Table IV. Histological characteristics of experimental tumors and enhancement ratio's.

Tumor	Origin	Strain	Histology	Schedule dFdC and radiation	Enhancement ratio	Reference
		Mice				
FaDu	Human squamous carc.	Balb/c nude	Poorly to moderately diff.	10 x 2.3 mg/kg daily + 10 x (2 x 2 Gy)		(1)
				once weekly, 2 x 430 mg/kg + 10 x (2 x 2 Gy)	1.6	
				twice weekly, 4 x 50 mg/kg + 10 x (2 x 2 Gy)	2.6	
				twice weekly, 4 x 160 mg/kg 10 x (2 x 2 Gy)	2.4	
					3.3	
MiaPaCa-2	Pancreatic carc.	Balb/c nude	Undiff.	6 x 120 mg/kg + 6 x 3 Gy	>3	(8, 38)
Sa-NH	Sarcoma	C3Hf/Kam	Poorly diff.	50 mg/kg + 25 Gy, time interval	1.68 – 2.03	(2) (personal communication)
				50 mg/kg + graded doses (cure) 5 x 3 Gy, 5x5 Gy or 5x7 Gy +	1.54	
				1 x 25, 2 x 12.5 and 5 x 5mg/kg	1.34 –1.46	(3)
SCC VII	Squamous carc.	C3H	Poorly diff.	1 x 800 mg/kg + 5 x 5.5 Gy daily	1.6	(4)
				2 x100 mg/kg + 5 x 5.5 Gy	1.8	
BxPC-3	Pancreatic adenocarc.	Balb/c nude	Poorly to moderately diff.	6 x 120 mg/kg + 6 x 3 Gy	>2	(8, 40)
CH3/TIF	Mammary adenocarc.	C3D2F1	Moderately diff.	60/120 mg/kg + 10 Gy	1.76 /1.66	(6,7)
				60/120mg/kg + 20 Gy	1.55 /1.96	
				4 x 60 mg/kg + 10 x 2 Gy	4.86	
				4 x 60 mg/kg + 4 x 10 Gy	2.17	
Hepatoma	Hepatocarc.	C3H/HeL	"Looks like a well-diff. tumor."	50 mg/kg + 25 Gy	1.6	(5, personal communication)
		Rats				
L44	Adenosquam. carc.	BN	Undiff.	30 mg/kg + 10 Gy	1.37	present
MLL	Prostate carc.	Cop/Hsd	Undiff.	30 mg/kg + 20 or 30 Gy	1.36 / 1.23	present
L42	Squamous carc.	WAG/Rij	Well diff.	30 mg/kg + 15 Gy	1.0	present

VII squamous cell carcinoma (4, 39) all are undifferentiated or poorly differentiated. The mouse mammary adenocarcinoma CH3/TIF (6, 7) and human BxPC-3 pancreatic tumor (8, 40) are poorly- to-moderately differentiated. The mouse hepatocarcinoma Hca-I might be a well-differentiated tumors (personal communication, 2004) and may be an exception. However, this tumor was described as "looking as a well differentiated tumor", leaving other possibilities open. In all these tumors dFdC enhanced the radioresponsiveness.

The enhancement factors described were 1.6 to 3.3 for the human squamous carcinoma FaDu, depending on the dFdC dose and administration schedule (1) and larger than 3 for the MiaPaCa-2 xenograft (8). For the Sa-NH tumors the enhancement factors were 1.54 to 2.03, also depending on time-interval between dFdC and radiation administration and end-point (cure, growth delay) (2), and 1.34 to 1.46 for growth delay (3). Fields *et al*. (4) reported an enhancement ratio of 1.6 to 1.8 for the SCC VII squamous tumors. An enhancement ratio larger than 2 for the BxPC-3 xenograft could be derived from the experiments described by Buchsbaum *et al*. (8). Cividalli *et al*. (7) reported an enhancement ratio of 1.55 to 1.96 for single dose irradiation and 2.17 to 4.86 for fractionated irradiation. The ER was 1.6 for the hepatoma (5). These dose schedules and enhancement ratios are summarized, in Table IV. From this table it is clear that our dFdC dose of 30 mg/kg was relatively low. Only in the experiments of Mason *et al*. and Joschko *et al*. (1, 3) were comparable dose levels used.

In this study the response of the MLL tumor to combined treatment - ER = 1.23 to 1.36 - may be somewhat less than that of L44 tumor with an ER of 1.37, depending on the radiation dose. This may be caused by the inappropriate vasculature of the tumor, preventing dFdC from adequately reaching all tumor cells. In earlier experiments interaction with the radiosensitizer Motexafin was not observed (41). For our L42 tumors, no enhancement at all could be found.

The specific growth delays after combined treatment in the L44 and MLL tumors are larger than the sum of the SGDs of the treatments with dFdC or radiation only (Table II). In contrast, although L42 tumors were more affected by the single dFdC dose than the two other tumors, the combined effect of dFdC and radiation did not show any radiosensitization at all.

Normal tissues. We did not find any radioenhancement by dFdC (30 mg/kg) in the rat foot skin; on the contrary, some protection was observed. This effect was also reported for a nude mice model by Classen *et al.* (42), who found that acute and late toxicity of skin and underlying soft tissues of the hind leg of NMRI-nu/nu-nude mice was not significantly increased after single-dose irradiation in combination with dFdC (550 mg/kg) with time intervals of –36 to + 24 h. Even a slight radioprotective effect for dFdC was suggested. Cividalli *et al.* (6) in their study of acute skin reactions in mouse hind leg, reported that the addition of dFdC to radiation did not, in any case, modify the results. The response of the jejunum of C3Hf/Kam mice with the microcolony assay was strongly dependent on the schedule of dFdC administration, single dose of 25 mg/kg, 2x12.5 mg/kg or 5x5 mg/kg. A slight radioprotection to enhanced radiation response was observed ranging from 0.96 to 1.23 (3). Gastrointestinal toxicity was also investigated by Gregoire *et al.* (9), who applied whole-body irradiation. Depending on the time interval between dFdC administration (150 mg/kg) and irradiation, an enhancement ratio of 0.9 to 1.3 was observed. These ratios are quite similar to those found by Mason *et al.* (3). These results indicate that the enhancement ratio's observed are not related to relatively high dFdC concentrations. An increase in oral mucosa reaction of C3H mice was observed with the combination of 5 daily fractions of 5.5 Gy and dFdC administered as a single dose of 800 mg/kg or 2 x 100 or 2x150 mg/kg versus radiation only (4). From the figures shown by Fields *et al.* (4), it can be deduced that the combined treatment (27.5 Gy and dFdC) is equivalent to radiation alone at about 29 Gy. The enhancement ratio thus is about 1.05. However, the dFdC doses alone produced a weight loss of about 10% and were much higher than in our experiments or in those of Mason *et al.* (3). Gregoire *et al.* (43) studied the effect of dFdC (150 mg/kg) on the tolerance of the lung to single-dose irradiation in C3H mice. The time interval between dFdC and irradiation varied from 3 to 48 h. Their data indicated a minimal effect of dFdC on lung tolerance after irradiation. LD_{50} values for the combination were reduced by about 10%.

From this short review on normal tissue tolerance, (Table V), we may conclude that a slight protection to enhanced radiation response was observed for normal tissues. The observed enhancement ratio's are, in general, less ($\leq$ 1.3), than those observed for undifferentiated to poorly-/moderately-differentiated tumors, ranging from 1.23 to larger than 4, (Table IV), hence indicating a therapeutic gain. These findings support the concept of using full dose radiation and of attempting to improve local

control with dFdC applied at a relatively low dose as a radiosensitizing agent.

Conclusion. Radiosensitization due to a relatively low dose dFdC was observed in the undifferentiated L44 and MLL tumors, but not in the well-differentiated L42 tumors or skin. Our data support further trials to evaluate the usefulness of dFdC as radiosensitizer for undifferentiated tumors.

Table V. Enhancement ratio (ER) of some normal tissues.

Tissue	Strain	dFdC (mg/kg)	Interval* (h)	ER	Reference
Skin	NMRI-nu/nu	550	36 - 2; 24 h after irr.	ns	(42)
Skin	C3D2F1	30, 60, 120	24	1	(6)
Jejunum	C3Hf/Kam	25	24	0.96 - 1.23	(3)
Jejunum	C3H	150	3 - 48	0.9 - 1.3	(9)
Oral mucosa	C3H	800	6	1.05	(4)
		2x100/150		1.05	(4)
Lung	C3H	150	3 - 48	1.1	(43)
Skin	BN, Copenh., WAG/Rij	30	24	<1	present

dFdC = gemcitabine

*interval between dFdC and irradiation

References

1. Joschko MA, Webster LK, Groves J, *et al*: Enhancement of radiation-induced regrowth delay by gemcitabine in a human tumor xenograft model. Radiat Oncol Investig 5: 62-71, 1997.
2. Milas L, Fujii T, Hunter N, *et al*: Enhancement of tumor radioresponse in vivo by gemcitabine. Cancer Res 59: 107-114, 1999.
3. Mason KA, Milas L, Hunter NR, *et al*: Maximizing therapeutic gain with gemcitabine and fractionated radiation. Int J Radiat Oncol Biol Phys 44: 1125-1135, 1999.
4. Fields MT, Eisbruch A, Normolle D, *et al*: Radiosensitization produced in vivo by once- vs. twice-weekly 2′2′-difluoro-2′-deoxycytidine (gemcitabine). Int J Radiat Oncol Biol Phys 47: 785-791, 2000.
5. Seong J, Kim SH, Suh CO: Enhancement of tumor radioresponse by combined chemotherapy in murine hepatocarcinoma. J Gastroenterol Hepatol 16: 883-889, 2001.
6. Cividalli A, Livdi E, Ceciarelli F, *et al*: Combined use of gemcitabine and radiation in mice. Anticancer Res 21: 307-312, 2001.
7. Cividalli A, Ceciarelli F, Livdi E, *et al*: Radiosensitization by oxaliplatin in a mouse adenocarcinoma: influence of treatment schedule. Int J Radiat Oncol Biol Phys 52: 1092-1098, 2002.
8. Buchsbaum DJ, Bonner JA, Grizzle WE, *et al*: Treatment of pancreatic cancer xenografts with Erbitux (IMC-C225) anti-EGFR antibody, gemcitabine, and radiation. Int J Radiat Oncol Biol Phys 54: 1180-1193, 2002.
9. Gregoire V, Beauduin M, Rosier JF, *et al*: Kinetics of mouse jejunum radiosensitization by 2′,2′-difluorodeoxycytidine (gemcitabine) and its relationship with pharmacodynamics of DNA synthesis inhibition and cell cycle redistribution in crypt cells. Br J Cancer 76: 1315-1321, 1997.
10. Crul M, van Waardenburg RC, Bocxe S, *et al*: DNA repair mechanisms involved in gemcitabine cytotoxicity and in the interaction between gemcitabine and cisplatin. Biochem Pharmacol 65: 275-282, 2003.
11. Wachters FM, van Putten JW, Maring JG, *et al*: Selective targeting of homologous DNA recombination repair by gemcitabine. Int J Radiat Oncol Biol Phys 57: 553-562, 2003.
12. Kooistra R, Pastink A, Zonneveld JB, *et al*: The Drosophila melanogaster DmRAD54 gene plays a crucial role in double-strand break repair after P-element excision and acts synergistically with Ku70 in the repair of X-ray damage. Mol Cell Biol 19: 6269–6275, 1999.
13. Essers J, Hendriks RW, Swagemakers SM, *et al*: Disruption of mouse RAD54 reduces ionizing radiation resistance and homologous recombination. Cell 89: 195–204, 1997.
14. Essers J, Van Steeg H, De Wit J, *et al*: Homologous and non-homologous

recombination differentially affect DNA damage repair in mice. EMBO J 19: 1703–1710, 2000.

15. Kal HB, Meijnders PJ, van Berkel AH, *et al*: Response to chemotherapy of non-small cell bronchial rat tumors growing subcutaneously or in the lung. In Vivo 5: 301-306, 1991.

16. Kal HB, van Berkel AH, Broers JL, *et al*: Cytokeratins expressed in experimental rat bronchial carcinomas. Int J Cancer 53: 506-513, 1993.

17. Kal HB, van Berkel AH, Goedoen HH: Growth rate, morphology and drug responses of rat lung tumors growing at different sites. Anticancer Res 14: 495-499, 1994.

18. Dijkman GA, Van Moorselaar RJA, Van Ginckel R, *et al*: Antitumoral effects of liarozole in androgen-dependent and independent R3327-Dunning prostate adenocarcinomas. J Urol 151: 217-222, 1994.

19. Moorselaar RJA van, Hendriks BTh, van Stratum P, *et al*: Synergistic antitumor effects of rat-gamma-interferon and human tumor necrosis factor alpha against androgen-dependent and –independent rat prostatic tumors. Cancer Res 51: 2329-2334, 1991.

20. Shewach DS, Hahn TM, Chang E, *et al*: Metabolism of 2',2'-difluoro-2'-deoxycytidine and radiation sensitization of human colon carcinoma cells. Cancer Res 54: 3218–3223, 1994.

21. Lawrence TS, Chang EY, Hahn TM, *et al*: Radiosensitization of pancreatic cancer cells by 2',2'-difluoro-2'-deoxycytidine. Int J Radiat Oncol Biol Phys 34: 867–872, 1996.

22. Latz D, Fleckenstein K, Eble M, *et al*: Radiosensitizing potential of gemcitabine (2',2'-difluoro-2'-deoxycytidine) within the cell cycle in vitro. Int J Radiat Oncol Biol Phys 41: 875–882, 1998.

23. Plunkett W, Gandhi V, Chubb S, *et al*: 2`,2`-difluoro-deoxycytidine metabolism and mechanism of action in human leukaemia cells. Nucleosides Nucleotides 8: 775-785, 1989.

24. Plunkett W, Huang P, Gandhi V: Preclinical characteristics of gemcitabine. Anticancer Drugs 6 (Suppl 6): 7-13, 1995.

25. Plunkett W, Huang P, Xu YZ, *et al*: Gemcitabine: metabolism, mechanisms of actions, and self-potentiation. Semin Oncol 22 (Suppl 11): 3-10, 1995.

26. Huang NJ, Hittelman WN: Transient inhibition of chromosome damage repair after ionizing radiation by gemcitabine (abstract). Proc Am Assoc Cancer Res 36: 612, 1995.

27. Van Putten JWG, Groen HJM, Smid K, *et al*: End-joining deficiency and radiosensitization induced by gemcitabine. Cancer Res 61: 1585-1591, 2001.

28. Asaad NA, Zeng ZC, Guan J, *et al*: Homologous recombination as a potential target for caffeine radiosensitization in mammalian cells: Reduced caffeine radiosensitization in XRCC2 and XRCC3 mutants. Oncogene 19: 5788–5800, 2000.

29. Cui X, Brenneman M, Meyne J, *et al*: The XRCC2 and XRCC3 repair genes

are required for chromosome stability in mammalian cells. Mutat Res 434: 75–88, 1999.

30. Liu N, Lamerdin JE, Tebbs RS, *et al*: XRCC2 and XRCC3, new human Rad51-family members, promote chromosome stability and protect against DNA cross-links and other damages. Mol Cell 1: 783–793, 1998.

31. Jones NJ, Cox R, Thacker J: Isolation and cross-sensitivity of X-ray-sensitive mutants of V79-4 hamster cells. Mutat Res 183: 279–286, 1987.

32. Cartwright R, Tambini CE, Simpson PJ, *et al*: The XRCC2 DNA repair gene from human and mouse encodes a novel member of the recA/RAD51 family. Nucleic Acids Res 26: 3084–3089, 1998.

33. Tambini CE, George AM, Rommens JM, *et al*: The XRCC2 DNA repair gene: Identification of a positional candidate. Genomics 41: 84–92, 1997.

34. Johnson RD, Liu N and Jasin M: Mammalian XRCC2 promotes the repair of DNA double-strand breaks by homologous recombination. Nature 401: 397–399, 1999.

35. Fuller LF and Painter RB: A Chinese hamster ovary cell line hypersensitive to ionizing radiation and deficient in repair replication. Mutat Res 193: 109–121, 1988.

