# CLINICAL STUDIES OF THE EFFECT OF RADIOTHERAPY DOSE AND FRACTIONATION ON SURVIVAL IN PATIENTS WITH LIMITED NON-SMALL CELL LUNG CANCER

A THESIS SUBMITTED IN ACCORDANCE WITH THE REQUIREMENTS FOR ADMISSION TO THE DEGREE OF DOCTOR OF MEDICINE OF THE UNIVERSITY OF ADELAIDE

by

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**Declaration.**

This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

I give consent to this copy of my thesis, when deposited in the University library, being available for loan and photocopying.

David L Ball

13 December 2001

Date

**Preface.**

The work presented here was based on patients treated during the period 1984 to 1995, throughout which I was Head of the Lung Unit at Peter MacCallum Cancer Institute (PMCI), Melbourne. The vast majority of patients were treated at the Institute under my care or supervision, although a small proportion of patients included in the second part of the thesis were treated at other Australian centres as part of a multicentre trial. The work is entirely my own, with the following exceptions:

The database on which the first part of the thesis is based was designed by myself with the assistance of Ms Valentina Worotniuk B Appl Sc, Medical Records Administrator. Ms Worotniuk wrote the associated procedure manual, created the edit checks and maintained and updated the database.

Statistical analyses of the database were performed by Dr Jane Matthews PhD, AStat, Director of the PMCI Statistical Centre.

The design of the multicentre trial which forms the second part of the thesis was a collaborative effort with medical oncologists Dr James Bishop MD, FRACP, FRCPA and Dr Ian Olver MD, PhD, FRACP. The radiotherapy component of the trial was designed entirely by myself. Of 204 patients entered on the trial, 156 were from my unit at Peter MacCallum Institute, and treated by myself or under my supervision; the remaining patients were from Royal Adelaide Hospital, Queensland Radium Institute, Mater Misericordiae Hospital Newcastle and The Geelong Hospital. Statistical analyses of the trial data were performed by Dr Jennifer Smith PhD, AStat, Deputy Director, PMCI Statistical Centre.

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Ball D, Bishop J, Smith J, O'Brien P Davis S, Olver I, Walker Q, Ryan G, Joseph D A phase III study of accelerated or standard fractionation radiotherapy with and without carboplatin in NSCLC. Presented at a workshop of the International Association for the Study of Lung Cancer "Controversies in staging and combined treatment modalities in lung cancer", Bruges, Belgium, June 1996

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Dedicated to my family: Mary, Sam, Kate, Ginny and William.

## List of abbreviations

| | |
|---|---|
| a-p | antero-posterior |
| AUC | Area under the curve |
| CALGB | Cancer and Leukemia Group B |
| CT | Computerized tomography |
| DER | Dose enhancement ratio |
| ECOG | Eastern Cooperative Oncology Group |
| EORTC | European Organisation for Research and Treatment of Cancer |
| IASLC | International Association for the Study of Lung Cancer |
| iv | intravenous |
| MRA | Medical record administrator |
| MTD | Maximum tolerated dose |
| NSCLC | Non-small cell lung cancer |
| PMCI | Peter MacCallum Cancer Institute |
| PS | Performance status |
| SCC | Squamous cell carcinoma |
| SVC | Superior vena cava |
| UICC | International Union Against Cancer |
| VA | Veterans Administration |

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**Abstract**

The role of radiotherapy in the management of non-small cell lung cancer [NSCLC] is controversial. Although radiotherapy has a well-established place in the palliation of symptoms in patients with advanced disease there is still argument as to whether or not radiotherapy is capable of influencing survival in patients who are unsuitable for resection. There is only a limited amount of data from randomised trials in which radiotherapy has been compared with " best supportive care" in patients with NSCLC limited to the primary site and regional lymph nodes. These studies have shown either a small survival advantage for radiotherapy or no benefit; none has shown a detrimental effect. Although increasing dose has been clearly identified with increasing response rates, there is very little evidence that this has resulted in detectable improvements in survival. This is a paradox, since any treatment method which, like surgery, improves local control in NSCLC ought, based on first principles, to result in improved survival, *unless* it is associated with toxicity severe enough to counteract any beneficial effect of improved local control.

To examine the proposition that higher doses of radiotherapy might be associated with longer survival in patients with non-metastatic NSCLC we analysed the survival outcomes for patients treated with a variety of radiotherapy doses according to a standardised policy and using modern treatment planning and delivery techniques. A large prospective database provided the material for this part of the study. Between 1984 and 1990 demographic and prognostic details were collected at the time of first consultation on 4123 patients referred to Peter MacCallum Cancer Institute [PMCI] with a diagnosis of lung cancer. Using multivariate analysis the most influential prognostic factors were determined for 920 previously untreated patients with non-small cell lung cancer [NSCLC] whose disease was confined to the primary site and intrathoracic lymph nodes. The survivals of patients planned for low and high doses

of radiotherapy were compared after adjustment for the effect of the most significant prognostic factors. The most important prognostic factors were performance status and weight loss. After adjusting for the influence of these factors patients planned to have the highest dose [60 Gy] had significantly better survival than patients planned to have the lowest dose [20 Gy]. The result of this study was thus consistent with the original hypothesis and so provided justification for the continuing use of a dose of 60 Gy in the radical treatment of selected patients with NSCLC. Although 60 Gy has become a standard radical dose internationally, there is probably no better evidence in support of its use than the results from the Peter MacCallum database. Part one of the thesis is devoted to a detailed account of this study.

