ANTICANCER RESEARCH *25*: 4655-4662 (2005)

# Tumour Control Probability of Stage III Inoperable Non-small Cell Lung Tumours after Sequential Chemo-radiotherapy

S.Y. EL SHAROUNI, H.B. KAL and J.J. BATTERMANN

*Department of Radiation Oncology, Q 00.118, University Medical Centre Utrecht, Post Box 85500, 3508 GA Utrecht, The Netherlands*

**Abstract.** *The aim of this study was to investigate the influence of the duration of waiting time between the end of induction chemotherapy and the 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 the end of induction chemotherapy and the start of radiotherapy was 80 days; in this period, the median tumour volume increased by 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 on the day of restaging or on the 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. Conclusion: 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.*

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 is employed 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, with 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 found previously that the growth of NSCLC after induction chemotherapy was faster than that of untreated tumours (9). In the waiting period between the 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 the tumour cure rate loss in the waiting period between the end of induction chemotherapy and start of radiotherapy,

*Correspondence to:* Dr S.Y. El Sharouni, University Medical Centre Utrecht, Department of Radiation Oncology, Q 00.118, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands. Tel: +31 30 2508800, Fax: +31 30 2581226, e-mail: S.Y.ElSharouni@azu.nl

*Key Words:* NSCLC inoperable stage III, chemo-radiotherapy, TCP.

and compared the results with the actual treatment outcome and results found in the literature.

## Patients and Methods

*Patient 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, The Netherlands, 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/m$^2$ on days 1 and 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. 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 cm$^3$ and at the moment of the CT-planning they varied between 45 and 793 cm$^3$. 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 days.

The given dose for curatively-intended radiotherapy was 66 Gy in 33 fractions, 5 times/week in 45 days, and for palliative radiotherapy 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 cure probability analysis.* The Poisson model for tumour cure 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:

$$TCP=\exp(-VN) \quad \textbf{(1)},$$

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:

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

where $N_0$ is the number of clonogens per cm$^3$ before radiation treatment, $D$ is the total dose, $d$ is the fraction dose, $\alpha$ and $\beta$ 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 $\gamma$ is the time factor for accelerated repopulation. For the factor $\gamma$ 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:

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

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:

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

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

The TCP were analysed according to $\alpha=0.30$ Gy$^{-1}$ with a spread $\sigma=0.02$ Gy$^{-1}$ as an 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 accelerated repopulation and 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 parameter $\alpha$ 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.

## Results

*Survival.* After induction chemotherapy, 23 patients were referred to the radiotherapy department 22 of whom for curative intent. However, 9 out of these 22 patients (41%) had progression of disease in the waiting period to such an 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, 2 of the 3 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 2-year survival of patients treated with curative intent was 8% (1 out of 13). However, this patient developed local recurrence.

Survival as a function of time after the 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

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

| Parameter | Value |
|---|---|
| $N$ | $10^7$ cells/cm$^3$ |
| $\alpha$ | 0.30+/–0.02 resp. 0.32+/–0.02 Gy$^{-1}$ |
| $\alpha/\beta$ | 15 Gy |
| *Tpot* | 5 days |
| *To* | 45 days |
| *Tdel* | 14 days resp. 0 days |
| *D* | 66 Gy (33 x 2 Gy) |

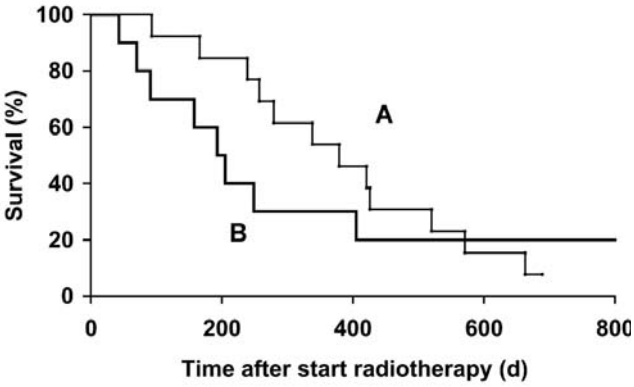


Figure 1. *Overall survival as a function of time after start of curatively-intended radiotherapy (radiation dose of 66 Gy), curve A, and palliative radiotherapy (dose of 30 Gy), curve B.*

figure. The 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.

*Tumour cure probability, radiation only.* TCP was modelled for radiotherapy only (no induction chemotherapy) and it was assumed that accelerated repopulation started on day 14 after the 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, $\alpha=0.30$, 0.28 and 0.32 Gy$^{-1}$, and for the *TCP* as a mean for a population with different sensitivities:

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

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$^3$, the *TCP* is less than 2.5%.

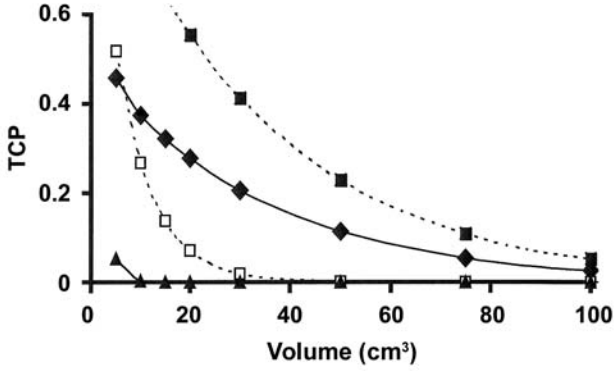


Figure 2. *Tumour cure probability (TCP) after radiotherapy only as function of tumour volume of previously untreated tumours. TCP was calculated for $\alpha=0.32$ Gy$^{-1}$ (large squares), $\alpha=0.30$ Gy$^{-1}$ (open squares), $\alpha=0.28$ Gy$^{-1}$ (triangles), and the average of the TCPs for $\alpha=0.32$ Gy$^{-1}$ and $\alpha=0.28$ Gy$^{-1}$ (diamonds); D=66 Gy, $N_0=10^7$/cm$^3$, $\alpha/\beta=15$ Gy, Tdel=14 days.*