36. Pierce AJ, Johnson RD, Thompson LH, *et al*: XRCC3 promotes homology-directed repair of DNA damage in mammalian cells. Genes Dev 13: 2633–2638, 1999.

37. Takata M, Sasaki MS, Sonoda E, *et al*: Homologous recombination and non-homologous end-joining pathways of DNA double-strand break repair have overlapping roles in the maintenance of chromosomal integrity in vertebrate cells. EMBO J 17: 5497–5508, 1998.

38. Yunis AA, Arimura GK, Russin DJ: Human pancreatic carcinoma (MIA PaCa-2) in continuous culture: sensitivity to asparaginase. Int J Cancer 19: 218-235, 1977.

39. Matsumoto G, Ohmi Y, Shindo J: Angiostatin gene therapy inhibits the growth of murine squamous cell carcinoma in vivo. Oral Oncol 37: 369-378, 2001.

40. Tan MH, Nowak NJ, Loor R, *et al*: Characterization of a new primary human pancreatic tumor line. Cancer Invest 4: 15-23, 1986.

41. Dehnad H, Kal HB, Stam T, *et al*: Response to motexafin gadolinium and ionizing radiation of experimental rat prostate and lung tumors. Int J Radiat Oncol Biol Phys 57: 787-793, 2003.

42. Classen J, Paulsen F, Hehr T, *et al*: Effect of gemcitabine on acute and late radiation toxicity of skin and underlying soft tissues to single-dose irradiation in a nude mice model. Int J Radiat Oncol Biol Phys 53: 197-205, 2002.

43. Gregoire V, Cvilic S, Beauduin M, *et al*: Effect of gemcitabine on the tolerance of the lung to single-dose irradiation in C3H mice. Radiat Res 151: 747-749, 1999.

Chapter 6

Weekly docetaxel/cisplatin and concurrent thoracic radiotherapy followed by surgery in patients with stage III non-small cell lung cancer, a multicentre phase II study

K.W. Maas
S.Y. El Sharouni
E.C.J. Phernambucq
J.A. Stigt
H.J.M. Groen
G.J.M. Herder
B.E.E.M. van den Borne
S. Senan
M.A. Paul
E.F. Smit
F.M.N.H. Schramel

Abstract

Background: Concurrent chemoradiotherapy is the standard of care in stage III non-small cell lung cancer (NSCLC) patients. This prospective study analyzed the feasibility and efficacy of weekly docetaxel/cisplatin (DC) and concurrent radiotherapy (RT) followed whenever possible by surgery.

Methods: Between March 2005 and September 2006, 45 patients were included, of whom 42 patients were evaluable, 25 with stage IIIA and 17 patients with stage IIIB. DC consisted of docetaxel 20 mg/m^2 and cisplatin 20 mg/m^2 at days 1, 8, 15, 22, 29 and 36. RT was given in once-daily fractions of 1.8 Gy, 5 fractions a week to a total dose of 45 Gy, started on day 8 of the DC. When complete mediastinal clearance of malignant disease was achieved, surgery was performed. The primary endpoint was radiological response. The secondary endpoints included toxicity, efficacy of surgery, postoperative morbidity and mortality and overall survival.

Results: One patient developed fatal haemoptysis after 4 cycles of chemoradiotherapy. Forty-one patients were evaluable for radiological response. Nineteen of the 41 patients achieved partial and complete responses (46%), 14 patients stable disease (34%) and 8 progressive disease (20%). Toxicity was mild. Surgery was performed in 24 patients (59%). Complete clearance of mediastinal malignant disease was achieved in 22 patients (54%). Twenty patients achieved a complete resection (49%). Four patients showed complete pathological response. The 30-day mortality after surgery was 4%.

Conclusion: Weekly docetaxel/cisplatin with concurrent radiotherapy resulted in radiological response of 46% and complete clearance of mediastinal malignant disease in 54%. The complete resection rate was 49%. This regimen is feasible with limited toxicity and seems to be effective in stage III NSCLC.

Introduction

The 2003-ASCO guidelines (1) recommend (platinum-based) chemotherapy in association with thoracic radiotherapy for selected patients with unresectable locally advanced non-small cell lung cancer (NSCLC). However, the optimal sequencing of chemotherapy and radiotherapy has not been established and it is unclear whether surgery plays a role in combined modality treatment for stage III NSCLC.

A variety of multimodality therapies that include chemotherapy, surgery and/or radiotherapy have recently been assessed in clinical phase III trials but none showed a significant survival difference (2-4).

Taxanes are known to have radiosensitizing potential (5, 6). Docetaxel has demonstrated greater radiosensitizing potential, possibly through different mechanisms such as immunomodulation or antiangiogenesis effects (7-10). Toxicity of docetaxel can be decreased by administration in a weekly schedule (11). Several phase-I and -II studies showed that cisplatin and docetaxel both administered at 20 mg/m^2 once a week can be combined with radical thoracic radiotherapy (12-20).

This study analyses the results of a chemoradiotherapy regimen consisting of docetaxel and cisplatin and involved-field thoracic radiotherapy for a total dose of 45 Gy. Following invasive mediastinal restaging, patients with pathological mediastinal downstaging underwent a thoracotomy with the aim of a radical resection. The remaining patients continued radiotherapy for a maximum of 60 Gy in order to maximize local control rates.

The primary endpoint of this phase II study was radiological response; the secondary endpoints included toxicity, efficacy in terms of radical resection rate and pathologic response, postoperative morbidity and mortality and overall survival (OS).

Methods

Patients
From March 2005 to September 2006, 45 patients with stage IIIA/ IIIB NSCLC were entered into this prospective multicenter phase II trial. Patients were staged according to the guidelines of the National Comprehensive Cancer Network in the United States and the American College of Chest Physicians (ACCP) guidelines (21).

Eligibility criteria included pathologically proven primary NSCLC stage

Table 1: Pre-treatment characteristics of patients and type of mediastinal lymph-node assessment in patients eligible for treatment.

	Number of patients (%)
Gender	
Male	27 (64%)
Female	15 (36%)
Median age (range), year	59 (41-78)
ECOG performance status	
0	26 (62%)
1	16 (38%)
Histological type	
Squamous cell carcinoma	16 (38%)
Adenocarcinoma	4 (10%)
Large cell carcinoma	22 (52%)
Stage	
IIIA	25 (60%)
cT1-3N2M0	25 (60%)
IIIB	17 (40%)
cT4N0-1M0	4 (9%)
cT4N2M0	10 (24%)
cT1-3N3M0	3 (7%)
Type of mediastinal staging	
Mediastinoscopy	7 (17%)
EUS	17 (41%)
Mediastinoscopy anterior	1 (2%)
Thoracotomy	1 (2%)
TBNA	6 (14%)
No invasive staging	10 (24%)

ECOG: Eastern Cooperative Oncology Group
EUS: Esophageal ultrasonography
TBNA: Transbronchial needle aspiration

IIIA/IIIB (every T, N2 and/or N3 and M0, except malignant pleural effusion or scalene/supraclavicular lymph node involvement), age between 18 and 76 years, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, platelet count > 100 x 10^9/l, absolute neutrophil count > 2 x 10^9/l, normal liver and renal functions with a creatinine clearance > 60 ml/min.

The calculated postoperative forced expiratory volume in 1 second (FEV1) and CO transfer coefficient should be for both > 40% of the predicted values and maximum oxygen consumption (VO_{2max}) had to be more than 15 ml/min/kg.

Out of the 45 patients with stage IIIA/IIIB NSCLC, 3 patients were excluded from the study: 2 patients did not meet the criteria of stage III and one patient was diagnosed with a mesothelioma on pathological review. The characteristics of the 42 patients are provided in Table 1.

Thirty-two patients had pathological proof of mediastinal involvement of which 29 had mediastinal lymph node metastases (N2-disease). Ten patients with cT4 disease were not staged invasively before chemoradiotherapy because of gross involvement of the mediastinum (Table 1).

All patients were entered after written consent was obtained according to local medical ethical committee regulations.

Chemotherapy
Chemotherapy consisted of six cycles of docetaxel and cisplatin. Both drugs were administered on day 1, 8, 15, 22, 29 and 36 at a dose of 20 mg/m^2 as an intravenous infusion along with an appropriate hydration and antiemetic regimen.

Treatment was stopped if disease progressed or unacceptable toxicity occurred. Dose reductions were specified per protocol.

Radiotherapy
Following one cycle of docetaxel/cisplatin, concurrent radiotherapy started on day 8 of the chemotherapy. Radiotherapy was delivered in once-daily fractions of 1.8 Gy, five fractions a week, to a total dose of at least 45 Gy. The overall treatment time of the radiotherapy was five weeks and was not interrupted except in the event of a grade III or IV esophageal or pulmonary toxicity, or a grade IV haematological toxicity (NCIC-CTC grading). The use of a planning CT-scan and a 3-D treatment-planning program with a beam-eye-view facility was mandatory. The gross tumor

volume (GTV) included all tumor identified prior to start of the treatment by means of radiological imaging, PET-scan, bronchoscopy, cervical mediastinoscopy, esophageal ultrasonography (EUS), mediastinoscopy, video-assisted thoracoscopic surgery (VATS) or thoracotomy. Mediastinal lymph nodes with a short-axis diameter of > 1 cm were included in the GTV. The GTV was contoured using both the lung and mediastinal windows settings. The clinical target volume (CTV) included the ipsilateral hilus even if this was radiologically normal. The CTV included the GTV plus a symmetrical margin of 1 cm. The planning target volume (PTV) was delivered by adding a margin of 1 cm to the CTV but this margin should only be 0.5 cm in case of a contralateral N3 node. The full dose of 45 Gy could be delivered to the spinal cord, and preference was given sparing pulmonary tissue in order to limit the V20, which was defined as volume of both lungs minus the PTV, which receives a dose of 20 Gy (22).

In patients who were not eligible for complete resection due to persistent N2/N3 - or non-resectable T4 disease, additional radiotherapy up to 60 Gy was given when the gap between the end of the 45 Gy and restarting the radiotherapy was limited to less than three weeks and when disease progression outside the previous planning target volume was absent.

Response assessment
Tumor response after concurrent chemoradiotherapy (CRT) was assessed with CT-scan and PET-scan using the response-evaluation-criteria in solid tumors *(RECIST)*. PET-scan was also used to evaluate disease progression outside the chest.

Invasive restaging
A planned re-evaluation following CRT took place within a few days after completion of the treatment. Patients initially staged as having T4N0-1 disease, who did not show radiological progress after CRT proceeded directly to explorative thoracotomy. Patients initially staged as having N2 or N3 disease, and did not progress during or after the treatment, proceeded to a mediastinal evaluation using (repeat)-mediastinoscopy, EUS, VATS or mediastinotomy anterior. During mediastinoscopy, biopsies were taken from lymph node stations 2R, 2L, 4R, 4L and 7 (according to Naruke).

Surgery
All patients who at re-evaluation had potentially resectable disease and no progressive disease outside the thorax proceeded to thoracotomy with

intent to achieve a complete resection (R0 resection) (23). Surgery was to be performed between three to four weeks after the last fraction of the radiotherapy.

Statistics
In this phase II study the primary endpoint was the summed percentage of radiological complete and partial responses. For a sample size calculation a summed proportion of complete and partial responses of 0.6-0.65 is expected and progress into a comparative randomised phase III is decided upon, when the lower end of the one-sided 95% confidence interval exceeds 0.5. A sample size of 40 patients was required.

Interim analysis was performed after the inclusion of ten patients; if more than three patients died due to the treatment or more than four patients experienced grade IV esophageal toxicity, the study would have been terminated.

Survival was estimated from the date of inclusion, using the Kaplan-Meier survival analysis method (24). Survival comparisons were analyzed by the log-rank test (25). The difference was considered statistically significant when the p value was < 0.05.

Results

Chemoradiotherapy
Thirty-six patients (86%) received six cycles of docetaxel and cisplatin without dose reduction or delays. No grade III or IV haematological toxicity was observed. The reasons for stopping the treatment in the remaining 6 patients are as follows: in two patients treatment was discontinued after two and three cycles of chemotherapy respectively because of tumor progression. One patient developed fatal haemoptesis after 4 cycles of chemoradiotherapy. One patient needed dose reduction after one cycle of chemotherapy and was subsequently stopped after four cycles because of hepatic dysfunction. One patient discontinued chemotherapy and continued radiotherapy after 5 cycles of chemotherapy because of fever of unknown origin. For one patient the last two cycles were carboplatin/docetaxel because of a cerebro-vascular accident. The results are shown in Table 2. The mean V_{20} was 21.4% (range: 6.0-34.0). One patient (2%) developed grade II radiation pneumonitis after chemoradiotherapy. Esophagitis grade III was observed in 3 patients (7%). One patient (2%) developed skin rash grade II. In 9 patients who had persistent N2/N3

disease radiotherapy up to 60 Gy was considered, except for one patient who received 65 Gy. One patient received concurrent chemoradiotherapy up to 75 Gy (Table 2). In all patients who underwent radiotherapy up to 60 Gy the median gap was 8 days (mean: 17 days, range 6-52 days).

Table 2. Treatment results with list of complications.

	Number of patients
Chemotherapy (n=42)	
Patients receiving 6 cycles	36
Patients receiving less than six cycles	6
Progression during chemotherapy	2
Fatal haemoptysis †	1
Hepatic dysfunction	1
Fever of unknown origin,	1
change to other regimen because of cerebro-vascular accident	1
Radiotherapy (n=42)	
Patients receiving 45 Gy:	30
CRT and surgery	23
Unknown	2
Because of metastasis after CRT	5
Patients receiving up to 75 Gy (54-75 Gy)	9
50 Gy*	1
54 Gy	3
58 Gy	1
60 Gy	2
65 Gy	1
75 Gy	1
Patients receiving less than 45 Gy	3
Fatal haemoptysis	1
Brain metastasis	1
Leptomeningeal metastasis	1
Side-effects after chemoradiotherapy	5
Radiation pneumonitis grade II	1
Esophagitis grade III	3
Skin rash grade II	1

Continuation **Table 2**

	Number of patients
<u>Restaging procedures</u>	<u>35</u>
Mediastinoscopy	16
Remediastinoscopy	2
EUS	9
Surgical exploration	1
TBNA	6
Transthoracal needle aspiration	1
<u>Patients undergoing surgery</u>	<u>24</u>
Pneumonectomy	<u>10</u>
Right-sided/Left-sided	<u>1/9</u>
Sleeve lobectomy	1
Bilobectomy	1
Lobectomy	11
Explorative thoracotomy	1
<u>Complications after surgery</u>	<u>18</u>
<u>Major complications <30 days</u>	
ARDS †	1
Re-thoracotomy	
Subcutaneous emphysema/hemorrhage	1
Empyema	1
<u>Major complications > 30 days</u>	
Hypovolemic shock due to gastric hemorrhage †	1
Re-thoracotomy	
Persisting atelectasis	1
Pneumonia †	1
<u>Minor complications < 30 days</u>	
Atrium fibrillation	5
Upper airway infection	1
Pneumonia	4
Wound dehiscence	1
Gastric hemorrhage	1

CRT: Concurrent chemoradiotherapy
EUS: Esophageal ultrasonography
TBNA: Transbronchial needle aspiration
ARDS: Acute respiratory distress syndrome
*: progression during radiotherapy
†: deceased

Response rate
Forty-one patients were evaluable after chemoradiotherapy for radio-logical response.
Radiological response rate after chemoradiotherapy is presented in Table 3. Nineteen patients had complete or partial radiological response (46%). Fourteen patients had stable disease (34%) and in 8 patients progressive disease (20%).

Table 3: Radiological response after chemoradiotherapy compared to mediastinal restaging and surgery (n=41).

Radiological response	Mediastinal restaging (path) (n=35)	Surgery (n=24)
CR 3 (7%)	3 downstaging (1 micrometastasis)	2 R0, 1R2 (pN2)
PR 16 (39%)	12 downstaging 2 persistent N2 2 not performed	12 R0 1 explorative thoracotomy (pN2) 1 R0, 1 R2 (pN2)
SD 14 (34%)	7 mediastinal downstaging (1 trachea carcinoma) 7 persistent N2	5 R0 1 R0 (resection margin +)
PD 8 (20%)	3 persistent N2 1 persistent N3	

CR: Complete response
PR: Partial response
SD: Stable disease
PD: Progressive disease

Restaging
Thirty-five patients (85%) underwent invasive restaging (Table 3). Complete clearance of mediastinal disease was achieved in 22 patients (54%). Different methods of restaging were used (Table 2). No complications occurred during restaging procedures. None of the patients showed persistent N2 disease during thoracotomy when downstaging was found at mediastinal restaging.
Seven patients out of 14 with radiologically stable disease did have complete clearance of tumor in mediastinal lymph node metastases by invasive restaging and 6 patients proceeded to thoracotomy. The seventh patient had a trachea carcinoma (Table 3).