During the 1980's efforts to improve survival in patients with unresectable NSCLC disease have employed three broad radiotherapeutic strategies which have been tested in randomised trials using fractionated radiotherapy to a dose of 60 Gy or thereabouts as the standard treatment arm. These are: (a) dose escalation above 60 Gy; (b) combined chemotherapy and radiotherapy; and (c) shortening overall treatment time. The results of these studies have provided convincing evidence that the combination of chemotherapy and radiotherapy is more effective than radiotherapy alone, and supporting evidence that shortening overall treatment time improves survival. The two approaches probably work through different mechanisms and had not been compared directly or used in combination. In 1989 we began a randomised trial in which combined chemotherapy/radiotherapy and shortened treatment time were compared with one another as well as against standard therapy [60 Gy]. The trial closed in 1995 after 204 eligible patients had been randomised. Although none of the treatments had a statistically significant influence on survival compared with standard radiotherapy, the best survival was seen in patients having combined chemotherapy and radiotherapy. There was no suggestion of a benefit for shortening overall treatment time. The results of this trial thus

support the hypothesis that the addition of concurrent platinum based chemotherapy to radical radiotherapy [60 Gy] may provide at least a similar, if not greater, survival advantage to that achievable by shortening overall treatment time. There has been no other randomised trial in which the two new major treatment strategies have been compared directly. Part two of the thesis is devoted to a detailed account of this study.

# Part 1.

# Radiotherapy dose studies in non-small cell lung cancer

## 1.1 History and background: definitive radiotherapy for non - small cell lung cancer [NSCLC]

Before the Second World War lung cancer was relatively uncommon and the most effective treatment was unknown. Writing in 1932, Pancoast and Pendergrass described the state of knowledge at the time: 'Carcinoma of the lung is either increasing in frequency or it is being diagnosed more often. The accepted forms of therapy have been either surgery or irradiation, or a combination of the two procedures. Good results have been reported from radiation therapy, but for the most part, the results have been discouraging.' [1] Subsequently, with improvements in thoracic surgery, the role of radiotherapy was relegated to the treatment of patients deemed unsuitable for surgery. Patient selection thus favoured survival in surgically treated individuals. Yet there was good evidence that radiotherapy was not only active against lung cancer but that it was also capable of achieving histologically confirmed complete responses. In 1955 Bromley and Szur reported on 66 patients with a pathologic diagnosis of lung cancer who had been treated with high dose radiotherapy [intended dose 5000-5500r in five to six weeks using kilovoltage equipment] and who had then proceeded to surgery [2]. In 24 [46.7%] no tumour was identified in the resected specimen and in a further 14 [22.5%] tumour was said to be present but degenerate. Eleven patients had oat cell carcinoma and since it is not stated how many of these were disease-free at operation the result cannot be taken to apply exclusively to non-oat cell carcinoma, although at the very least 13 [19.6% of 53] of the complete responders must have had NSCLC.

The apparent superiority of surgery was challenged in 1956 by Smart and Hilton who reported a 32% actuarial survival at five years in a cohort of 33 resectable patients treated by

radiotherapy alone [5000-5500r for patients with squamous cell carcinoma and 4000-4500r for anaplastic histology over seven to eight weeks][3]. This was an exceptional result [even by today's standards], comparable with contemporary survival figures reported for patients treated surgically in the 1950's. They concluded 'that radiotherapy in selected cases may be an adequate alternative to surgery'.

The issue of surgery versus radiotherapy was finally resolved by a randomised trial which was to have a profound effect on the modern management of patients with operable lung cancer[4]. In this trial, conducted at the Hammersmith Hospital between 1954 and 1958, patients with all histologic types of lung cancer were randomized either to treatment with radiotherapy [megavoltage irradiation, 4500 rad in daily fractions over four weeks] or to surgical resection. Eligibility criteria included age under 70 years, 'fairly good general health', no evidence of spread to the mediastinum or areas outside the chest and fitness to undergo pneumonectomy. Of the 58 patients treated, 19 had oat cell or anaplastic tumours. Twenty eight patients were treated with radiotherapy and 30 with surgery. Although survival favoured the radiotherapy group at one year [64% vs 43%], at four years it was in favour of the surgically treated patients [23% vs 7%]. The difference was said to be 'almost' significant at the 5% level. If the survival analysis was restricted to patients with squamous histology there was a significant advantage in favour of the surgery patients [four year survival 30% vs 6%, $p = 0.05$]. Although a small trial, it was well conducted and survival was analysed according to intention to treat rather than treatment received. If the trial were to be repeated today, restricted to patients with early stage [I and II] disease and non-small cell histology, there is no reason to believe that a similar result favouring surgery would not be obtained again, and resection has become standard therapy for patients with operable NSCLC.

The Hammersmith study design did not include a 'no treatment' control arm, and it has been argued that the result does not therefore constitute evidence that surgery is better than no treatment at all[5]. However it seems unlikely that a trial designed to directly answer this question would ever win ethics committee approval, since in a non-randomised study the survival of patients with stage I disease detected by screening who did not undergo surgical resection was vastly inferior at five years compared with that of patients who did [10% versus 70%, p=0.02 ][6]. The inference to be drawn from the emergence of surgical resection as standard treatment is that local disease control must be important for survival in a sizeable proportion of patients with early NSCLC. In support of this notion are the results of a randomised trial conducted by the Lung Cancer Study Group[7]. Patients with T1 N0 NSCLC were allocated to either lobectomy or limited resection. Local control was significantly inferior in patients randomised to limited resection and although this was associated with a 30% increase in death rate, the difference did not achieve statistical significance [p=0.08].