*TCP, repopulation and radiosensitivity.* After induction chemotherapy, *Tdel* was assumed =0 days, 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 $\alpha=0.30$ Gy$^{-1}$, *To*=45 days, *Tdel*=0 days and *Tdel*=14 days, $\gamma=0.693/Tpot$ d$^{-1}$, *Tpot*=5 days, *d*=2 Gy, *D*=66 Gy, $\alpha/\beta=15$ Gy:

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

$N_0\exp[-0.30\text{x}66\text{x}[1+2/15]+0.693\text{x}(45-14)/5]=N_0\exp[-0.30\text{x}(66+Dr)\text{x}[1+2/15]+0.693\text{x}(45-0)/5]$.

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 $\alpha=0.30$+/– 0.02 Gy$^{-1}$, *Tdel*=0 days and V=30 cm$^3$, however, was less than 0.1% (Figure 3, triangles). Hence, a smaller tumour volume did not compensate for 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 $\alpha$ was increased.

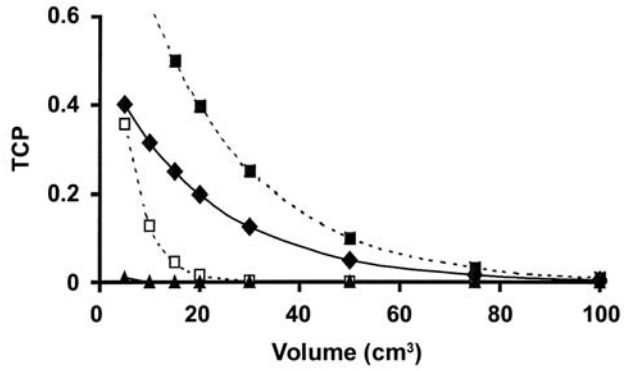


Figure 3. *Tumour cure probability (TCP) as function of tumour volume after sequential chemo-radiotherapy assuming accelerated repopulation. TCP was calculated for $\alpha$=0.34 Gy$^{-1}$ (large squares), $\alpha$=0.32 Gy$^{-1}$ (open squares), $\alpha$=0.30 Gy$^{-1}$ (triangles), and average of TCPs for $\alpha$=0.34 Gy$^{-1}$ and $\alpha$=0.3 Gy$^{-1}$ (diamonds); D=66 Gy, $N_0$=10$^7$/cm$^3$, $\alpha/\beta$=15 Gy, Tdel=0 days.*

For a tumour volume of 30 cm$^3$, *Tdel*=0 days and $\alpha$=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 $\alpha$=0.34 and 0.32 Gy$^{-1}$ are also depicted in Figure 3.

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

| Patient no. | 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), on the 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 the 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 the 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 $\alpha$=0.32+/–0.02 Gy$^{-1}$, at CT-restaging was 13.3%+/–10.8%. The mean TCP at RT1 was 0.5+/–0.7%. Thus, due to the mean waiting period of 73 days 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 a 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). In our patient population 2 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, the 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

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 (months) |
|---|---|---|
| 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 | 26.0±6.9 | 13.6±2.2 |
| Present study | 8% | 12.6±2.8 months |

months, within the range found in the 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 subsequent 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 progressed and 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.* The response rate after induction chemotherapy in our patients was 78% (9). We 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 12.5%. 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 mean 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.

## Conclusion

In the waiting period of 80 days between the end of induction chemotherapy and start of radiotherapy, the median tumour volume in our patients increased by a factor of about 6. As a consequence, the observed 2-year survival of patients treated with curatively-intended radiotherapy was only 8%, while from other studies a mean 2-year survival value of about 26% was found for sequential chemo-radiotherapy. This is also reflected in the calculated TCP for the curative intent-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 and 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 and 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 and Barton MB: The effect of waiting for radiotherapy for grade III/IV gliomas. Radiother Oncol *57*: 131-136, 2000.
5 Wyatt RM, Beddoe AH and 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 and 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 and 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 and Hordijk GJ: Does waiting time for radiotherapy affect local control of T1N0M0 glottic laryngeal carcinoma? Clin Otolaryngol *25*: 215-218, 2000.

9 Sharouni SY El, Kal HB and 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 and 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 and 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 and 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 and 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 and 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 and 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 and 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 and 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 and 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 and 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 and 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 and 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 and 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 and Leer JW: Radiotherapy as an alternative to surgery in elderly patients with resectable lung cancer. Radiother Oncol *13*: 83-89, 1988.

33 Oehler W and Eichhorn HJ: Primary tumor volume and prognosis in bronchial carcinoma. Strahlenther Onkol *168*: 73-78, 1992.

34 Sandler HM, Curran WJ Jr and 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 and 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 and 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 Am 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 and Overgaard J: Impact of delay on diagnosis and treatment of primary lung cancer. Acta Oncol *41*: 147-152, 2002.

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

*Received May 25, 2005*
*Accepted August 16, 2005*