Surgery and treatment-related complications
The median time from the end of CRT to surgery was 27 days (range 10-43 days). Results of surgical therapy are shown in Table 3. Histopathologically proven downstaging and a complete resection (R0 resection) were obtained in 20 patients (49%). Three patients were diagnosed with persistent N2-disease. One had a complete mediastinal response on PET-scan after chemoradiotherapy and proceeded directly to thoracotomy, a second patient showed mediastinal micrometastases and proceeded also to thoracotomy and the third patient had already N2 disease at mediastinal restaging and explorative thoracotomy was performed.
Four patients showed a pathological complete response after CRT and surgery.
Treatment-related complications after surgery are shown in Table 2. Major complications < 30 days and > 30 days were observed in 3 and 3 patients, respectively. In-hospital (30-day) mortality was 4% (one patient). This patient underwent a right-sided pneumonectomy and developed acute respiratory distress syndrome three days after the operation and expired one day later. Minor complications < 30 days were observed in 12 patients.

Survival
Until March 2009, 28 patients died after a median follow-up of 24 months. The survival of the whole group was 60% at one year, 50% at 2 years and 38% at 3 years. Survival in responders treated with chemoradiotherapy and surgery (n=24) or chemoradiotherapy alone (n=18), p=0.001, is shown in Figure 1. The 1-, 2-, and 3-year survival of the responders was 70%, 65% and 57%, respectively, and for the non-responders it was 48, 37%, and 5%,

respectively. At the time of this analysis (March 2009), 14 patients are still alive of which 13 were operated upon.
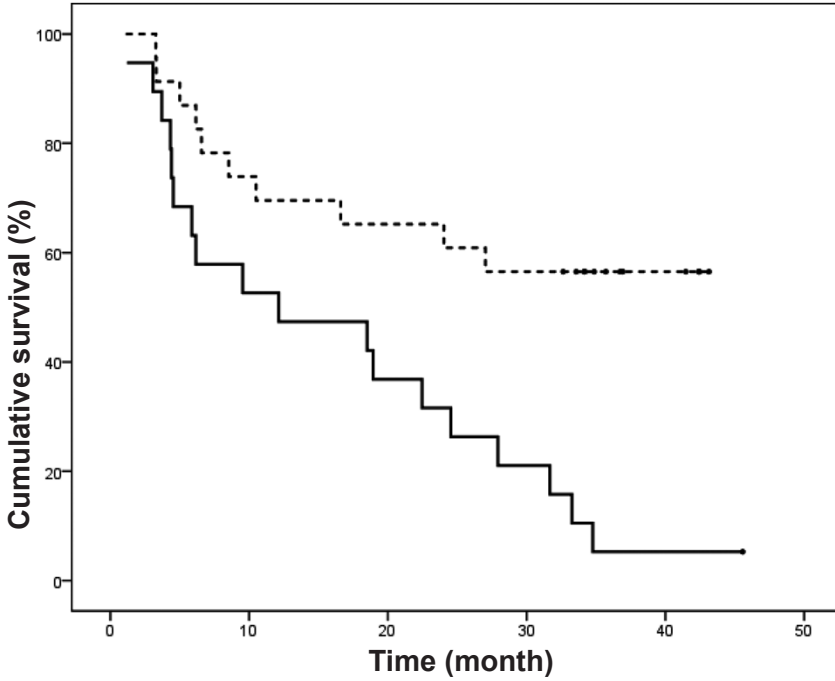
Figure 1: Survival in responders treated with chemoradiotherapy and surgery (n=24), dotted line, and in non-downstaged patients who only received chemoradiotherapy (n=18), full line (p=0.001).

Patterns of disease failure

Patterns of disease failure are shown in Table 4. Local and distant failures after CRT/adjuvant radiotherapy were observed in 6 and 1 patients, respectively, and after CRT/surgery in 1 and 8 patients, respectively (p=0.003).

Table 4: Patterns of disease failure after CRT/surgery and CRT/adjuvant radiotherapy (n=32).

	Local failure n	Distant failure n
CRT/Adjuvant radiotherapy (n=9)	6	1
CRT/Surgery (n=23)	1	8

CRT: concurrent chemoradiotherapy

Discussion

Complete and partial response, the primary endpoint of this study, was observed in 46% of patients. In addition, pathological clearance of malignant mediastinal disease was achieved in 22/41 (54%) patients. No acute (non)-haematological toxicity was encountered and a low incidence of treatment related pneumonitis was observed (2%) probably due to the constraints put on the V20 (median 20.4%) (22). Esophagitis grade III was encountered in 3 patients (7%). The low toxicity is probably due to the use of high-technology radiotherapy. These results are comparable to those obtained by Katayama et al. using a similar treatment schedule (26). Although in their study the objective response rate after CRT was higher (73%), pathological downstaging of mediastinal lymph nodes was achieved in 59% of patients.

In this study twenty patients (49%) underwent a complete resection of which six patients (15%) that had stable disease as their best response to CRT achieved complete mediastinal clearance, 5 of which achieved complete resection.
Several studies have shown that pathological response in mediastinal lymph nodes predicts prolonged survival (2, 3, 27-30). Albain *et al*. published data on 126 patients with stage IIIA and IIIB NSCLC, treated with concurrent chemoradiotherapy followed by surgery (2). Of the patients that were resected the strongest predictor for long-term survival was the absence of mediastinal lymph node metastasis. Therefore, a careful selection of patients through accurate pathological restaging at completion of concurrent chemoradiotherapy is critical, preferably by using restaging tools such as (re) mediastinoscopy, EUS-FNA or thoracotomy. In case downstaging is not

established, adjuvant radical radiotherapy has to be continued at least up to 60 Gy as this is the standard treatment for patients with irresectable stage III NSCLC. Chemoradiotherapy can induce extensive fibrosis and necrosis of the tumor and mediastinum (2). As a consequence, radiological response is not the optimal parameter to select patients for surgery as patients with radiological stable disease may have complete clearance of mediastinal malignant disease, as was found in our study.

The types of surgery and CRT used are the major determinants of morbidity and mortality. Pneumonectomy has been reported to have significant negative influence on survival (3, 29). Three recent randomized studies observed a significant higher mortality after induction therapies followed by a right-sided- and complex left-sided pneumonectomy as compared to lesser resections (2-4). Therefore, several authors advocate against pneumonectomy after pre-operative chemoradiotherapy (2, 4).

In our study, the 30-day mortality of one patient (4%) was due to right-sided pneumonectomy.

In our study, 13 (57%) patients with curative resection are alive after 46 months compared to 1 of the non-operated patients (p=0.024). Japanese investigators reported comparable results with a median follow up of 32 months, the 3-year overall survival rate was 66% (26).

Two phase-III trials have been conducted in the last decade that investigated the role of preoperative chemoradiotherapy. In the Intergroup trial 0139 (2) concurrent chemoradiotherapy followed by surgery vs concurrent chemoradiotherapy, the 5-year progression-free survival rate of 22.4% in the concurrent/surgical arm was better than in the concurrent arm, 11.1%. There was an absolute 5-year survival benefit of 7% for the surgery arm (2). In contrast, in the GLCCG trial, surgery preceded by chemoradiotherapy in addition to preoperative chemotherapy, or chemotherapy alone failed to show significant differences in progression free survival or overall survival between the treatment groups (4). The two studies mentioned above (2, 4) used some form of consolidation chemotherapy. Following the report by Hanna and colleagues (31) that showed no difference in survival between patients who received consolidation chemotherapy as compared to those who did not and also showed increased rate of hospitalization and premature death, we decided to omit consolidation chemotherapy.

It can be concluded that although weekly docetaxel/cisplatin with concurrent involved-field radiotherapy resulted in radiological response of 46%, a complete clearance of mediastinal malignant disease of 54% can

be reached, resulting in a complete resection rate of 49%. This regimen is feasible with limited toxicity and seems to be effective in stage III NSCLC.

References

1. Pfister DG, Johnson DH, Azzoli CG, *et al*. American Society of Clinical Oncology. Treatment of unresectable non-small-cell-lung cancer guideline: update 2003. J Clin Oncol 2004; 22: 330-353.
2. Albain KS, Swann RS, Rush V, *et al*. Phase III study of concurrent chemo-radiotherapy and radiotherapy (CT/RT) vs CT/RT followed by surgical resection for stage IIIA (pN2) non-small-cell cancer (NSCLC): Outcomes update of North American Intergroup 0139 (RTOG 9309). J Clin Oncol 2005; 23: 624s (suppl; abstr 7014).
3. Van Meerbeeck JP, Kramer GW, Van Schil PE, *et al*. Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small cell lung cancer. J Natl Cancer Inst 2007; 99: 442-450.
4. Thomas M, Rube C, Hoffknecht P, *et al*. Effect of preoperative chemoradiation in addition to preoperative chemotherapy: a randomised trial in stage III non-small cell lung cancer. Lancet Oncol 2008; 9: 636-648.
5. Choy H, Rodriquez FF, Koester S, *et al*. Investigation of taxol as a potential radiation sensitizer. Cancer 1993; 71: 3774-3778.
6. Choy H, Browne MJ. Paclitaxel as a radiation sensitizer in non-small cell lung cancer. Semin Oncol 1995; 22 (3 suppl 6): 70-74.
7. McGuire WP, Rowinsky EK, Rosenshein NB. Taxol: a unique antineoplastic agent with significant activity in advanced ovarian epithelial neoplasms. Ann Int Med 1989; 111: 273-279.
8. Amarino GP, Hamilton VM, Choy H. Enhancement of radiation effects by combined cisplatin and carboplatin treatment in vitro. Radiat Oncol Invest 1999; 7: 343-352.
9. Mason K, Staab A, Hunter N. Enhancement of tumor radioresponse by docetaxel: involvement of immune system. Int J Oncol 2001; 18: 599-606.
10. Dicker AP, Williams T, Iliakis G, Grant D. Inhibition of angiogenic processes in endothelial cells by Docetaxel (taxotere) and Paclitaxel (taxol) induced radiosensitization: A potential anti-angiogenic strategy. Int J Radiat Oncol Biol Phys 2000; 48 (supplement 3): 267 (abstract).
11. Tomiak E, Piccart MJ, Kerger J. Phase I study of docetaxel administered as a 1-hour intravenous infusion on a weekly basis. J Clin Oncol 1994; 12: 1458-1467.
12. Mudad R, Ramsey M, Kovitz K, *et al*. Concomitant weekly docetaxel, cisplatin and radiation therapy in locally advanced non-small cell lung cancer: a dose finding study. Lung Cancer 2003; 39: 173-177.

13. Mauer AM, Masters GA, Hara DJ, *et al*. Phase I study of docetaxel with concomitant thoracic radiation therapy. J Clin Oncol 1998; 16: 159-64.

14. Koukourakis MI, Kourousis C, Kamilaki M, *et al*. Weekly docetaxel and concomitant boost radiotherapy for non-small cell lung cancer. A phase I/II dose escalation trial. Eur J Cancer 1998 34: 838-844.

15. Koukourakis MI, Bahlitzanakis N, Froudarakis M, *et al*. Concurrent conventionally fractionated radiotherapy and weekly docetaxel in the treatment of stage IIIB non-small cell lung carcinoma. Br J Cancer 1999; 80: 1792-1796.

16. Choy H, DeVore RF, Hande KR, *et al*. Phase I trial of outpatient weekly docetaxel, carboplatin and concurrent thoracic radiation therapy for stage III unresectable non-small cell lung cancer: a Vanderbilt cancer center affiliate network (VCCAN) trial. Lung Cancer 2001; 34: 441-449.

17. Segawa Y, Ueoka H, Kiura K, *et al*. A phase I/II study of docetaxel (TXT) and cisplatin (CDDP) with concurrent thoracic radiotherapy (TRT) for locally advanced non-small cell lung cancer (NSCLC). Proc Am Soc Clin Oncol 2000; 19: 508a (abstract).

18. Sato K, Tsuchiya S, Minato K, *et al*. A phase I trial of weekly docetaxel and cisplatin in advanced non-small cell lung cancer. Lung Cancer. 2001; 33: 69-73.

19. Moriyama A, Komiya K, Yamamoto N, *et al*. A phase I trial of weekly docetaxel (DXT) and cisplatin (CDDP) concomitant with thoracic radiotherapy (TRT) for patients with unresectable locally advanced non-small cell lung cancer (NSCLC). Ann Oncol 2000; 11 (Suppl 4): 110 (abstract).

20. Wu HG, Bang YJ, Choi EK, *et al*. Phase I study of weekly docetaxel and cisplatin concurrent with radiotherapy in stage III non-small cell lung cancer. Int J Radiat Oncol Biol Phys 2002; 52: 75-80.

21. Diagnosis and Management of lung Cancer: ACCP Evidence-Based Clinical Practice Guidelines (2nd Edition) 2007; 132: supplement 3.

22. Senan S, De Ruysscher D, Giraud, *et al*. Literature-based recommendations for treatment planning and execution in high-dose radiotherapy for lung cancer. Radiother Oncol 2004; 71: 139-146.

23. Rami-Porta R, Wittekind C, Goldstraw P. Complete resection in lung cancer surgery: proposed definition. Lung Cancer 2005; 49: 25-33.

24. Kaplan EL, Meier P. Non parametric estimations from incomplete observation. J Am Stat Assoc 1958; 53: 457-481.

25. Peto R, Peto J. Asymptotically efficient rank invariant test procedures. J R Stat Soc (series A) 1972; 135: 185-198.

26. Katayama H, Ueoka H, Kiura K, *et al*. Preoperative concurrent chemo-

radiotherapy with cisplatin and docetaxel in patients with locally advanced non-small cell lung cancer. Brit J Canc 2004; 90: 979-984.

27. Farray D, Mirkovic N, Albain KS. Multimodality therapy for stage III non-small cell lung cancer. J Clin Oncol 2005; 23: 3257-3269.

28. Betticher DC, Schimitz SFH, Tötsch M, *et al*. Mediastinal lymph node clearance after docetaxel-cisplatin neoadjuvant chemotherapy is prognostic of surival in patients with stage IIIA pN2 non-small cell lung cancer: a multicenter phase II trial. J Clin Oncol 2003; 21: 1752-1759.

29. Martin J, Ginsberg RJ, Venkatraman ES, *et al*. Long-term results of combined-modality therapy in resectable non-small cell lung cancer. J Clin Oncol 1995: 20: 1989-1995.

30. Albain KS, Rush VW, Crowly JJ, *et al*. Concurrent cisplatin/etoposide plus chest radiotherapy followed by surgery for stages IIIA (N2) and IIIB non-small cell lung cancer: Mature results of South-West Oncology Group Phase II study 8805. J Clin Oncol 1995; 13: 1880-1892.

31. Hanna NH, Neubauer M, Ansari R, *et al*. Phase III trial of cisplatin (P) plus etoposide (E) plus concurrent chest radiation (XRT) with or without conso-lidation docetaxel (D) in patients (pts) with inoperable stage III non-small cell lung cancer (NSCLC): HOG LUN 01-24/USO-023. J Clin Oncol 2007; 25 (18S): 7512.

Chapter 7

Concurrent versus sequential chemotherapy and radiotherapy in limited-disease small-cell lung cancer: a retrospective comparative study

S.Y. El Sharouni
H.B. Kal
A. D. Barten-van Rijbroek
H. Struikmans
J.J. Battermann
F.M.N.H. Schramel

Abstract

Our patients with limited-disease (LD) small-cell lung cancer (SCLC) were treated with chemotherapy only and chemotherapy combined with radiotherapy. The treatment schemes with curative intention were sequential and concurrent chemoradiotherapy, both combined with prophylactic cranial irradiation (PCI).