If radiation therapy is capable of achieving complete responses[2], and presumably local cure, it too should have a favourable effect on survival compared with no treatment at all. This hypothesis was first tested in a large randomised trial conducted by the Veterans Administration Lung Cancer Study Group in the United States[8]. Male patients with medically or technically unresectable lung cancer, pathologically proven and confined to one hemithorax, were randomised either to radiotherapy or placebo [lactose]. The result, originally published in 1966, appeared to confirm the original hypothesis, with 18.2% of patients in the radiotherapy arm alive at the end of one year compared with 13.9% in the control arm. Because the number of patients involved in the comparison was large – 554 – the difference in the survival curves, though small, was statistically significant at the level p = 0.05. There are a number of aspects of this study which lessen its relevance to modern practice. The randomisation procedure did not apparently stratify for known prognostic factors, and there

are some imbalances in the arms with the control arm having a smaller proportion of patients with small cell histology and a greater proportion with poor performance status. Although patients with small cell histology were included, there were no differences in survival between control and radiotherapy arms in this subgroup; the only differences were observed in patients with NSCLC. The report provided no information about tumour stage, other than patients with palpable supraclavicular nodes or disease beyond one hemithorax being ineligible. Finally, the radiotherapy was given in 90% of cases using now outmoded kilovoltage equipment, to a tumour dose of 4000 to 5000 r in four to five weeks. In spite of its deficiencies, the result of the Veterans Administration study provided the evidence for the adoption of radiotherapy as standard management of inoperable NSCLC, and led to a new generation of randomised trials - on one side of the Atlantic at least.

British practice, on the other hand, was heavily influenced by a smaller trial of similar design, conducted in Oxford, and reported in *The Lancet* in 1971[9]. Two hundred and forty nine patients with inoperable lung cancer, including small cell histology, were randomised to one of four policies: wait-and-see; radiotherapy [4000 rad in 13 or 14 fractions or biologic equivalent]; chemotherapy alone [mustine]; and a combination of the same radiotherapy plus chemotherapy. Pathologic confirmation of diagnosis was not an eligibility criterion for study entry with 21% having no histology, and a further 18% having small cell lung cancer. No pretreatment information on prognostic factors such as disease stage and performance status was included in the report. Not one patient survived more than four years; mean survivals for each of the policy arms were approximately eight months with no differences whether treatment was given immediately or the approach was wait-and-see. The small number of patients actually known to have NSCLC, the heterogeneity of the patient population, the modest doses of radiotherapy and the overall poor survival suggesting a high incidence of adverse prognostic factors all render the result of this study irrelevant to modern policies of

management of NSCLC. But the failure of the Oxford study to show an influence of immediate radiotherapy on survival did have one powerful effect: it created a generation of therapeutic nihilists and resulted in a virtual disappearance of prospective studies of radical radiotherapy for NSCLC from the British scene.

The importance of non-treatment related prognostic factors as critical influences on survival – essentially ignored by the Oxford triallists – was emphasized by Stanley in an extensive analysis of the Veterans Administration Lung Group protocols spanning the period 1968-1978[10]. Seventy seven factors were considered in 5138 male patients. Performance status, as measured using the Karnofsky scale, was the most influential factor, followed by disease extent and weight loss. The reliability and independence of these three factors has been confirmed as recently as 1996 in a consensus report of a workshop conducted by the International Association for the Study of Lung Cancer [IASLC][11]. To quote Stanley: 'Reporting of results without the consideration of such strong prognostic factors severely hampers any comparisons between investigations and will yield virtually meaningless results in many circumstances.'[10] Clearly, the next generation of trials would need to incorporate these factors both in trial design [eligibility and pre-randomisation stratification] and in interpretation of results.

In 1973, the Radiation Therapy Oncology Group [RTOG] in the United States commenced a randomised trial [73-01] for which the earlier Veterans Administration study provided the foundation. In essence 73-01 was a comparison of the effect of four different radiotherapy dose schedules on response and survival in inoperable NSCLC. That radiotherapy was beneficial was implicit – there was no control arm. The first report of the results of this study was published in 1980[12], and further publications followed in 1982[13] and 1987[14]. Patients with inoperable stage III NSCLC were eligible provided they had a Karnofsky performance status

of 40 or greater. Before randomisation patients were stratified according to institution, histology and performance status. In contrast to the VA study, all patients were treated with megavoltage irradiation [cobalt-60 or higher energy] and radiotherapy protocol compliance was rigorously assessed[13]. The randomisation was either to 40 Gy in four weeks [split course], 40 Gy in four weeks continuous, 50 Gy in five weeks continuous or 60 Gy in six weeks continuous. A total of 365 patients were eligible for analysis. Patients randomised to the split course had a significantly lower complete response than the continuous dose groups [8% vs 20-24%, $p < 0.02$] and a higher probability of intrathoracic recurrence. Although patients randomised to the highest dose [60 Gy] had the highest response rate and the best survival, there were no statistically significant differences in survival between arms.

How can we explain the failure of a clear dose-response relationship as demonstrated in 73-01 to translate into a survival effect? Competing risks for death which include metastatic disease, treatment toxicity and serious comorbidities will clearly diminish the power of a study of the size of 73-01 to detect an influence of local disease control on survival. Distant metastases developed in 72% and 79% of patients with squamous cell and adenocarcinoma/ large cell histologies respectively[14]. In some of these patients, better local control may have *delayed* death by averting fatal intrathoracic complications before the dominant risk of death shifted to metastatic disease, but all will ultimately die regardless of how successfully local control had been achieved.

The second possible explanation for the observed lack of an effect of local control on survival – treatment related toxicity – is not supported by the reported incidence of severe complications. Although the highest dose [60 Gy] produced the best response, it might also be expected to be associated with the highest risk of fatal complications, offsetting any survival

advantage resulting from improved local control. In fact no treatment related deaths were reported for any of the four dose levels[12].

