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,
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/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 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-planning as stage IIIB, and were treated according to intended radiotherapy. These patients were diagnosed at 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 α was increased.

**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
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 cm3 (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 $T_{del}=14$ days, $\alpha=0.30$, 0.28 and 0.32 Gy–1, and for the TCP as a mean for a population with different sensitivities:

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

is given in Figure 2. For the population average (Figure 2, diamonds) the TCP at 75 cm3 is 5%. For volumes in excess of 100 cm3, the TCP is less than 2.5%.

TCP, repopulation and radiosensitivity. After induction chemotherapy, $T_{del}$ was assumed =0 days, thus accelerated repopulation was still present when radiotherapy started. The dose to compensate for the repopulation after induction chemotherapy $D_r$ can be derived from equation (2).

For $\alpha=0.30 \text{ Gy}^{-1}$, $T_{o}=45$ days, $T_{del}=0$ days and $T_{del}=14$ days, $\gamma=0.693/T_{pot} \text{ d}^{-1}$, $T_{pot}=5$ days, $d=2$ Gy, $D=66$ Gy, $\alpha/\beta=15$ Gy:

$N$(after radiation treatment, $T_{del}=14$ days, $D$) = $N$(after radiation treatment following induction chemotherapy, $T_{del}=0$ days, $D+D_r$).

$N_0 \exp[-0.30\times66x(1+2/15)+0.693x(45–14)/5]=N_0 \exp[-0.30x(66+D_r)x(1+2/15)+0.693x(45–0)/5].$

This results in a $D_r$ 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 cm3. The mean TCP calculated for $\alpha=0.30+/–0.02$ Gy–1, $T_{del}=0$ days and $V=30$ cm3, 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.

Table 1. Parameters and values used in the TCP analysis.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$N$</td>
<td>$10^7$ cells/cm$^3$</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>$0.30+/–0.02$ resp. $0.32+/–0.02$ Gy–1</td>
</tr>
<tr>
<td>$\alpha/\beta$</td>
<td>15 Gy</td>
</tr>
<tr>
<td>$T_{pot}$</td>
<td>5 days</td>
</tr>
<tr>
<td>$T_o$</td>
<td>45 days</td>
</tr>
<tr>
<td>$T_{del}$</td>
<td>14 days resp. 0 days</td>
</tr>
<tr>
<td>$D$</td>
<td>66 Gy (33 x 2 Gy)</td>
</tr>
</tbody>
</table>

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 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, $T_{del}=14$ days.

Sharouni et al: TCP of Stage III NSCLC after Chemo-radiotherapy
For a tumour volume of 30 cm$^3$, $T_{del}$ = 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.

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
is correlated with tumour volumes in excess of 100 cm³. The from 29 to 141 days. The higher stage (from IIIA to IIIB) be given. Nine of the 22 patients (41%) were treated with and the planned curatively-intended radiotherapy could not even larger percentage of patients in our study progressed their 29 lung cancer patients (21%) became incurable. An independent association between tumour volume and survival was reported (25, 53-55). O’Rourke and Edwards in the waiting period for potentially cure is almost impossible with the doses usually applied in TCP analysis revealed that, for tumours of that size, local probability. In the waiting period of 80 days (i.e. the mean waiting period in our study, almost 3 mean doubling times), the median volume of about 30 cm³ was increased to about 180 cm³, 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


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

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

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 cm³. The TCP analysis revealed that, for tumours of that size, local cure is almost impossible with the doses usually applied in radiotherapy.