Patient -, treatment - and outcome – related items were retrospectively assessed. Up till 2001, LD-SCLC patients received 4-5 cycles of cyclophosphamide, doxorubicin and etoposide. In case of no complete response, palliative radiotherapy was given in 13 fractions of 3 Gy (CT-RT group, N=26). Because of different reasons, 89 patients did not receive radiotherapy after the chemotherapy (CT group). After complete response, curatively intended radiotherapy was given in 16 fractions of 2.5 Gy, concurrently with PCI in 15 fractions of 2 Gy (SCT-RT group, N=111). From 2001, 40 patients received 4-5 cycles of cisplatin and etoposide concurrently with radiotherapy in 25 fractions of 1.8 Gy. PCI was applied to patients with complete response (CCT-RT group). Primary endpoints were median survival time (MST) and overall survival (OS); secondary endpoints included tumour-related death and frequency of metastases.

Median survival times of CT only, CT-RT, SCT-RT and CCT-RT schemes were 8.1, 12.5, 14.0 and 21.8 months, and the 5-year OS 3.5, 4.8, 10.5 and 26.9%, respectively. The cause of death of SCT-RT and CCT-RT patients was tumour related in 76.3% and 89.3% of the patients, respectively. Brain metastases frequencies after PCI in SCT-RT and in CCT-RT patients were 16.4% and 8.7%, respectively.

In conclusion, concurrent chemoradiotherapy resulted in longer median survival time and higher overall survival than sequential chemoradiotherapy, chemotherapy with palliative radiotherapy or chemotherapy only.

Introduction

Small-cell lung cancer (SCLC) accounts for 17% of all lung cancer cases (1). SCLC is the most aggressive form of lung cancer, having greater potential to metastasise than other types of lung cancer. Nearly all patients (> 95%) diagnosed with SCLC are current or ex-smokers (2). Staging systems divide SCLC into limited disease (LD) and extensive disease. About one third of the SCLC patients have LD. LD is by definition confined to one side of the chest, and the remaining patients have extensive disease (2). SCLC is characterized by rapid tumour growth, early manifestation of metastases and an overall poor prognosis. Without treatment, tumour progression in LD SCLC is rapid, with a median survival time of only a few months (3, 4). The role of chemotherapy (CT) has been extensively tested. Long-term survival in these cases is <10% (5, 6). For palliative reasons, thoracic radiotherapy (RT) was given to CT patients who did not respond completely to chemotherapy. Thoracic radiotherapy, given in addition to chemotherapy after complete response, resulted in significantly improved survival rates when compared to those treated with CT only (7, 8). Furthermore, it was noted that prophylactic cranial irradiation (PCI) improved survival of SCLC patients who achieved complete response following primary therapy (9-12). Hence, the main treatment regimen for LD SCLC nowadays consists of a combination of chemotherapy, thoracic radiotherapy and PCI. Takada *et al.* (13) reported results of a randomized multicenter trial and concluded that concurrent chemoradiotherapy (CCT-RT) is more effective than sequentially applied chemotherapy and radiotherapy (SCT-RT). We analysed, retrospectively, treatment efficacy of our patients with LD SCLC who underwent CT only, CT with no complete response followed by palliative thoracic RT (CT-RT), SCT-RT or CCT-RT.

Patients and methods

Patients
The database on pathologically confirmed LD-SCLC patients provided by the Comprehensive Cancer Centre (IKMN), Utrecht, the Netherlands, was analysed. Patients were treated in 10 regional hospitals in the period 1996-2005. The radiation therapy was applied at the University Medical Centre Utrecht, the Netherlands. Eighty-nine patients received CT only, 26 patients received CT with no complete response followed by palliative

thoracic RT (CT-RT), and 111 patients who achieved complete response after CT were referred for curatively intended radiotherapy (SCT-RT). Starting in 2001, 40 patients were offered CCT-RT. Patient characteristics are shown in Table 1.

Table 1. Patient characteristics: gender, age, and tumour volume.

	CT	CT-RT	SCT-RT	CCT-RT
	N=89	N=26	N=111	N=40
Gender				
Male	63 (70.8%)	16 (61.5%)	68 (61.3%)	26 (65%)
Female	26 (29.2%)	10 (38.5%)	43 (38.7%)	14 (35%)
Age (y)				
Mean +/- SD	68.3 +/- 8.8	63.9+/-9.0	63.1 +/- 9.7	61.7 +/- 9.2
Range	34.7 – 86	49.7-80.6	32 - 81.7	42 – 76
			N=43	N=23
Tumour volume before CT (cm^3)				
Median			81	40
Range			8-883	16-526

CT: chemotherapy; CT-RT: CT and palliative thoracic radiotherapy; SCT-RT: sequentially applied chemotherapy and radiotherapy; CCT-RT: concurrently applied chemoradiotherapy; N: number of patients; SD: standard deviation.

Chemotherapy only and sequentially applied chemotherapy and radiotherapy
The CT consisted of 4 or 5 cycles, given in a 3-week cycle, of cyclophosphamide ($1000 \, mg/m^2$ on day 1), doxorubicin ($45 \, mg/m^2$ on day 1) and etoposide ($100 \, mg/m^2$ on days 1, 2 and 3) (CT group, N=89). When the chemotherapy did not result in complete response as determined by bronchoscopy, CT-scan and or chest X-ray, palliative thoracic irradiation with 13 fractions of 3 Gy, 4 fractions/week was the preferred treatment (CT-RT group, N=26). The reasons for the 89 patients not to receive

radiotherapy after chemotherapy were tumour progression during chemotherapy, pancytopenia, refusal of further therapy, worsening of patient's condition or death.

In case of complete response, patients received thoracic RT with 16 daily fractions of 2.5 Gy, 5 fractions/week, with a total dose of 40 Gy (SCT-RT group, N=111). The volume that has been irradiated was based on the pre-treatment CT-scan. Concurrently with the thoracic irradiation, prophylactic cranial irradiation was applied consisting of 15 fractions of 2 Gy, 5 fractions/week with a total dose of 30 Gy.

Concurrent chemoradiotherapy

The chemotherapy applied consisted of 4 or 5 cycles, given in a 3-week cycle, of cisplatin and etoposide. The cisplatin dose was 60 mg/m^2 on day 1, and that of etoposide 120 mg/m^2 on days 1, 2 and 3. The RT started on day 22 after the start of the first chemotherapy cycle and consisted of 25 fractions of 1.8 Gy, 5 fractions/week, to a total dose of 45 Gy with 3D-treatment planning (CCT group, N=40). The planning CT-scan was made in the week before the start of the chemotherapy or in the first week of the first cycle. PCI was applied to patients with a complete response after completion of the chemotherapy. A total dose of 30 Gy was given in 15 fractions of 2 Gy/day, 5 fractions/week.

Tumour volume measurement

The tumour dimensions of the SCT-RT and CCT-RT patients were taken from the CT diagnostic scan made prior to chemotherapy. The maximum diameter in medio-lateral or ventro-dorsal direction was measured, d_1, as well as the maximum diameter in cranial-caudal direction, d_2, i.e. the number n of CT slices in cranial-caudal direction on which the tumour was visible, times the slice thickness t, $d_2 = nt$. The tumour volume was calculated as V= $0.5d_1^2 d_2$ in case d_1 was the smallest dimension or V=$0.5d_1 d_2^2$ when d_2 was the smallest value.

Endpoints

Primary endpoints were median survival time (MST) and overall survival (OS). The MST is defined as the time from the start of the treatment, when half of the patients were found to be still alive. Overall survival time is defined as the interval between the start of the treatment and death (from all causes) or last known follow-up. Secondary endpoints were tumour-related cause of death and frequency of metastases.

Statistics

The Kaplan-Meier method was applied to determine the MST and the OS-rates and the log rank (Mantel-Cox) test to compare treatment results. The X^2 test was applied to determine differences in metastases frequency. Tests were performed using the Statistical Package for Social Sciences, version 13.0 (SPSS, Chicago, IL).

Results

Patient population

The four groups of patients did not differ significantly with one another with respect to the distribution of gender and age although the percentage of males and a higher mean age were present in the CT group. The tumour volumes as derived from the CT-diagnostic scans of 43 SCT-RT patients and 23 CCT-RT patients show some differences, relatively more larger tumour volumes were present in the SCT-RT group as shown by the median values and range, Table 1.

Chemotherapy only

In the group of 89 patients who received CT only, 12 patients were lost to follow-up. Of the 77 evaluable patients the MST was 8.1 months. The 1-, 3- and 5- year OS was 32.5, 5.2 and 3.5%, respectively, Table 2, Figures 1-3. The radiological response after CT was evaluated: 6 patients had complete response of which 2 were long survivors (more than 5 years). All other patients had partial response, stable or progressive disease. No information was available about the tumour volume at the start of the therapy.

Chemotherapy followed by palliative thoracic radiotherapy

From the IKMN database 26 patients were recorded who had palliative thoracic radiotherapy because chemotherapy did not achieve complete response. Five patients were lost to follow-up. One long survivor was identified. The MST of 21 evaluable patients was 12.5 months. The 1-, 3- and 5-year OS was 52.4, 4.8 and 4.8%, respectively, Table 2, Figures 1-3. Data on tumour volumes were not recorded.

Table 2. Median survival time and overall survival of patients treated with chemotherapy only, chemotherapy and thoracic radiotherapy, sequential and concurrent chemoradiotherapy.

	CT	CT-RT	SCT-RT	CCT-RT
Evaluable patients	N=77	N=21	N=95	N=40
MST +/- SE (month)	8.1+/-0.9	12.5+/-1.0	14.0+/-0.6	21.8+/-3.2
95% confidence int.	6.6-9.9	10.6-14.4	12.9-15.1	15.5-28.0
Overall survival +/- SE (%)				
1-year	32.5+/-5.3	52.4+/-10.9	67.4+/-4.8	75.0+/-6.8
3-year	5.2+/-2.5	4.8+/-4.6	17.3+/-3.9	32.2+/-7.7
5-year	3.5+/-2.2	4.8+/-4.6	10.5+/-3.2	26.9+/-8.1

CT: chemotherapy; CT-RT: CT and palliative thoracic radiotherapy; SCT-RT: sequentially applied chemotherapy and radiotherapy; CCT-RT: concurrently applied chemoradiotherapy; MST: median survival time; SE: standard error.

Sequential chemotherapy and radiotherapy

Of the 111 SCT-RT patients, 16 were lost to follow up. Of the 95 evaluable patients, the MST was 14.0 months and the 1-, 3- and 5-year OS was 67.4, 17.3 and 10.5%, respectively, Table 2, Figures 1-3.

The median tumour volume of 43 patients, measured from the CT-scans made prior to the CT, was 81 cm^3, Table 1.

Of 69 patients information on the interval between end of chemotherapy and start of RT as well as on the total overall treatment time was available. The interval between the end of the CT and the start of the RT varied between 25 and 194 days with a mean of 66 days. The mean overall treatment time (OTT) was 182 days, Table 3. Sixty-seven of these 69 patients (97%) had a complete response, and 2 a partial response. The complete responders received PCI, however, 11 patients (16.4%) developed brain metastases after PCI.

In 59 patients the cause of death was known and it was tumour related in 45 patients (76.3%). Local recurrence was present in 19 patients, 7 of which had also distant metastases. The remaining 26 patients developed distant metastases.

Table 3. Interval between the end of chemotherapy and start of radiotherapy, of patients treated with sequentially and concurrently applied chemoradiotherapy.

	SCT-RT	CCT-RT
Evaluable patients	N=69	N=40
	Interval end CT-start RT/PCI (d)	*Interval end CT/RT-start PCI (d)*
Mean+/-SD	66+/-25	55+/-22
Median	62	48
Range	25-194	27-109
	Interval start CT-start RT/PCI (d)	*Interval start CT-start PCI (d)*
Mean+/-SD	159+/-20	139+/-22
Median	156	133
Range	115-215	107-177
OTT (d)		
Mean+/- SD	182+/-25	88+/-22; with PCI: 159+/-20
Median	177	91; with PCI: 154
Range	141-308	42-128; with PCI: 123-197

CT: chemotherapy; RT: radiotherapy; SCT-RT: sequentially applied chemotherapy and radiotherapy; CCT-RT: concurrently applied chemoradiotherapy; PCI: prophylactic cranial irradiation; OTT: overall treatment time; SD: standard deviation.

Concurrent chemoradiotherapy

The median tumour volume at start of the CCT-RT of 23 patients was 40 cm^3, Table 1. The mean OTT was 159 days with a range of 123-197 days. Without PCI the OTT was 88 days, with a range of 42 to 128 days. This implies that not all patients received the planned full CT in the treatment time of 65 days (4 cycles of 3 weeks) or 86 days for 5 cycles. For those patients who had a shorter OTT than the median treatment time of 91 days, the MST was 15.3 months. The other patients had a MST of 24.1 months. The overall MST was 21.8 months and the 1-, 3- and 5-year overall survival was 75, 32.2 and 26.9%, respectively, Table 2, Figures 1-3.

Five patients received palliative cranial irradiation of 8 fractions of 3.5 Gy

in two weeks because of the presence of brain metastases at the end of chemotherapy.

After CCT-RT, 24 (60%) of the 40 patients had a complete response and 23 patients received PCI. Later on, brain metastases were observed in 2 patients (8.7%) out of the 23 patients who received PCI.

The causes of death in 25 (89.3%) of 28 evaluable patients were tumour related. Ten patients had local recurrence of which 2 patients had also distant metastases. The remaining 16 patients developed distant metastases.
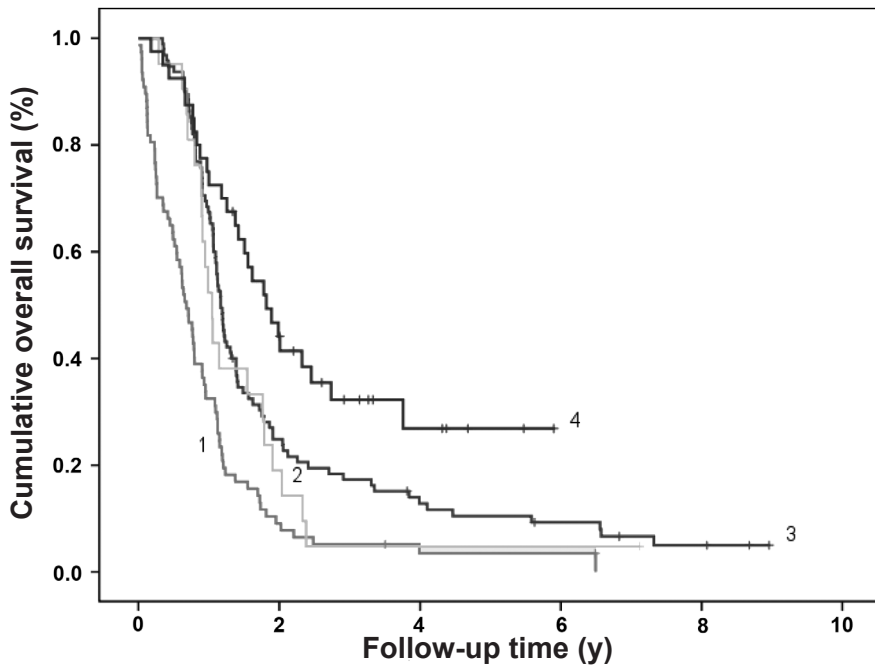
Figure 1. Cumulative overall survival as a function of time after start of treatment. Curve 1: chemotherapy (CT) only; curve 2: CT and palliative radiotherapy (CT-RT); curve 3: sequentially applied chemotherapy and radiotherapy (SCT-RT) and curve 4: concurrently applied chemoradiotherapy (CCT-RT).
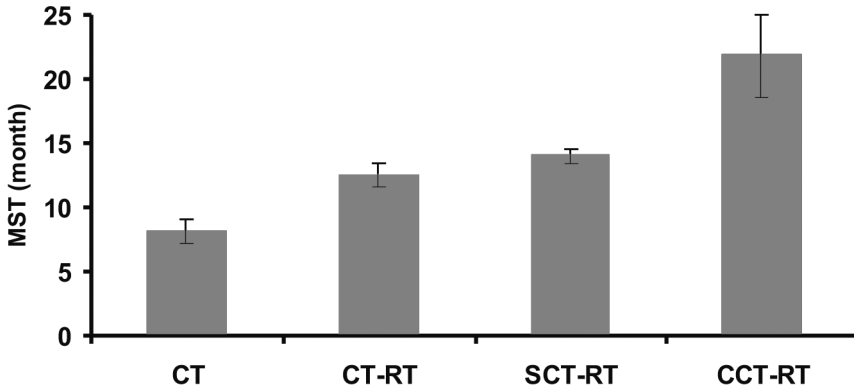
Figure 2. Median survival time (MST) of patients treated with chemotherapy (CT) only, CT and palliative radiotherapy (CT-RT), sequential applied chemotherapy and radiotherapy (SCT-RT) and concurrently applied chemoradiotherapy (CCT-RT)**.** Error bars indicate standard deviation.
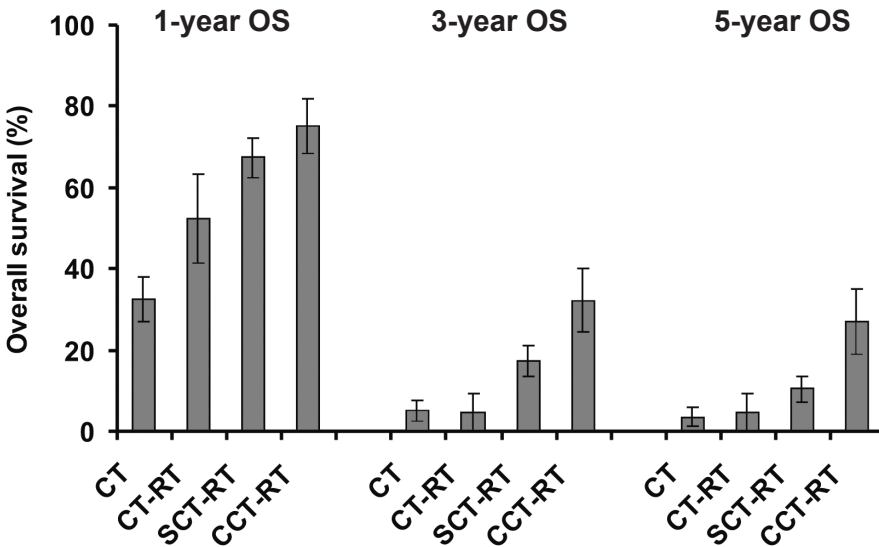
Figure 3. Overall survival (OS) at 1, 3 and 5 year of patients treated with chemotherapy (CT) only, CT and palliative radiotherapy (CT-RT), sequentially applied chemotherapy and radiotherapy (SCT-RT) and concurrently applied chemoradiotherapy (CCT-RT)**.** Error bars indicate standard deviation.