The 1982 report of 73-01 drew attention to a further factor confounding any analysis of the effect of dose on local control: the importance of tumour size[13]. In Stanley's analysis of the Veterans Administration data, tumour size was not ranked in the top 25 prognostic factors, but the number of cases for which adequate information was available for analysis was small[10]. Tumour size was not acknowledged to be an independent prognostic factor in the IASLC consensus report, although TNM stage was[11]. However, the stage grouping III, based on the TNM classification, has never placed restrictions on the allowable size of the primary tumour[15], even though most stage III patients are treated by radiotherapy. It is a fundamental principle of radiobiology that the probability of controlling a tumour by a given dose of radiation diminishes as the size of the tumour increases[16]. In 73-01, the intrathoracic recurrence rate decreased with increasing dose if the tumour was less than six cm in diameter; but for larger tumours dose had no effect on local control[13]. These results are in line with classical radiobiologic thinking, and with observed tumour control probability curves obtained for other irradiated epithelial cancers[17]. It could be argued that the inclusion of patients with the largest tumours [> 6 cm, 12% of the total number randomised] weakened the power of 73-01 to detect a survival advantage for patients treated with the higher doses, since the $TCD_{50}$ [dose of radiation required to control 50% of tumours] for most of these cancers was probably well above the range of doses studied.

RTOG 73-01 was the most important study in NSCLC published in the 1980's, and it has had a lasting influence on the practice of thoracic radiation oncology, especially in the USA. It established the importance of dose in obtaining local tumour control, and the safety of giving higher doses. If we concede that many patients could never have obtained a survival

advantage from improved local control because of the competing risk of metastatic disease, and that others had tumours too large to be controlled by any of the doses used, then the small difference in survival at three years [15% for patients randomised to 60 Gy compared with 6% for patients randomised to 40 Gy], although not statistically significant, may nevertheless have been real, demonstrable as being significant only by a larger trial, or in a trial using tighter eligibility criteria. Thus did the result of an inconclusive trial provide the justification for the routine use of 60 Gy in 30 fractions over six weeks as therapy for unresectable NSCLC localised to the primary site and regional nodes. In the Lung Unit of the PMCI, we adopted the same dose and fractionation schedule as the basis of our radical treatment policy for selected patients with NSCLC from the early 1980's onwards, and systematic data collection on all patients began in 1984.

## 1.2 Treatment Policies of the Peter MacCallum Lung Cancer Unit 1981 –1995.

**Historical background**. Until 1981, the overriding philosophical approach to the treatment of NSCLC cancer at PMCI was one of palliation, in line with the standard teaching of the British school of the time. It was an approach strongly supported by the respiratory physicians, mostly British trained, who played the major role in the diagnosis of lung cancer and subsequent referral for treatment. After diagnosis, patients with disease localised to the chest were often observed if they had no symptoms, but if they developed a cough, haemoptysis or airways or superior vena caval obstruction, they were referred for a short course of palliative radiotherapy. The standard course of treatment was an empirical regimen consisting of 30 Gy given as ten treatments, treating three days per week; the patient's progress was reassessed at 30 Gy, and if there had been no adverse effects, a further two treatments were given to a total of 36 Gy. In the selection of patients for treatment, little account was taken of prognostic factors such as stage and performance status, since the radiotherapy prescription seldom varied and higher doses were rarely used. The treatment planning procedure was simple: patients were simulated in a chair and treated with anterior and posterior fields with a non-isocentrically mounted 4 Mv linac. Experience had shown that this dose and technique was within spinal cord tolerance, and that dysphagia due to radiation oesophagitis was the main acute untoward effect. If higher doses were prescribed, the spinal cord was excluded from the treated volume by the use of lateral fields [determined by conventional simulation] but because this usually resulted in the treatment of a large volume of normal lung, to reduce the probability of radiation pneumonitis the additional dose was limited to a further 9 Gy, that is a total dose of 45 Gy in 15 fractions.

**Patient selection after 1981**. In 1981, I was appointed head of the Lung Unit at PMCI and I determined to establish management policies for NSCLC that were based on the best evidence

available at that time. In this process the recently published studies of Stanley[10] [prognostic factors] and the RTOG[12] [the 73-01 dose response study] were pivotal.

If we were going to adopt the higher dose policies of RTOG 73-01, selection of patients based on favourable pretreatment prognostic characteristics seemed essential. The three most important prognostic factors identified by Stanley were, in order, performance status [Karnofsky scale], extent of disease, and weight loss [10]. Rather than use the more elaborate ten point Karnofsky scale, we decided to use the Eastern Cooperative Oncology Group's [ECOG] simpler five point scale to measure performance status[18] [Table I]. In essence this enabled patients to be divided into two groups: ambulatory [ECOG 0 – 1], or otherwise [ECOG 2 – 4]. Initially, only patients with performance status zero to two were deemed suitable for a radical treatment approach, but in time this was restricted even further to those patients whose performance status was strictly ambulatory.

**Table I. Performance status scale of the Eastern Cooperative Oncology Group [18]**

| | |
|---|---|
| 0 | Asymptomatic, activity unrestricted. |
| 1 | Restricted in physically strenuous activity, but able to carry out light work. |
| 2 | Capable of self care but unable to work, up and about more than 50% of waking hours. |
| 3 | Capable of limited self care, confined to bed or chair more than 50% of waking hours |
| 4 | Incapable of self-care, bedridden. |

Weight loss is a loosely defined prognostic parameter relying in most cases on patient memory. It should be characterised according to amount and duration, but in the absence of standard definitions we arbitrarily chose our own criteria. In Stanley's study, weight loss was defined as less than or greater than ten pounds[10]. We grouped our patients into one of three categories: no loss of weight, less than ten per cent in the preceding three months, and loss

greater than ten per cent. We excluded patients from a radical treatment policy if their weight loss exceeded ten per cent.

The winnowing process thus applied distinguished patients for whom further staging procedures were appropriate to establish disease extent: patients with poor performance status [ECOG 2-4] and/or weight loss greater than ten per cent were not subjected to further investigation unless there was a clinical indication. These individuals were regarded as suitable for palliative treatment only, and they were treated only if they had symptoms thought likely to benefit from a short course of radiotherapy. It is notable that this major fork in the management decision algorithm can be reached by simple history-taking without the need for extensive investigation.

Patients with good performance status [ECOG 0 and 1] and with minimal [<10%] or no weight loss were then selected for radical treatment if they had no evidence of metastatic disease, based on history and physical examination, chest x-ray, CT scan of the chest and upper abdomen and nuclear bone scan. Patients with adenocarcinoma or large cell undifferentated histology were also staged with a CT scan of the brain. If there was any evidence of metastatic disease, patients were treated palliatively according to symptoms. This included patients with involvement of any cervical lymph nodes.

If the staging investigations confirmed that the disease was localised to the primary site with or without involvement of regional [hilar and mediastinal] lymph nodes, a decision was made in consultation with the thoracic surgeon whether the disease was resectable. If technically possible surgical resection was recommended to patients if they had adequate lung function and were fit for a thoracotomy. Thus the majority of patients with stage I or II disease had

operations, and those with early stage disease not fit for surgery were treated with radical radiotherapy.

Patients with radiologic or mediastinoscopic lymph node involvement were generally treated with radiotherapy, based on a belief, since confirmed by Shields, that such patients, if treated surgically, have a poor outcome with five year survival rates in the region of 2%[19]. Mediastinoscopy was not routinely used, and in some patients mediastinal lymph node involvement was found incidentally at the time of resection. Postoperative radiotherapy was routinely given to patients whose disease was incompletely resected, or in whom there was evidence of lymph node involvement.

**Radiotherapy technique and dose.** Before 1981, the standard dose of radiotherapy for the majority of patients with lung cancer at PMCI, 30 or 36 Gy given in ten or twelve fractions, treating three days a week, resulted in unnecessary protraction of treatment, particularly for patients with poor performance status in whom the goal of treatment was palliation. Nevertheless, the total dose was one in common use throughout the international radiation oncology community for the palliation of symptomatic disease at other sites, notably bone and brain. In an effort to shorten treatment times without any loss of palliative efficacy, increasing hypofractionation was explored in two randomised trials conducted by the Radiation Therapy Oncology Group in patients with bone[20] and cerebral[21] metastases. These studies did in fact show that regimens of 20 Gy given in five fractions over a week were as effective as longer courses. There seemed no reason why a similar schedule should not also be used for the palliation of symptoms due to primary lung cancer. The choice of palliative regimen was left to the treating clinician, but from 1981 on there was increasing use of 20 instead of 30 Gy, particularly in patients with poorer performance status, and all patients were now treated five instead of three days per week, regardless of total dose. A clinical impression, not quantified

but not unexpected, that the degree of oesophagitis was less with the lower dose may have progressively increased its popularity.

Most palliative patients were treated sitting in a chair with the non-isocentrically mounted 4 Mv linac at 100 cm FSD, using anterior and posterior parallel opposed fields. These patients were simulated in the diagnostic radiology suite as there was no facility for filming patients in a chair using the dedicated radiotherapy simulator. The target volume consisted of the primary tumour and ipsilateral hilar and mediastinal lymph nodes [whether involved or uninvolved] with a margin of 1.5 – 2.0 cm. The field to encompass this volume was marked directly on the a-p radiograph. The dose was calculated at the midplane without correction for tissue inhomogeneities.

Patients for whom radical radiotherapy was recommended were planned for a dose of 60 Gy in 30 fractions over six weeks. The planning of these patients involved a higher level of precision, and was CT-based. The target volume was similar for palliative patients: the primary lesion and the ipsilateral hilar and mediastinal nodes to the level of the sternal notch using a margin of 1.5 – 2 cm. All nodes thought to be involved [generally those whose greatest diameter was more than 1cm] were included and this may have required extension of the target volume to include the contralateral mediastinum, since patients with N3 disease were not excluded from radical treatment unless the involved nodes were in the supraclavicular region. Where there was no radiological evidence of nodal involvement, only the ipsilateral hilar and mediastinal nodes were electively irradiated.

The planning process involved both conventional simulation, and the acquisition of at least three CT images of the thorax with the patient supine in the treatment position, with arms above the head. Contrast was not used. The levels at which the CT images were obtained were

based on the anticipated upper and lower limits, the central axis and the slice containing the maximum tumour dimension, if this was not the central axis. These levels were chosen from the conventional simulator radiograph, which had to be obtained beforehand. The CT images were transferred to the Theraplan planning system, and the target volume was contoured based on the maximum tumour dimensions on the central axis. At that time three dimensional reconstuction of the CT image allowing beam's eye view analysis of the target volume was not available, and so interpolation of the target volume between the limited number of contoured slices was necessary. Nevertheless, CT- assisted planning enabled three significant advances beyond conventional simulation/planning: better definition of the gross tumour volume [especially in the mediastinum]; dose correction for tissue inhomogeneities; and the ability to choose an angled beam arrangement to avoid the spinal cord, rather than having to use direct lateral beams which usually irradiate excessive volumes of normal lung. Any blocks to be placed in the beam were drawn on the a-p simulator film, and the position of the spinal cord for shielding purposes [for any oblique field arrangement] was defined by interpolation between its position on the upper level and central axis CT slices. Because of the lack of a beam's eye view reconstruction, no other shielding was possible on the oblique field.