Discussion and conclusion

The observed bad results of our patients who received CT only are in line with results obtained by others (5, 6). The combination chemotherapy with radiation therapy has improved the results significantly. In our patients when chemotherapy was followed by palliative radiotherapy, the MST increased significantly (p<0.05) from 8.1 to 12.5 months, with curatively intended radiotherapy to 14 months, and with CCT-RT to 21.8 months. The MST of the CCT-RT group is significantly longer than those of the other treatment groups, p<0.05. Also the 5-year survival increased, from 3.5% (CT) to 10.5% for the SCT-RT and to 26.9% for the CCT-RT. Survival was significantly higher in the CCT-RT group as compared to the SCT-RT group as determined with the log-rank test (p=0.016).

The SCT-RT and CCT-RT groups did not differ significantly with respect to the distribution of gender and age. The pre-treatment tumour volumes in the CCT-RT group were smaller than in the SCT-RT group as shown by the median values, Table 1.

Our data for CCT-RT patients showed an MST of 21.8 months; and 2- and 5-year survivals of 44.1% and 26.9%, respectively. Our results with CCT-RT are comparable with those of others (13-17). Takada *et al*. reported on a randomized multicenter trial (13). The MSTs they noted were 19.7 months with SCT-RT and 27.2 months with concurrent therapy. The 2-, 3- and 5-year survivals for SCT-RT were 35.1, 20.2 and 18.3%, respectively, for CCT-RT 54.4, 29.8 and 23.7%, respectively. Turrisi *et al*. (14) reported for a single and a twice-daily radiotherapy scheme for CCT-RT patients an MST of 19 and 23 months; for the 2-year survival 41 and 47%, and for the 5-year survival 16 and 26%, respectively, Table 4. Baas *et al*. reported on a Dutch multicenter phase II study (15). They concluded that combination of CT with concurrent involved-field radiation therapy is an effective treatment for LD SCLC. The 2- and 5-year survival rates were 47 and 27%, respectively. The MST was 19.5 months. Park *et al*. reported no significant differences between concurrent and sequential chemoradiotherapy in overall response rates (78% versus 63%, respectively, p=0.13) or MST (mean 18.3 months versus 13.2 months, respectively, p=0.33), Table 4 (16). However, the data were limited and with only 51 patients the trial was likely underpowered to detect a statistical significant survival difference; anyhow, the trend is that a concurrently applied scheme yields better results. De Ruysscher *et al*. also concluded from a systematic review and meta-analysis of randomized trials, that with platinum CT and early chest

radiotherapy, i.e. radiotherapy started within 30 days after start of the CT, resulted in higher survival rates than when radiotherapy was applied later (17).

Table 4. Median survival time and overall survival at 2, 3 and 5 years of patients treated with sequentially and concurrently applied chemoradiotherapy. Results of several studies.

	SCT-RT MST	CCT-RT MST (month)	SCT-RT OS (%)			CCT-RT OS (%)		
Reference			2-y	3-y	5-y	2-y	3-y	5-y
(13)	19.7	27.2	35.1	20.2	18.3	54.4	29.8	23.7
(14)*		19; 23				41; 47	28; 32	16; 26
(15)		19.5				47		27
(16)	13.2	18.3	27.7	8.8		29	13.8	
Present study	14.0	21.8	23.5	17.3	10.5	44.1	32.2	26.9

SCT-RT: sequentially applied chemotherapy and radiotherapy; CCT-RT: concurrently applied chemoradiotherapy; OS: overall survival; MST: median survival time.
*Results of once-daily and twice-daily thoracic radiotherapy.

In our study we noted that the overall treatment time (OTT) in the SCT-RT group, when compared to that of the CCT-RT group, was significantly longer, $p<0.05$. This is caused by the time required for restaging procedures (CT-scan, chest X-ray, bronchoscopy) and referring the patient to the department of radiotherapy. SCLC have a shorter tumour volume doubling time, when compared to that of squamous cell carcinoma and adenocarcinoma (23 days versus 88 and 161 days, respectively) (18-20). Accelerated growth during the interval time may cause a substantial tumour volume increase. For example, we observed in an earlier study accelerated tumour growth for non-small cell lung carcinomas in the interval between the end of induction chemotherapy and start of radiotherapy (21). The mean tumour volume-doubling time was about half that of non-treated tumours. Therefore, analogous to non-small cell lung cancer, the overall treatment time in SCLC must be shortened or RT

must be given concurrently with the CT.

PCI has shown to be effective in preventing cerebral metastases (9-11) and to improve survival when applied to patients with LD SCLC who had achieved complete response after primary therapy (12). A trend towards decrease in brain metastases was also noted with earlier administration of PCI (12). Even with extended disease SCLC, PCI has also improved the survival (22).

In our study SCT-RT patients received PCI on an average of 159 days after the start of the CT and the CCT-RT patients on an average of 139 days after the start of CT. The frequency of brain metastases in patients who received PCI was 16.4% for the SCT-RT patients and 8.7% in CCT-RT patients. Although the 16.4% is not statistically different from 8.7%, it may indicate that early PCI is warranted. For example, PCI may start about two weeks after the chemotherapy instead of the 7-9 weeks after end of CT for the CCT-RT and SCT-RT patients, preventing a mean of about 5-7 weeks of cell proliferation, respectively. Furthermore, it may also be important that delay of radiotherapy of the primary tumour may also allow ongoing cumulative risk of metastatic events in the brain.

In the present study, the OTTs, without PCI, of concurrent treated patients were in the range of 42 to 128 days. There are several reasons why this range is that large. Expected is an overall treatment time of about 65 days (4 cycles of 3 weeks) or 86 days (5 cycles of 3 weeks). The OTTs in excess of 86 days were a consequence of interruptions in the treatment caused by side effects. Those patients with the relatively short OTT did not receive the planned full course chemotherapy because of severe chemotherapy side effects. In this group of patients the mean survival time is to be expected shorter than in the group of patients who received the planned course of CT. The MST is indeed lower for the patients with the short OTT as compared to the remaining patients, 15.3 months versus 24.1 months. It indicates the importance of having the planned chemotherapy course.

When the PCI is included in the OTT of CCT-RT patients, the mean OTT is 159 days (median 154, range 123-197 days). Here again the interval between end of the chemotherapy and start of the PCI is relatively long. The mean interval is 55 days, the median 48, and the range 27-109 days. Probably, the delay is caused by restaging procedures (CT-scan and or a chest X-ray, bronchoscopy) and referring the patient again to the department of radiotherapy. However, the total OTT is shorter than that of SCT-RT with a mean value of 182 days. The question can be raised whether the interval between the end of chemotherapy and start of the

PCI can be shortened. In the interval, micro metastases not recognizable on CT- or MRI-scan may grow to a size for which the total PCI dose of 30 Gy is not sufficient to kill all cells. From the radiobiological point of view, a dose of 30 Gy may eliminate all tumour cells with a volume of up to 1 mm^3, larger sizes harbouring more than 10^6 cells may still not be recognizable on the CT- or MRI-scan but still will survive the PCI dose.

Our results indicate that CCR-RT resulted in a significantly longer median survival time and higher survival rate than SCR-RT. These results are comparable with those of others. However, in this retrospective study some of the base line data of the CCT-RT group were slightly different from those of the SCT-RT group: the follow-up time was shorter, the mean age lower and the median tumour volume smaller. Only in a randomized trial these differences in base line data can be avoided.

Improvements of the CT-scan technology would have resulted in stage migration, resulting in better staging of the more recent cohort of patients receiving concurrent chemoradiotherapy. Furthermore, the cyclophosphamide-based chemotherapy has been demonstrated inferior to etoposide and cisplatin in a randomized trial where the sequence of chemotherapy and radiotherapy was kept constant (23). Improvements of CT-scan technology and change in chemotherapy may also result in the improved overall survival of the concurrent therapy cohort as compared to the sequential therapy cohort.

In conclusion, the concurrently applied chemoradiotherapy resulted in longer median survival time and higher survival rates than sequentially applied chemotherapy and radiotherapy. Probably, results may improve further by applying PCI at an earlier stage.

References

1. Youlden DR, Cramb SM, Baade PD. The international epidemiology of lung cancer: geographical distribution and secular trends. J Thorac Oncol 3: 819-31, 2008.
2. Jackman DM, Johnson BE. Small-cell lung cancer. Lancet 366: 1385-1396, 2005.
3. Agra Y, Pelayo M, Sacristan M, *et al*. Chemotherapy versus best supportive care for extensive small cell lung cancer. Cochrane Database Syst Rev 4: CD001990, 2003.
4. Zelen M. Keynote address on biostatistics and data retrieval. Cancer Chemother Rep 3: 31-42, 1973.
5. Kelly K. New chemotherapy agents for small cell lung cancer. Chest 117: 156S-162S, 2000.
6. Hoschek S, Hoschek-Risslegger U, Fiegl M, *et al*. Small cell lung cancer. Wien Klin Wochenschr 119: 697-710, 2007.
7. Warde P, Payne D. Does thoracic irradiation improve survival and local control in limited-stage small-cell carcinoma of the lung? A meta-analysis. J Clin Oncol 10: 890-895, 1992.
8. Pignon JP, Arriagada R, Ihde DC, *et al*. A meta-analysis of thoracic radiotherapy for small-cell lung cancer. N Engl J Med 327: 1618-1624, 1992.
9. Aupérin A, Arriagada R, Pignon JP, *et al.* Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. N Engl J Med 341: 476-484, 1999.
10. Kotalik J, Yu E, Markman BR, Evans WK; Cancer Ontario Practice Guidelines Initiative Lung Cancer Disease Site Group. Practice guideline on prophylactic cranial irradiation in small-cell lung cancer. Int J Radiat Oncol Biol Phys 50: 309-316, 2001.
11. Pugh TJ, Gaspar LE. Prophylactic cranial irradiation for patients with lung cancer. Clin Lung Cancer 8: 365-368, 2007.
12. Prophylactic Cranial Irradiation Overview Collaborative Group. Cranial irradiation for preventing brain metastases of small cell lung cancer in patients in complete remission. Cochrane Database Syst Rev 4: CD002805, 2000.
13. Takada M, Fukuoka M, Kawahara M, *et al.* Phase III study of concurrent versus sequential thoracic radiotherapy in combination with cisplatin and etoposide for limited-stage small-cell lung cancer: results of the Japan Clinical Oncology Group Study 9104. J Clin Oncol 20: 3054-3060, 2002.
14. Turrisi AT 3rd, Kim K, Blum R, *et al*. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etopo-side. N Engl J Med 340: 265-271, 1999.

15. Baas P, Belderbos JS, Senan S, *et al*. Concurrent chemotherapy (carboplatin, paclitaxel, etoposide) and involved-field radiotherapy in limited stage small cell lung cancer: a Dutch multicenter phase II study. Br J Cancer 94: 625-630, 2006.
16. Park SK, Kim GH, Jeong SS, *et al*. The effects according to the timing of thoracic radiotherapy in limited stage small cell lung cancer. Tuberc Respir Dis 43: 903-915, 1996.
17. De Ruysscher D, Pijls-Johannesma M, Vansteenkiste J, *et al*. Systematic review and meta-analysis of randomised, controlled trials of the timing of chest radiotherapy in patients with limited-stage, small-cell lung cancer. Ann Oncol. 17: 543-552, 2006.
18. Spratt JS, Spjut HJ, Roper CL. The frequency distribution of the rates of growth and the estimated duration of primary pulmonary carcinomas. Cancer 16: 687-693, 1963.
19. Meyer JA. Growth rate versus prognosis in resected primary bronchogenic carcinomas. Cancer 31: 1468-1472, 1973.
20. Chahinian P. Relationship between tumor doubling time and anatomoclinical features in 50 measurable pulmonary cancers. Chest 61: 340-345, 1972.
21. El Sharouni SY, Kal HB, Battermann JJ. Accelerated regrowth of non-small-cell lung tumours after induction chemotherapy. Br J Cancer 89: 2184-2189, 2003.
22. Slotman B, Faivre-Finn C, Kramer G, *et al*. Prophylactic cranial irradiation in extensive small cell lung cancer. N Engl J Med 357: 664-672, 2007.
23. Sundstrøm S, Bremnes RM, Kaasa S, *et al*. Cisplatin and etoposide regimen is superior to cyclophosphamide, epirubicin, and vincristine regimen in small-cell lung cancer: results from a randomized phase III trial with 5 years' follow-up. J Clin Oncol 20: 4665-4672, 2002.

Chapter 8

General discussion, conclusions and recommendations

Lung cancer is one of the main causes of cancer death in the world, accounting for 25-29% of all male deaths from neoplasia in the United States and Europe. The incidence in women is lower although it is rapidly increasing and, since 1987, it has overtaken breast cancer as the primary cause of death in the United States (Weir *et al*, 1997) and since 2007 also in the Netherlands (CBS 1, 2). The 5-year survival of lung cancer patients worldwide is between 6 to 14% among males and 7 tot 18% among females (Youlden *et al*, 2008).

Of the two main types of lung cancer, non-small cell lung cancer (NSCLC) is the most frequent and represents about 83% of the cases in the western world (Youlden *et al*, 2008). Only 20% of patients with NSCLC are candidates for surgery at presentation. The optimal management of patients with stage III NSCLC is still unclear. The standard of care for this group of patients is a combination of chemotherapy and radiation, often referred to as combined modality treatment (Pfister *et al*, 2004).

Small-cell lung cancer (SCLC) accounts for 17% of all lung cancer cases (Youlden *et al*, 2008). Staging systems divide SCLC into limited disease (LD) and extensive disease. About one third of the SCLC patients have LD (Jackman *et al*, 2005). The main treatment regimen for LD SCLC nowadays consists of a combination of chemotherapy, thoracic radiotherapy and prophylactic cranial irradiation (Takada *et al*, 2002).