An example of the process is illustrated on the following three pages. Figure 1 shows a conventional ap/pa simulation film with shielding added. A port verification film for the same patient is shown in Figure 2. The dose to the spinal cord was kept at 45 Gy or below; to enable this, the first four weeks of treatment were given with ap/pa isocentric fields to a total of 40 Gy in 20 fractions; the final 20 Gy were given in 10 fractions using a parallel opposed pair of obliques angled so as to avoid spinal cord. This is demonstrated in Figure 3 which shows the central axis CT image with the target volume delineated and a superimposed isodose plot resulting from a pair of parallel opposed oblique beams.

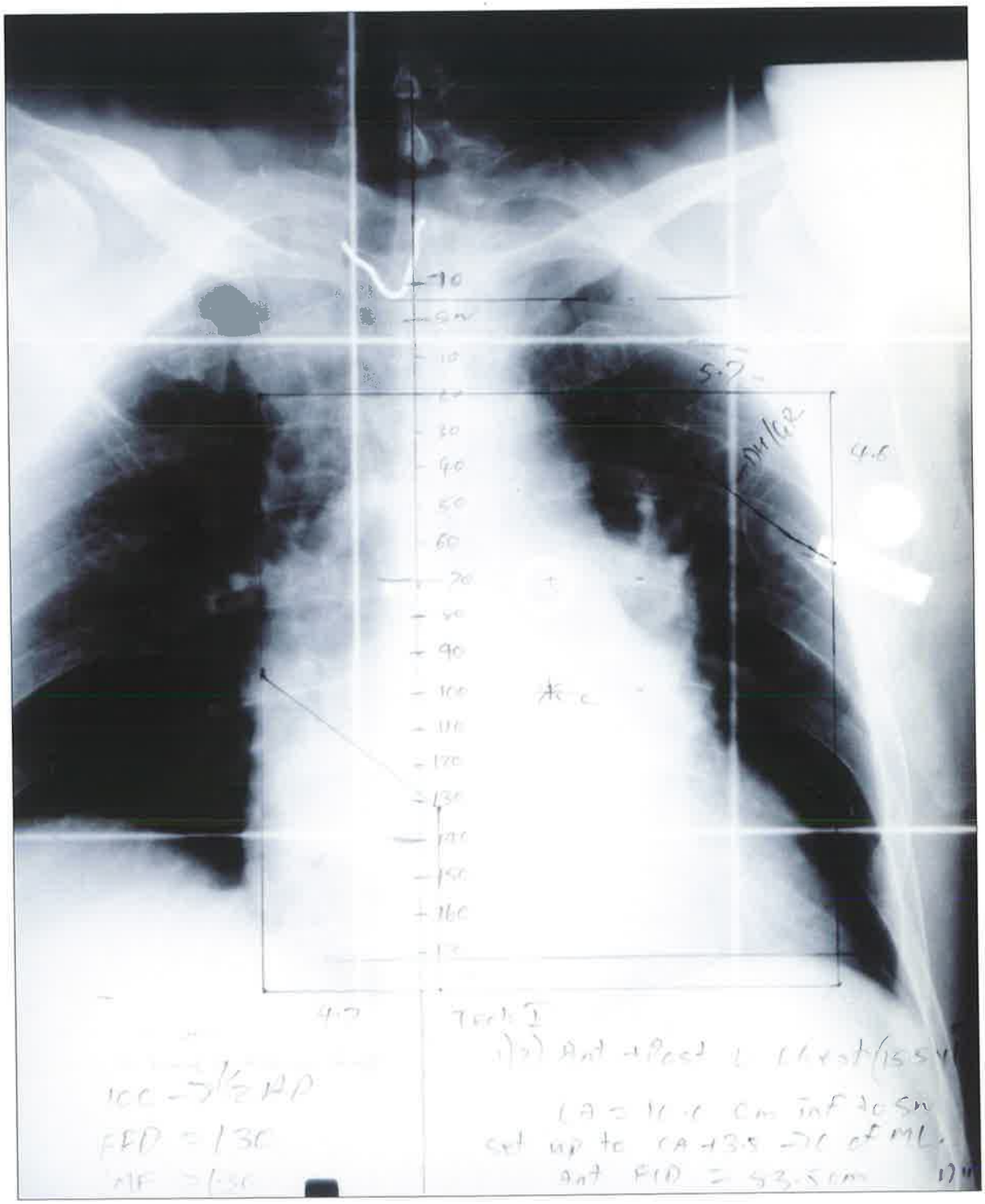

**Figure 1. AP/PA simulation film for patient having radical radiotherapy.**

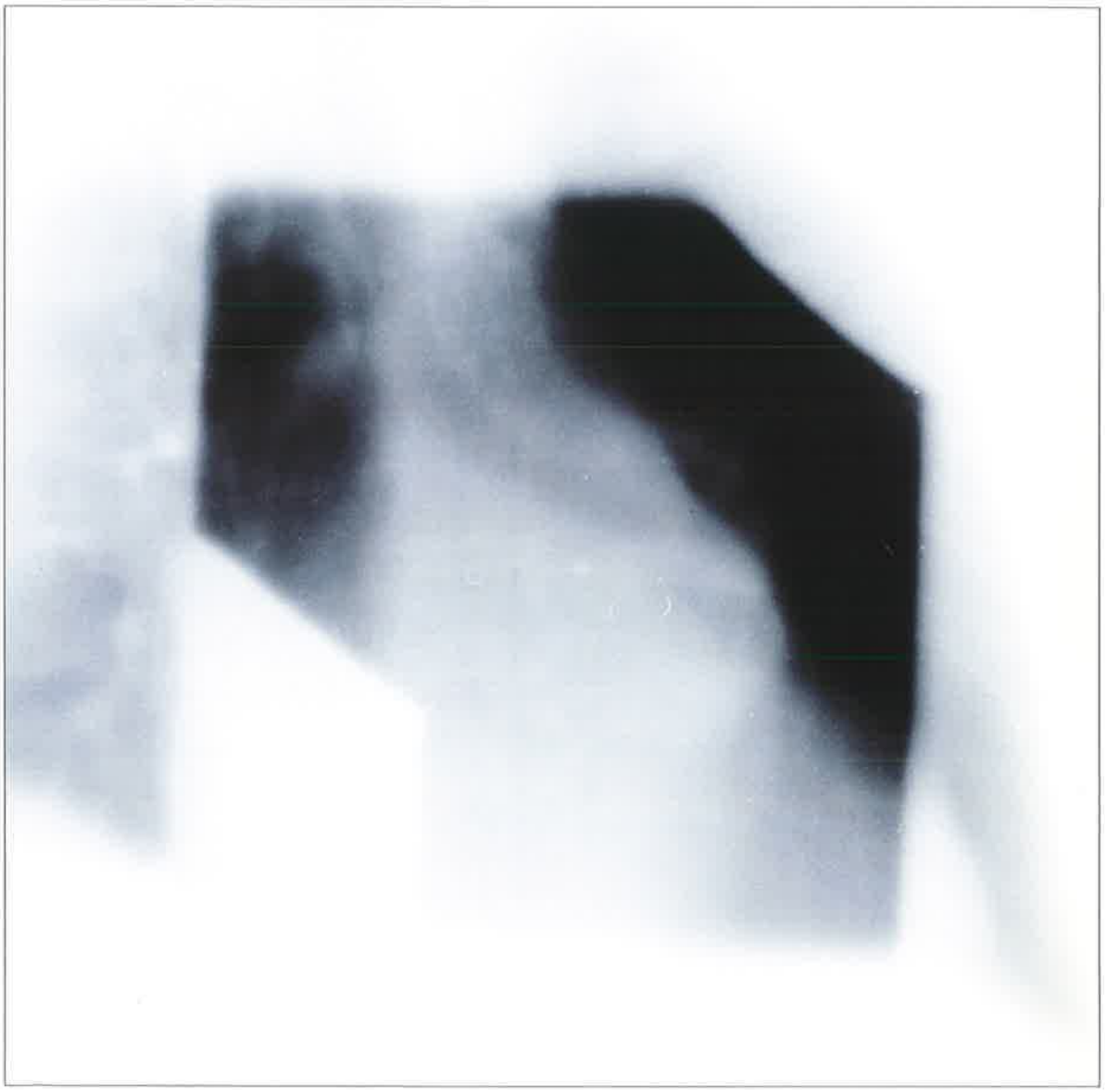

**Figure 2. AP/PA treatment verification film for same patient as in Figure 1**

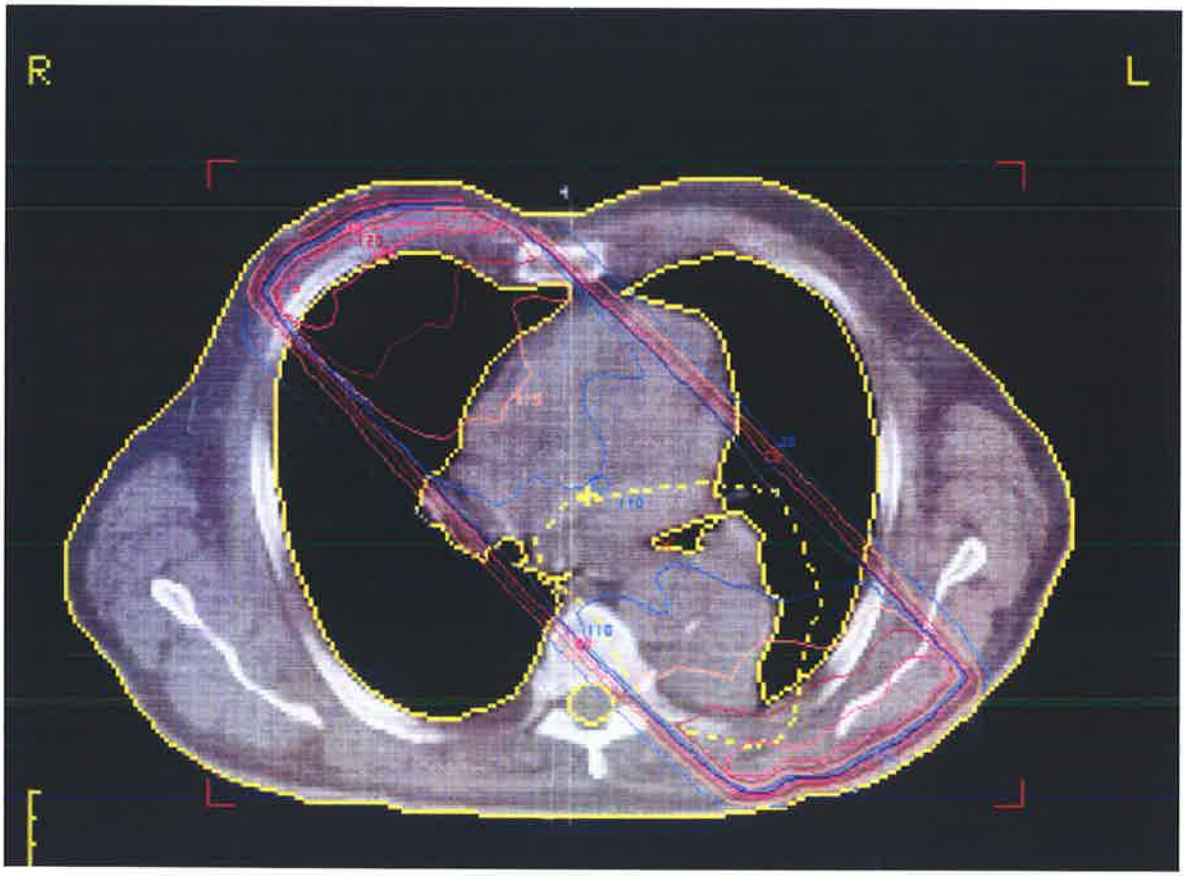


**Figure 3. Central axis planning CT image with target volume indicated by interrupted yellow line. The isodose plot for a pair of parallel opposed obliques angled to avoid spinal cord is superimposed.**

Sometimes, if the contribution to cord dose was unavoidably excessive from the oblique fields, the change in technique was made two or three fractions earlier. All doses were corrected for the effect of tissue inhomogeneities. The prescribed tumour dose was selected using the isodose which allowed for a variation of plus or minus five per cent within the target volume on the central plane. Check films were taken with the treatment machine during the first week of treatment for each phase [ap/pa and obliques] to verify patient and beam position. Patients were reviewed weekly by a radiation oncologist while on treatment, and medications prescribed as required for acute side effects, such as nausea and vomiting, dysphagia due to oesophagitis etc. If there was a decline in performance status during treatment to a level of ECOG two or greater, a treatable cause was sought, for example, infection, but if the decline was attributable to the effects of radiotherapy, consideration was given to truncating treatment at a lower dose than planned.

In 1989 we started treating patients according to a phase III trial protocol which is described in detail in section 2.3. Patients who did not meet the eligibility criteria for randomisation but were still suitable for radical treatment continued to be treated off protocol in the same way as before. During the 1990's there was a gradual increase in the use of three-dimensional planning with beam's eye view reconstruction of the target volume and the use of more conformal shielding, but these developments came after the closure of the database.

**Follow up.** After completion of treatment, patients were followed regularly at two monthly intervals with a physical examination and chest x-ray. Recurrent disease at the primary or metastatic sites was treated palliatively as required, mostly by radiotherapy. Even those patients who had previously been given a radical course of treatment [60 Gy] were given further radiotherapy for biopsy proven local recurrence if it was felt their symptoms warranted

it. We were able to show that many of these patients obtained symptomatic benefit with low doses of palliative irradiation to previously treated sites with little risk of serious treatment related complications[22]. Chemotherapy was rarely given during the study period outside a trial setting since there was at that time no evidence to support its routine use as a palliative treatment[23]. Surgery was used as appropriate, for example, decompression of acute spinal cord compression. Laser surgery was used for major airways obstruction by endobronchial tumour from 1986 onwards[24].

## 1.3 The PMCI Lung Cancer Database

### 1.3.1 Introduction.

After I was appointed head of the Lung Unit at PMCI, I began work on the development of a prospective database that would contain basic information on all new patients with lung cancer referred to the Lung Unit and to my private practice within the Institute. The database was designed, not with any specific hypothesis in mind, but to capture: [a] information that was known or thought potentially to be of prognostic significance: [b] details of treatment intent and treatment given; and [c] the outcome of treatment. It would thus act as a resource for audit and quality control, and provide a reservoir of information that could be tapped to address more specific but as yet unborn hypotheses in the future.