In the review presented in chapter 2, it is clear that progress has been made in the past decade for patients with unresectable stage III NSCLC. The 5-year survival has increased from about 7% for radiotherapy alone to 10% for sequential and about 15% for concurrent chemoradiotherapy (El Sharouni *et al*, 2006). For the clinician, it is a challenge to optimise the treatment, e.g., by delivering a large radiation dose to the target area (Senan *et al*, 2004, Socinski *et al*, 2004), keeping the dose to surrounding tissues as low as possible. In addition, schemes for drug delivery have to be optimised. Further improvements may be obtained with consolidation chemotherapy after concurrent chemoradiotherapy (Sakai *et al*, 2004, Gandara *et al*, 2003, Gaafar *et al*, 2004).

Although the predominant cause of death in NSCLC is believed to be distant metastases, local recurrence is still a major cause of failure (Ramsay *et al*, 1988, Fu *et al*, 1996, Freiha *et al*, 1984, Whelan *et al*, 2000). Therefore, a further increase of local control for NSCLC could lead to improvement in survival.

In the analysis in chapter 3, we presented evidence that after induction chemotherapy fast regrowth of NSCLC occurs; the accelerated repopulation of surviving tumour cells is responsible for the fast regrowth. It is clear that the beneficial result of induction chemotherapy, i.e. tumour volume regression, has faded away in the waiting time between the end of induction chemotherapy and the start of the radiotherapy (El Sharouni *et al*, 2003). It is tragically that interval times up to more than three months are found whereas radiotherapy can be started within one month after induction chemotherapy. Forty-one percent of potentially curable patients became incurable in that waiting period. We recommend that radiotherapy should start as soon as possible, preferably within two to three weeks after the last chemotherapy cycle. Due to the accelerated cell proliferation observed, accelerated radiotherapy should be given serious consideration to keep overall treatment time short. A growing body of data shows that concurrent chemoradiotherapy improves survival in selected patients in stage III NSCLC (Schaake-Koning *et al*, 1994, Furuse *et al*, 1999, Curran *et al*, 2003, Aupérin *et al*, 2007, El Sharouni *et al*, 2008).

In chapter 4, we showed in our patients that in the mean waiting period of 80 days between end of induction chemotherapy and start of radiotherapy the median tumour volume increased with a factor of about 6 (El Sharouni *et al*, 2005). As a consequence, the observed two-year survival of the patients treated with curatively intended radiotherapy is only 8% while from other studies for sequential chemo-radiotherapy a mean two-year survival value of about 26% was found. This is also reflected in the calculated tumour control probability (TCP) for the curatively intended treated patients, the TCP decreased in the waiting period from 13.3% to less than 1%. It is clear that the interval time between chemo- and radiotherapy should be as short as possible.

In chapter 5 we described results of experiments of the combination of radiotherapy and gemcitabine (dFdC) on rat tumours and skin. It was speculated that the radiosensitizing effect of dFdC in patients might be less in normal healthy tissue and more restricted to (undifferentiated) tumour cells, making it a tumour-selective radiosensitizer. Therefore it was of interest to study responses of undifferentiated and well-differentiated experimental tumours and skin to dFdC and radiotherapy.
Indeed, with respect to tumour growth delay, the dose enhancement ratios were up to 1.37 for the undifferentiated L44 and MLL tumours (Kal

et al, 2006). No radiosensitization was observed for the well-differentiated L44 tumours and rat skin.

Our data support further trials to evaluate the usefulness of dFdC as radiosensitizer for undifferentiated tumours.

In our multicentre phase II study described in chapter 6 we analysed the feasibility and efficacy of weekly docetaxel/cisplatin and concurrent thoracic radiotherapy followed by surgery in patients with stage III non-small cell lung cancer. We observed a complete and a partial radiological response, the primary endpoint of this study, in 46% of the patients. Chemoradiotherapy can induce extensive fibrosis and necrosis of the tumour and mediastinum. It follows that radiological response is not the optimal parameter to select patients for postinduction surgery. Studies have shown that pathological response in mediastinal lymph nodes predicts prolonged survival (Van Meerbeeck *et al*, 2007, Farray *et al*, 2005, Betticher *et al*, 2003, Martin *et al*, 1995, Albain *et al*, 1995).

Pathological clearance of malignant mediastinal disease was achieved in 54% in our patients. No acute (non)-haematologic toxicity was encountered and a low incidence of treatment-related pneumonitis and esophagitis grade III was observed. Twenty patients (49%) underwent a complete resection of which six patients (15%) that had stable disease as their best response to induction treatment.

The 30-day mortality was 4%. The types of surgery and induction treatment used are the major determinants of morbidity and mortality. Pneumonectomy has been reported to have significant negative influence on survival. (Albain *et al*, 2005, Van Meerbeecke *et al*, 2007, Thomas *et al*, 2007, Martin *et al*, 1995). Approximately 57% of our patients with a curative resection are alive after 46 months compared to 5% of the patients without resection (p=0.024). Japanese investigators reported comparable results (Katayama *et al*, 2004).

Although weekly docetaxel/cisplatin with concurrent involved-field radiotherapy resulted in radiological response of 46%, a complete clearance of mediastinal malignant disease of 54% can be reached, resulting in a radical resection rate of 49%. This induction regimen is feasible with limited toxicity and seems to be effective in stage III NSCLC.

The treatment of our patients with limited disease small-cell lung cancer is discussed in chapter 7. The combination chemoradiotherapy has improved the results significantly especially when they were concurrently ap-

plied, e.g. the 5-year survival increased from 10.5% for the sequential chemoradiotherapy to 26.9% for the concurrent treatment.

We noted that the overall treatment time (OTT) in the sequentially applied chemotherapy and radiotherapy group (SCT-RT), when compared to that of the concurrent chemoradiotherapy group (CCT-RT), was significantly longer, $p < 0.05$. This is caused by the time required for restaging procedures (CT-scan, chest X-ray, bronchoscopy) and referring the patient to the radiotherapy department. Accelerated growth during the interval time may cause a substantial tumour volume increase. Therefore, analogous to non-small cell lung cancer, as discussed in chapter 3, the overall treatment time in SCLC must be shortened or RT must be given concurrently with the CT.

Prophylactic cranial irradiation (PCI) has shown to be effective in preventing cerebral metastases and to improve survival when applied to patients with LD SCLC who had achieved complete response after primary therapy. A trend towards decrease in brain metastases was also noted with earlier administration of PCI (Aupérin *et al*, 1999, Kotalik *et al*, 2001, Pugh *et al*, 2007, Prophylactic Cranial Irradiation Overview Collaborative Group, 2000). In our study, SCT-RT patients received PCI on an average of 159 days after the start of the CT, the CCT-RT patients on an average of 139 days after the start of CT. The frequency of brain metastases in patients who received PCI was 16.4% for the SCT-RT patients and 8.7% in CCT-RT patients. Although the 16.4% is not statistically different from 8.7%, it may indicate that early PCI is warranted.

In conclusion, the concurrently applied chemoradiotherapy resulted in longer median survival times and higher survival rates than sequentially applied chemotherapy and radiotherapy. Probably, results may improve further by applying PCI at an earlier stage.

Conclusions and recommendations

Chapter 2: Concurrent chemoradiotherapy demonstrated increased efficacy over sequential chemoradiotherapy and should be the treatment of choice. The concurrent chemoradiotherapy schedules were associated with higher toxicity as compared to sequential therapy with the same drug doses.

The suggestion that amifostine may protect the oesophagus was not confirmed in a large RTOG randomised trial (Werner-Wasik *et al*, 2003). A

growing body of data shows that concurrent chemoradiotherapy improves survival in selected patients in stage III NSCLC (Schaake-Koning *et al*, 1994; Furuse *et al*, 1999; Curran *et al*, 2003; Aupérin *et al*, 2007; El Sharouni *et al*, 2008).

Chapters 3 and 4: In the time interval between end of induction chemotherapy and start of radiotherapy rapid tumour progression occurs as result of accelerated tumour cell proliferation. The mean tumour-doubling times are much shorter than those in not treated tumours. As a consequence, the gain obtained with induction chemotherapy with regard to volume reduction was lost in the waiting time for radiotherapy.
The calculated tumour control probability decreased in the waiting period from 13.3 to less than 1%. Hence, the relatively long interval time between chemo- and radiotherapy had a deleterious effect on local control.
We recommend diminishing the time interval between chemo- and radiotherapy to be as short as possible. Fortunately, most of the patients with stage III NSCLC are nowadays treated with concurrent chemoradiotherapy. The problem of the waiting time is disappearing.

Chapter 5: Radiosensitization by gemcitabine was observed in two undifferentiated tumours, not in a well-differentiated tumour and skin.
These data support further trials to evaluate the usefulness of dFdC as radiosensitizer in undifferentiated tumours.

Chapter 6: Weekly docetaxel/cisplatin with concurrent radiotherapy resulted in radiological response of 46%, and complete clearance of mediastinal malignant disease was achieved in 54% of the patients. The complete resection rate was 49%. This induction regimen is feasible with limited toxicity and seems to be effective in stage III NSCLC. A phase III study can be initiated for further investigation of the role of preoperative concurrent chemoradiotherapy.

Chapter 7: Treating limited-disease small-cell lung cancer with concurrent chemoradiotherapy resulted in longer median survival time and higher overall survival than sequential chemoradiotherapy, chemotherapy with palliative radiotherapy or chemotherapy only.
More investigations are needed for further improvements in survival of limited-disease small-cell lung cancer. Probably, results may improve further by applying PCI at an earlier stage.

References

1. Albain KS, Rush VW, Crowly JJ, *et al.* Concurrent cisplatin/etoposide plus chest radiotherapy followed by surgery for stages IIIA (N2) and IIIB non-small cell lung cancer: Mature results of South-west Oncology Group Phase II study 8805. J Clin Oncol 13: 1880-1892, 1995.

2. Albain KS, Swann RS, Rush V, *et al.* Phase III study of concurrent chemo-radiotherapy and radiotherapy (CT/RT) vs CT/RT followed by surgical resection for stage IIIA (pN2) non-small-cell cancer (NSCLC): Outcomes update of North American Intergroup 0139 (RTOG 9309). J Clin Oncol 2005; 23: 624s (suppl; abstr 7014).

3. Aupérin A, Arriagada R, Pignon JP, Le Péchoux C, *et al.* Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. N Engl J Med 341: 476-484, 1999.

4. Aupérin A, Rolland E, Curran WJ, *et al.* Concomitant radio-chemotherapy (RT-CT) versus sequential RT-CT in locally advanced non-small cell lung cancer (NSCLC): a meta-analysis using individual patient data from randomised clinical trials. J Thorac Oncol 2: S310, 2007.

5. Betticher DC, Schimitz SFH, Tötsch M, *et al.* Mediastinal lymph node clearance after docetaxel-cisplatin neoadjuvant chemotherapy is prognostic of surival in patients with stage IIIA pN2 non-small cell lung cancer: a multicenter phase II trial. J Clin Oncol 21: 1752-59, 2003.

6. CBS 1: http://www.cbs.nl/nl-NL/menu/themas/gezondheid-welzijn/publi-caties artikelen/archief/2008/2008-2571-wm.htm.

7. CBS 2: http://www.cbs.nl/nl-NL/menu/themas/bevolking/publicaties/arti-kelen/archief/2007/2007-2199-wm.htm.

8. Curran WJ, Scott CB, Langer CJ, *et al.* Long-term benefit is observed in a phase III comparison of sequential vs concurrent chemo-radiation for patients with unresected stage III non-small cell lung cancer: RTOG 9410. Annual meeting Am Soc Clin Oncol , May 31-June 3, Chicago, abstract no 2499, 2003.

9. El Sharouni SY, Kal HB, Battermann JJ. Accelerated regrowth of non-small-cell lung tumours after induction chemotherapy. Br J Cancer 89: 2184-2189, 2003.

10. El Sharouni SY, Kal HB, Battermann JJ. Tumour control probability of stage III inoperable non-small cell lung tumours after sequential chemo-radiotherapy. Anticancer Res 25: 4655-4661, 2005.

11. El Sharouni SY, Kal HB, Battermann JJ, Schramel FM. Sequential versus concurrent chemo-radiotherapy in inoperable stage III non-small cell lung

cancer. Anticancer Res 26: 495-505, 2006.

12. El Sharouni SY, Aerts JGJV, Senan S, *et al*. Behandeling van patiënten met niet-kleincellig longcarcinoom stadium III: gelijktijdig hooggedoseerde chemotherapie en radiotherapie, Ned Tijdschr Geneeskd 152: 2714-2717, 2008.

13. Farray D, Mirkovic N, Albain KS. Multimodality therapy for stage III non-small cell lung cancer. J Clin Oncol 23: 3257-3269, 2005.

14. Freiha FS, Bagshaw MA. Carcinoma of the prostate: results of post-irradiation biopsy. Prostate 5: 19-25, 1984.

15. Fu XL, Jiang GL, Wang LJ, *et al*. The value of local control in the radiation therapy for non-small cell lung cancer. Shanghai Med 19: 559-561, 1996.

16. Furuse K, Fukuoka M, Kawahara M, *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 17: 2692-2699, 1999.

17. Gaafar RM, Abdelbaki H, Safwat A, *et al*. Accelerated hyperfractionation radiotherapy and daily cisplatin followed by consolidation chemotherapy. A phase II trial for patients with inoperable stage III NSCLC. Abstract. Lung Cancer 45: S53-54, 2004.

18. Gandara DR, Chansky K, Albain KS, *et al*. Consolidation docetaxel after concurrent chemoradiotherapy in stage IIIB non-small-cell lung cancer: phase II Southwest Oncology Group Study S9504. J Clin Oncol 21: 2004-2010, 2003.

19. Jackman DM, Johnson BE. Small-cell lung cancer. Lancet 366: 1385-1396, 2005.

20. Kal HB, El Sharouni SY, Barten-van Rijbroek AD. Gemcitabine as a radio-sensitizer in undifferentiated tumors. Anticancer Res 26: 139-145, 2006.

21. Katayama H, Ueoka H, Kiura K, *et al*. Preoperative concurrent chemo-radiotherapy with cisplatin and docetaxel in patients with locally advanced non-small cell lung cancer. British J Cancer 90: 979-984, 2004.

22. Kotalik J, Yu E, Markman BR, Evans WK. Cancer Ontario Practice Guidelines Initiative Lung Cancer Disease Site Group. Practice guideline on prophylactic cranial irradiation in small-cell lung cancer. Int J Radiat Oncol Biol Phys 50: 309-316, 2001.

23. Martin J, Ginsberg RJ, Venkatraman ES, *et al*. Long-term results of combined-modality therapy in resectable non-small cell lung cancer. J Clin Oncol 20: 1989-1995, 1995.

24. Pfister DG, Johnson DH, Azzoli CG, *et al*. American Society of Clinical Oncology. Treatment of unresectable non-small cell lung cancer guideline: update 2003. J Clin Oncol 22: 330–353, 2004.

25. Prophylactic Cranial Irradiation Overview Collaborative Group. Cranial irradiation for preventing brain metastases of small cell lung cancer in patients in complete remission. Cochrane Database Syst Rev 4: CD002805, 2000.

26. Pugh TJ, Gaspar LE. Prophylactic cranial irradiation for patients with lung cancer. Clin Lung Cancer 8: 365-368, 2007.

27. Ramsay J, Suit HD, Sedlacek R. Experimental studies on the incidence of metastases after failure of radiation treatment and the effect of salvage surgery. Int J Radiat Oncol Biol Phys 14: 1165-1168, 1988.

28. Sakai H, Yoneda S, Kobayashi K, *et al*. Phase II study of bi-weekly docetaxel and carboplatin with concurrent thoracic radiation therapy followed by consolidation chemotherapy with docetaxel plus carboplatin for stage III unresectable non-small cell lung cancer. Lung Cancer 43: 195-201, 2004.

29. Schaake-Koning C, van den Bogaert W, Dalesio O, *et al.* Radiosensitization by cytotoxic drugs. The EORTC experience by the Radiotherapy and Lung Cancer Cooperative Groups. Lung Cancer 10, Suppl 1: S263-270, 1994.

30. Senan S, De Ruysscher D, Girraud P, *et al*. Literature-based recommendations for treatment planning and execution in high-dose radiotherapy for lung cancer. Radiother Oncol 71: 139-146, 2004.

31. Socinski MA, Zhang C, Herndon JE II, *et al*. Combined modality trials of the Cancer and Leukemia Group B in stage III non-small-cell lung cancer: analysis of factors influencing survival and toxicity. Ann Oncol 15: 1033-1041, 2004.

32. Takada M, Fukuoka M, Kawahara M, *et al*. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with cisplatin and etoposide for limited-stage small-cell lung cancer: results of the Japan Clinical Oncology Group Study 9104. J Clin Oncol 20: 3054-3060, 2002.

33. Thomas M, Rube C, Hoffknecht P, *et al*. Effect of preoperative chemoradiation in addition to preoperative chemotherapy: a randomised trial in stage III non-small cell lung cancer. Lancet Oncol 2008; 9: 636-648.

34. Van Meerbeeck JP, Kramer GW, Van Schil PE, *et al*. Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small cell lung cancer. J Natl Cancer Inst 2007; 99: 442-450.

35. Weir HK, Thun MJ, Hankey BF, *et al*. Annual report to the nation on the status of cancer, 1975-2000, featuring the uses of surveillance data for cancer prevention and control. J Natl Cancer Inst 95: 1276-1299, 2003.

36. Werner-Wasik M, Scott C, Movas B, *et al.* Amifostine as mucosal protectant in patients with locally advanced non-small cell lung cancer (NSCLC) receiving intense chemotherapy and thoracic radiotherapy (RT): results of

the Radiation Therapy Oncology Group (RTOG) 98-01 study. Abstract. Int J Radiat Oncol Biol Phys 57 (Suppl 2): S216, 2003.

37. Whelan TJ, Julian J, Wright J, *et al.* Does locoregional radiation therapy improve survival in breast cancer? A meta-analysis. J Clin Oncol 18: 1220-1229, 2000.

38. Youlden DR, Cramb SM, Baade PD. The international epidemiology of lung cancer: geographical distribution and secular trends. J Thorac Oncol 3: 819-31, 2008.

Summary

This thesis concerns the treatment of stage III non-small cell lung cancer (NSCLC) and limited disease (LD) small-cell lung cancer (SCLC).

In chapter 2 we described a systematic review on the clinical results of radiotherapy, combined or not with chemotherapy, for inoperable NSCLC stage III with the aim to define the best sequence of radiotherapy and chemotherapy. The mean median survival duration ± standard deviation for radiotherapy only was 10.4±1.8 months. For sequential chemoradiotherapy it was increased to 13.0±1.2 months. When induction chemotherapy was followed by concurrent chemoradiotherapy, the mean median duration was 15.8±2.6 months. For concurrent chemoradiotherapy it was further increased to 16.4±2.7 months. The mean 2- and 3-year overall survivals for radiotherapy alone, sequential and concurrent chemoradiotherapy were 17.1±4.6 and 10%, 23.8±6.3 and 18.5±7.0, and 32.5±8.7 and 25.7±6.3%, respectively. The 5-year survival has increased from about 7% for radiotherapy alone to 10% for sequential and about 15% for concurrent chemoradiotherapy. We concluded that concurrent chemoradiotherapy demonstrated increased efficacy over sequential chemoradiotherapy and should be the treatment of choice. However, the concurrent chemo-radiotherapy schedules were associated with higher toxicity as compared to sequential therapy with the same drug doses.
Although the predominant cause of death in NSCLC is believed to be distant metastases, local recurrence is still a major cause of failure. Animal experiments and clinical data in lung, prostate and mammary cancers indicated that improvements in local control would decrease distant metastases, since part of the distant metastases was derived from local recurrences of the cancer. Further improvements may be obtained by optimising the conditions for concurrent chemoradiotherapy.

In chapter 3 we investigated the influence of the waiting time for radiotherapy, i.e. the interval between the end of induction chemotherapy and the start of radiotherapy, on the rate of tumour growth for patients with NSCLC stage III. In the period 1999-2000, 23 patients with stage III NSCLC received induction chemotherapy with cisplatin and gemcitabine.
The mean time interval between the end of the chemotherapy and the day of diagnostic CT-scan was 15.8 days, and till the first day of the radiotherapy 80.3 (range 29 - 141) days. Forty-one percent of potentially curable patients became incurable in the waiting period. The ratio of gross tumour volumes of the two CT-scans ranged from 1.1 to 81.8 and

the tumour volume doubling times ranged from 8.3 to 171.4 days with a mean value of 45.8 days and median value of 29.4 days. This is far less than the mean tumour volume doubling time of NSCLC in untreated patients found in literature.

We demonstrated that in the time interval between the end of induction chemotherapy and the start of radiotherapy rapid tumour progression occurs as a result of accelerated tumour cell proliferation. As a consequence, the gain obtained with induction chemotherapy with regard to volume reduction was lost in the waiting time for radiotherapy. We recommend that radiotherapy should start as soon as possible, preferably within two to three weeks after the last chemotherapy cycle. Due to the accelerated cell proliferation observed, accelerated radiotherapy should be given serious consideration to keep overall treatment time short.

In chapter 4 we discussed the influence of the duration of the waiting time between end of induction chemotherapy and start of radiotherapy on tumour control probability (TCP). Twenty-three patients with inoperable stage III NSCLC received induction chemotherapy followed by radiotherapy. The mean waiting period between the end of induction chemotherapy and the start of radiotherapy was 80.3 days; in this period the median tumour volume increased with a factor of about 6.

The importance of tumour volume on local control and the strong independent association between tumour volume and survival are evident and were reported in the literature. Stage III NSCLC is correlated with tumour volumes in excess of 100 cm^3. The TCP analysis revealed that for tumours of that size local cure is almost impossible with the doses usually applied in radiotherapy.

The two-year survival of our patients treated with curative intent was 8%, lower than the mean value of 26% derived from other studies. Assuming that radiotherapy started at the day of restaging instead of at the first day of radiotherapy (RT1), for patients treated with curative intent the calculated mean TCP at restaging was 13.3%, at RT1 it was 0.5%. The relatively long interval time between chemo- and radiotherapy had a deleterious effect on local control and survival and we recommend the waiting time to be as short as possible.

In chapter 5 we investigated whether gemcitabine (dFdC) may cause radio-sensitization. dFdC may cause radiosensitization by specific interference with homologous recombination-mediated DNA double-strand breaks

repair. The radiosensitizing effect of dFdC might be less in normal tissue and more restricted to undifferentiated tumour cells, making it a tumour-selective radiosensitizer. We tested whether dFdC acted as radiosensitizer in undifferentiated and well-differentiated rat tumours and on rat foot skin.

We used undifferentiated L44 lung tumours in BN rats, MLL prostate tumours in Copenhagen rats, and well-differentiated L42 lung tumours in WAG/Rij rats. Tumours were treated with a single X-ray dose whether or not combined with dFdC (30 mg/kg) administered 24 h earlier. Tumour volume growth delay was the endpoint used. In addition, rat foot skin was treated with a single dose of 22.5 Gy with or without dFdC. The degree of skin damage was determined according to a scoring system.

For tumour growth delay, dose-enhancement ratios were 1.37 and 1.23-1.36 for the L44 and MLL tumours, respectivley. No radiosensitization was observed for the well-differentiated L42 tumour and foot skin. Our data support further trials to evaluate the usefulness of dFdC as radiosensitizer in undifferentiated tumours.

In chapter 6 we describe the results of a phase II national multicentre study with weekly docetaxel/cisplatin and concurrent thoracic radiotherapy followed, whenever possible, by surgery in patients with stage III non-small cell lung cancer.

Concurrent chemoradiotherapy is the standard of care in NSCLC stage III patients. This prospective study analysed the feasibility and efficacy of weekly docetaxel/cisplatin (DC) and concurrent radiotherapy followed by surgery. The primary endpoint was radiological response. The secondary endpoints included toxicity, efficacy of surgery, postoperative morbidity and mortality, and overall survival.

The chemotherapy consisted of docetaxel 20 mg/m^2 and cisplatin 20 mg/m^2 at days 1, 8, 15, 22, 29 and 36. The radiotherapy was given in once-daily fractions of 1.8 Gy, 5 fractions a week to a total dose of 45 Gy started on day 8 of the chemotherapy. When complete mediastinal clearance of malignant disease was achieved, surgery was performed.

Between March 2005 and September 2006, 45 patients were included, of whom 42 patients were evaluable. Twenty-five patients with stage IIIA disease and 17 patients with stage IIIB disease (10 patients cT4N2, 4 patients cT4N0/1, 3 patients N3) were included. One patient developed fatal haemoptysis after 4 cycles of chemoradiotherapy. Forty-one patients were evaluable for radiological response. Nineteen

partial and complete responses (46%), 14 stable disease (34%) and 8 progressive disease (20%) were observed. Esophagitis grade III was observed in 3 patients (7%). Surgery after chemoradiotherapy was performed in 24 patients (59%) of which 22 (54%) achieved complete clearence of mediastinal malignant disease. Twenty patients underwent a complete resection (49%). Four patients showed complete pathological response after surgery. The 30-days mortality after surgery was 4%. At the time of this analysis (March 2009), 14 patients are still alive of which 13 were operated upon. This induction regimen is feasible with limited toxicity and seems to be effective in stage III NSCLC.

In chapter 7 we analysed the treatment results of our patients' population with limited-disease small-cell lung cancer (LD-SCLC). They were treated with chemotherapy only and chemotherapy combined with radiotherapy. The treatment schemes with curative intention were sequential and concurrent chemoradiotherapy, both combined with prophylactic cranial irradiation (PCI).
Patient -, treatment - and outcome – related items were retrospectively assessed. Up till 2001, LD-SCLC patients received 4-5 cycles of cyclophosphamide, doxorubicin and etoposide. In case of no complete response, palliative radiotherapy was given in 13 fractions of 3 Gy (CT-RT group, N=26). Because of different reasons, 89 patients did not receive radiotherapy after the chemotherapy (CT group). After complete response, curative radiotherapy was given in 16 fractions of 2.5 Gy, concurrently with PCI in 15 fractions of 2 Gy (SCT-RT group, N=111). From 2001, 40 patients received 4-5 cycles of cisplatin and etoposide concurrently with radiotherapy in 25 fractions of 1.8 Gy. PCI was applied to patients with complete response (CCT-RT group). The primary endpoints were median survival time and overall survival and the secondary endpoints included tumour-related cause of death and frequency of metastases.
The median survival times of CT only, CT-RT, SCT-RT and CCT-RT schemes were 8.1, 12.5, 14.0 and 21.8 months, and the 5-year overall survival 3.5, 4.8, 10.5 and 26.9%, respectively. The cause of death of SCT-RT and CCT-RT patients was tumour related in 76.3% and 89.3% of the patients, respectively. Brain metastases frequencies after PCI in SCT-RT and in CCT-RT patients were 16.4% and 8.7%, respectively. SCT-RT patients received PCI on an average of 159 days after the start of the CT, the CCT-RT patients on an average of 139 days after the start of CT. Probably, results may improve further by applying PCI at an earlier stage.

Our results indicate that the concurrently applied chemoradiotherapy resulted in longer median survival time and higher overall survival than sequential chemoradiotherapy, chemotherapy with palliative radiotherapy or chemotherapy only.

Samenvatting

Dit proefschrift gaat over de behandeling van stadium III niet-kleincellig longcarcinoom (NKCLC) en kleincellig longcarcinoom (KCLC), limited disease (LD).

In hoofdstuk 2 beschreven wij een systematisch overzicht van de klinische resultaten van de radiotherapie, al dan niet gecombineerd met chemotherapie, voor inoperabel NKCLC stadium III met als doel te definiëren wat de beste volgorde is van de radiotherapie en de chemotherapie.

De gemiddelde mediane overlevingsduur ± standaarddeviatie voor alléén radiotherapie was 10,4±1,8 maanden. Voor sequentiële chemoradiotherapie steeg de waarde naar 13,0±1,2 maanden. Wanneer inductiechemotherapie gevolgd werd door concurrente chemoradiotherapy was de gemiddelde mediane waarde 15,8±2,6 maanden. Voor concurrente chemoradiotherapie steeg de waarde verder naar 16,4±2,7 maanden. De gemiddelde 2- en 3- jaars overall overleving voor radiotherapie alleen, sequentieel en concurrente chemoradiotherapie was 17,1±4,6 en 10, 23,8±6,3 en 18,5±7,0, en 32,5±8,7 en 25,7±6,3%, respectievelijk. De 5-jaars overleving steeg van circa 7% voor radiotherapie alleen naar 10% voor de sequentiële behandeling en voor de concurrente chemoradiotherapie was het circa 15%. We concludeerden dat concurrente chemoradiotherapie effectiever is dan sequentiële chemoradiotherapie en dat het de standaardbehandeling zou moeten zijn. De concurrente chemoradiotherapie schemata leidden echter tot meer toxiciteit in vergelijking met de sequentiële behandeling wanneer dezelfde dosis gegeven werd.

De belangrijkste doodsoorzaak van NKCLC is metastasen op afstand, maar lokaal recidief is nog steeds een groot probleem. Dierexperimenten en klinische data over long-, prostaat- en mammacarcinoom laten zien dat verbetering in lokale controle metastasen op afstand kan doen afnemen, omdat een deel van deze metastasen afkomstig is van het lokale recidief. Verdere verbetering kan bereikt worden door optimalisering van de condities voor concurrente chemoradiotherapie.

In hoofdstuk 3 onderzochten wij de invloed van de wachttijd voor de radiotherapie, dat wil zeggen het interval tussen het einde van inductiechemotherapie en de start van de radiotherapie, op de proliferatiesnelheid van tumoren bij patiënten met NKCLC stadium III. In de periode 1999-2000, kregen 23 patiënten met stadium III NKCLC

inductiechemotherapie met cisplatine en gemcitabine.

Het gemiddelde tijdsinterval tussen einde chemotherapie en de dag waarop de diagnostische CT-scan vervaardigd werd, was 15,8 dagen. Tot de eerste dag van de radiotherapie was het gemiddelde tijdsinterval 80,3 (spreiding 29 – 141) dagen.

Eenenveertig procent van potentieel curabele patiënten werd in de wachtperiode incurabel. De verhouding tussen de tumorvolumina van de twee CT-scans varieerde van 1,1 tot 81,8. De tumorverdubbelingstijd varieerde van 8,3 tot 171,4 dagen met een gemiddelde waarde van 45,8 dagen en een mediane waarde van 29,4 dagen. Deze gemiddelde verdubbelingstijd is veel korter dan de gemiddelde verdubbelingstijd van onbehandelde patiënten met NKCLC vermeld in de literatuur.

Wij lieten zien dat in het tijdsinterval tussen het einde van inductiechemotherapie en de start van de radiotherapie, versnelde tumorgroei werd waargenomen als resultaat van versnelde tumorcelproliferatie. Als consequentie werd de behaalde winst met inductiechemotherapie, met betrekking tot volumereductie, teniet gedaan in de wachtperiode op de radiotherapie. Wij adviseren dat radiotherapie zo spoedig mogelijk moet starten, bij voorkeur binnen twee tot drie weken na de laatste chemotherapie cyclus. Vanwege de geobserveerde versnelde celproliferatie moet versnelde radiotherapie serieus in overweging worden genomen.

In hoofdstuk 4 hebben wij de invloed van de duur van de wachttijd tussen einde inductiechemotherapie en start radiotherapie op "tumour control probability" (TCP) besproken. Drieëntwintig patiënten met inoperabel stadium III NKCLC kregen inductiechemotherapie gevolgd door radiotherapie. De gemiddelde wachtperiode tussen het einde van de inductiechemotherapie en de start van de radiotherapie was 80,3 dagen. In deze periode nam het mediane tumorvolume met een factor 6 toe. De invloed van het tumorvolume op de lokale controle en de sterke invloed van het tumorvolume op de overleving zijn evident en gerapporteerd in de literatuur. Stadium III NKCLC is geassocieerd met tumorvolumina van meer dan 100 cm^3. De TCP-analyse toonde aan dat lokale controle van tumoren met een dergelijk volume, met de gebruikelijke radiotherapie doseringen, vrijwel onmogelijk is.

De twee-jaars overleving van patiënten behandeld met curatieve intentie was 8%, deze is lager dan de gemiddelde waarde van 26% afgeleid van andere studies.

Voor patiënten behandeld met curatieve intentie, er van uit gaande dat radiotherapie op de dag van restadiëring gestart kon worden in plaats van op de geplande eerste radiotherapiedag (RT1), was de berekende gemiddelde TCP op de dag van restadiëring 13,3% en op RT1 slechts 0,5%.

Het relatief lange tijdsinterval tussen chemo- en radiotherapie had dus een desastreus effect op de lokale controle en de overleving. Wij adviseren om de wachttijd zo kort mogelijk te houden.

In hoofdstuk 5 onderzochten wij of gemcitabine (dFdC) een radiosensibiliserende werking heeft. dFdC kan radiosensibilisering veroorzaken via specifieke interferentie met herstel van DNA-dubbelstrengsbreuken via homologe recombinatie. De radiosensibiliserende werking van dFdC is misschien minder in gezond weefsel en meer beperkt tot ongedifferentieerde tumorcellen, waardoor het een tumor-selectieve radiosensibilisator is. We testten of dFdC een radiosensibiliserende werking in ongedifferentieerde en goed gedifferentieerde rattentumoren en in de voethuid van de rat heeft.

We gebruikten ongedifferentieerde L44 longtumoren in BN ratten, MLL prostaattumoren in Copenhagen ratten en goed gedifferentieerde L42 longtumoren in WAG/Rij ratten. Tumoren werden behandeld met een eenmalige röntgendosis al dan niet gecombineerd met dFdC (30 mg/kg), toegediend 24 uur eerder. Groeiuitstel van het tumorvolume was het eindpunt. De voethuid werd behandeld met een eenmalige dosis van 22,5 Gy met of zonder dFdC. De mate van de huidreactie werd vastgesteld op basis van een scoringssysteem. Voor tumorgroeiuitstel waren de dosis-modificerende ratio's 1,37 en 1,23-1,36 voor de L44 en MLL tumoren, respectievelijk. Geen radiosensibiliserende werking werd waargenomen voor de goedgedifferentieerde L42 tumor en de voethuid. Geconcludeerd werd dat dFdC radiosensibiliserend werkt in de ongedifferentieerde tumoren en niet in de goedgedifferentieerde tumor en de huid. Onze gegevens ondersteunen verdere studies ter evaluatie van het nut van dFdC als radiosensibilisator in ongedifferentieerde tumoren.

In hoofdstuk 6 beschreven we de resultaten van een prospectieve fase II studie met wekelijks docetaxel/cisplatine en gelijktijdige thoracale radiotherapie gevolgd, waar mogelijk, door een operatie bij patiënten met stadium III NKCLC.

Concurrente chemoradiotherapy is de standaardbehandeling van NKCLC

stadium III patiënten. In deze prospectieve studie werd de haalbaarheid en effectiviteit van de wekelijkse chemotherapie met concurrente radiotherapie, gevolgd door chirurgie geanalyseerd. Het primaire eindpunt was radiologische respons. De secundaire eindpunten omvatten toxiciteit, de effectiviteit van de operatie, de postoperatieve morbiditeit en mortaliteit en de overleving.

De chemotherapie bestond uit docetaxel 20 mg/m^2 en cisplatine 20 mg/m^2 op dag 1, 8, 15, 22, 29 en 36. De radiotherapie werd één keer per dag gegeven in fracties van 1,8 Gy, 5 fracties per week tot een totale dosis van 45 Gy vanaf dag 8 van de chemotherapie. Wanneer geen pathologische mediastinale lymfomen gevonden werden, werd de patiënt geopereerd.

Tussen maart 2005 en september 2006, werden 45 patiënten geïncludeerd, waarvan 42 patiënten werden geëvalueerd. Vijfentwintig patiënten met stadium IIIA en 17 patiënten met stadium IIIB werden geïncludeerd. Eén patiënt overleed na 4 cycli chemoradiotherapie ten gevolge van haemoptoë. Eenenveertig patiënten waren evaluabel voor radiologische respons. Negentien patiënten bereikten partiële of complete respons (46%), 14 hadden stabiele ziekte (34%) en 8 patiënten progressieve ziekte (20%). Behoudens graad III oesophagitis in slechts 3 patiënten (7%), was de toxiciteit beperkt. Vierentwintig patiënten (59%) werden geopereerd, waarvan 22 patiënten (54%) zonder pathologische mediastinale lymfomen. Twintig patiënten (49%) ondergingen een complete resectie. Vier patiënten vertoonden een complete pathologische respons. De 30-dagen mortaliteit na de operatie was 4%. Op het moment van deze analyse (maart, 2009), zijn 14 patiënten nog in leven waarvan 13 geopereerd waren. De bovenbeschreven behandeling is haalbaar met beperkte toxiciteit en lijkt doeltreffend te zijn in fase III NKCLC.

In hoofdstuk 7 analyseerden we de behandelingsresultaten van onze patiënten met limited disease kleincellig longcarcinoom, LD-KCLC. Ze werden behandeld met chemotherapie alleen en chemotherapie gecombineerd met radiotherapie. De behandeling met curatieve intentie bestond uit sequentiële en concurrente chemoradiotherapie, beide gecombineerd met profylactische schedelbestraling (PSB).

De patiëntendossiers werden retrospectief geanalyseerd. Tot 2001 kregen LD-KCLC patiënten 4-5 cycli van cyclofosfamide, doxorubicine en etoposide. Wanneer er geen complete respons bereikt werd, werd palliatieve radiotherapie (RT) gegeven in 13 fracties van 3 Gy (CT-RT-groep, N=26). Vanwege verschillende redenen, hebben 89 patiënten

geen radiotherapie na de chemotherapie gehad (CT-groep). Na complete respons, werd curatieve radiotherapie gegeven in 16 fracties van 2,5 Gy, gelijktijdig met PSB in 15 fracties van 2 Gy (SCT-RT-groep, N=111).

Vanaf 2001, kregen 40 patiënten 4-5 cycli van cisplatine en etoposide gelijktijdig met radiotherapie in 25 fracties van 1,8 Gy. PSB werd toegepast bij patiënten met een complete respons (CCT-RT-groep). De primaire eindpunten waren de mediane overlevingstijd en de overleving. De tumor-gerelateerde doodsoorzaak en de frequentie van de metastasen waren de secundaire eindpunten.

De mediane overleving van CT alleen, CT-RT, SCT-RT en CCT-RT schemata waren 8,1, 12,5, 14,0 en 21,8 maanden, en de 5-jaars overleving 3,5, 4,8, 10,5 en 26,9%, respectievelijk. De oorzaak van overlijden van SCT-RT en CCT-RT patiënten was tumor gerelateerd in 76,3% en 89,3% van de patiënten, respectievelijk. De frequentie van hersenmetastasen na PSB in SCT-RT en CCT-RT patiënten was 16,4% en 8,7%, respectievelijk. SCT-RT patiënten kregen PSB gemiddeld 159 dagen na het begin van de CT, en de patiënten van de CCT-RT-groep 139 dagen na het starten van de CT. Waarschijnlijk zullen de resultaten verder verbeteren door het toepassen van PSB in een eerder stadium.

Onze resultaten geven aan dat de concurrente chemoradiotherapie resulteerde in langere mediane overleving en in een hogere totale overleving dan sequentiële chemoradiotherapie, chemotherapie met palliatieve radiotherapie of chemotherapie alleen.

Publications

Articles

- Maas KW, El Sharouni SY, Phernambucq EC, Stigt BE, Groen JA, Herder GJM, van den Borne BEEM, Senan S, Paul MA, Smit EF, Schramel FMNH. Weekly docetaxel/cisplatin and concurrent thoracic radiotherapy followed by surgery in patients with stage III non-small cell lung cancer, a multicentre phase II study (submitted).

- El Sharouni SY, Kal HB, Barten-van Rijbroek AD, Struikmans H, Battermann JJ, Schramel FMNH. Concurrent versus sequential chemotherapy and radiotherapy in limited-disease small-cell lung cancer: a retrospective comparative study (submitted).

- El Sharouni SY, Aerts JGJV, Senan S, De Ruysscher DKM, Groen HJM, Paul MA, Smit EF, Vonk EJA, Verhagen AF, Schramel FMNH. Behandeling van patiënten met niet-kleincellig longcarcinoom stadium III: gelijktijdige hooggedoseerde chemotherapie en radiotherapie. Ned Tijdschr Geneeskd 2008; 152: 2714-2717.

- Van Vulpen M, El Sharouni SY, Taphoorn MJB, Baas P, Kal HB, Battermann JJ. Brain metastasis in lung cancer: Increasing blood-brain barrier permeability by radiotherapy to enhance the effect of chemotherapy. Focus on Cancer Research. Nova Science Publishers, Inc. New York, USA. Chapter 4: 63-81. ISBN: 978-160021-729-6. Editor: Carlos M. Alvarez. 2007.

- Maas KW, El Sharouni SY, Smit EF, Schramel FM. Sequencing chemotherapy, radiotherapy and surgery in combined modality treatment of stage III nonsmall cell lung cancer. Curr Opin Pulm Med 2007; 13: 297-304.

- El Sharouni SY, Kal HB, Battermann JJ, Schramel FM. Sequential versus concurrent chemo-radiotherapy in inoperable stage III non-small cell lung cancer. Anticancer Res 2006; 26: 495-505.

- Kal HB, El Sharouni SY, Barten-van Rijbroek AD. Gemcitabine as a radiosensitizer in undifferentiated tumors. Anticancer Res 2006; 26: 139-145.

- Van Vulpen M, El Sharouni SY, Taphoorn MJB, Baas P, Kal HB, Battermann JJ. Increasing blood-brain barrier permeability by radiotherapy to enhance the effect of chemotherapy on brain metastasis in lung cancer. Trends in Cancer Research. Nova Science Publishers, Inc. New York, USA. Chapter 2: 89-107. ISBN: 1-60021-100-3. Editor: L.P. Jeffries. 2006.

- El Sharouni SY, Kal HB, Battermann JJ. Tumour control probability of stage III inoperable non-small cell lung tumours after sequential chemo-radiotherapy. Anticancer Res 2005; 25: 4655-4661.

- Tersteeg RJHA, El Sharouni SY, Kal HB, Jansen GH, de Jong PM, Straver JS. Case report on combined radiation myelopathy and intramedullary metastases. Cancer Therapy 2004; 2: 423-428.

- El Sharouni SY, Kal HB, Battermann JJ. Versnelde tumorgroei van niet-kleincellige longtumoren in de wachttijd tussen inductiechemotherapie en langdurige radiotherapie. Ned Tijdschr Geneeskd 2004; 148: 1199-1202.

- El Sharouni SY, Kal HB, Battermann JJ. Accelerated regrowth of non-small-cell lung tumours after induction chemotherapy. Br J Cancer 2003; 89: 2184-2189.

- Van Vulpen M, Kal HB, Taphoorn MJ, El Sharouni SY. Changes in blood-brain barrier permeability induced by radiotherapy: implications for timing of chemotherapy? Oncol Rep 2002; 9: 683-688.

- Van Eijkeren MA, Van der Wijk I, El Sharouni SY, Heintz AP. Benefits and side effects of lateral ovarian transposition (LOT) performed during radical hysterectomy and pelvic lymphadenectomy for early stage cervical cancer. Int J Gynecol Cancer 1999; 9: 396-400.

- Kal HB, El Sharouni SY, Wijrdeman HK. Radiotherapy for oesophageal cancer. Ann Oncol 1999; 10: 359-360.

- El Sharouni SY, Smits HF, Wüst AF, Battermann JJ, Blankestijn PJ. Endovascular brachytherapy in arteriovenous grafts for haemodialysis does not prevent development of stenosis. Radiother Oncol 1998; 49: 199-200.

-   Kal HB, El Sharouni SY, Struikmans H. Postoperative radiotherapy in non-small-cell lung cancer. Lancet 1998; 352: 1385-1386.

-   El Sharouni SY, Berfelo MW, Theunissen PH, Jager JJ, de Jong JM. A unique case of intracranial metastasis from lung carcinoma. Clin Neurol Neurosurg 1993; 95: 257-260.

-   Burgers JMV, El Sharouni SY, van Leeuwen FE, Somers R, Hart AA. Ziekte van Hodgkin: invloed van leeftijd op de prognose. Ned Tijdschr Geneeskd 1988; 132: 1354-1357.

Published abstracts

-   El Sharouni SY, Kal HB, Barten-van Rijbroek AD, Struikmans H, Battermann JJ, Schramel FMNH. Concurrent versus sequential chemoradiotherapy in limited-disease small-cell lung cancer: a retrospective comparative study. Anticancer Res 28, 3273-3274, 2008.

-   Maas KW, El Sharouni SY, Phernambucq EC, Stigt JA, van den Borne BE, Groen HJ, Senan S, Smit EF, Paul MA, Schramel FM. A phase II study of weekly docetaxel/cisplatin and concurrent radiotherapy followed by surgery in patients with stage III non-small cell lung cancer (NSCLC). J Thoracic Oncol 2, supplement 4, S649, 2008.

-   El Sharouni SY, Kal HB, Barten-van Rijbroek AD, Struikmans H, Schramel FM. Retrospective analysis of sequential and concurrent chemoradiotherapy of limited small cell lung cancer (SCLC). J Thoracic Oncol 2, supplement 4, S818, 2007.

-   Maas KW, El Sharouni SY, Phernambucq EC, Stigt JA, van den Borne BE, Groen HJ, Senan S, Smit EF, Paul MA, Schramel FM. A phase II study of weekly docetaxel/cisplatin and concurrent radiotherapy followed by surgery in patients with stage III non-small cell lung cancer (NSCLC). J Thoracic Oncol 2, supplement 4, S649, 2007.

-   El Sharouni SY, Kal HB. Accelerated proliferation of non-small cell lung cancer cells after induction chemotherapy. 12th International Congress of Radiation Research, Brisbane, Australia, 17-22 August, p 149, 2003.

- Nieuwenhoven AL van, El Sharouni SY, Borel Rinkes IMH, Wijrdeman HK. Radiotherapy in the palliation of Oesophageal Cancer. Radiother Oncol 51, supplement 2, S24, 1999.

- Wárlám-Rodenhuis CC, de Leeuw AAC, El Sharouni SY, Bouma P. Regional hyperthermia in combination with radiotherapy in patients with locally advanced cervical cancer. International Congress Hyperthermia in Clinical Oncology, Venetië, 28-30 May, p 27, 1998.

- Wijk I van der, El Sharouni SY, Heintz, APM, van Eijkeren MA. Benefits and side effects of lateral ovarian transposition (LOT) during Wertheim´s radical hysterectomy. Abstract book Wertheim Operation Centenary Scientific Meeting, Cervical Cancer- Current status, Wenen, 17-19 September, p 42, 1998.

- El Sharouni SY, Wárlám-Rodenhuis CC, De Leeuw AAC, Bouma P, Heintz APM. Radiotherapy in Combination with Regional Hyperthermia in Treating Cervical Cancer Patients. Int J Gynaecol Cancer 7, supplement 2, p 38, 1997.

- El Sharouni SY, Smits HFM, Blankestijn PJ, Mali WPThM, Eikelboom BC, Battermann JJ. Technical aspects of endovascular brachytherapy in preventing stenosis in arterio venous grafts of haemodialysis patients. 9th International Brachytherapy Conference, 3-6 September 1997, Palm Springs, CA, USA, p 306-307, 1997.

- Crezee, J, Raaijmakers BW, El Sharouni SY, Lagendijk JJW. Feasibility test of the MECS interstitial system using isolated perfused bovine organs. Proc. 15th Annual Meeting ESHO, Oxford, p 29, 1995.

- El Sharouni SY, Berfelo MW, Theunissen PHMH, Jager JJ, De Jong JMA. A unique case of intracranial metastasis from lung carcinoma. J Neuro-Oncol 21, p 56, 1994.

- Burgers JMV, El Sharouni SY. Correlation between age and prognosis in Hodgkin's Disease. The Third International Conference on Malignant Lymphoma, Lugano, 10-13 June 1987.