The forms for recording data were kept as simple as possible to ensure good compliance from the Lung Unit clinicians who were expected to complete Form A [History and Examination] on the first day that the patient presented to PMCI. Treatment intent was also recorded on Form A. Form B, documenting details of radiotherapy treatment, was completed by the MRA, Tina Worotniuk, four to eight weeks after the end of radiotherapy. Form D recorded date of

death and Form E, date of last contact and any delayed complication of treatment; these forms were also completed by the MRA. A copy of the forms is included in Appendix A.

The information documented on Form A is shown in Table II. As well as containing essential demographic information such as sex, age, date of diagnosis, date first seen at PMCI and histologic subtype, the form also recorded smoking history, previous treatment and extent of disease including anatomical sites of involvement. Information on the most important prognostic factors identified by Stanley[10] were collected, namely performance status, weight loss, malaise and symptoms of metastatic disease. Performance status was recorded according to the Eastern Cooperative Oncology Group's scale[18] which was chosen because of its greater simplicity and more universal usage in comparison with the Karnofsky scale.

In contrast to Stanley's 77 separate prognostic factors[10], we collected information in only 18 categories. Nevertheless, the most important factors identified by Stanley [performance status, extent of disease, weight loss and systemic symptoms] were collected as were two of the three factors [performance status and weight loss, but not TNM stage] deemed to be of *definite* prognostic significance in NSCLC by the consensus group of the IASLC [11]. Of the seven factors thought to be of *possible* significance by the IASLC group, we collected information on three [sex, histology and age, but not LDH, albumin, haemoglobin and other biologic factors e.g. ploidy, p53 mutations etc.]. The major deficiency therefore in our dataset is the absence of TNM stage, or more precisely, information on T stage and some N stage characteristics [involvement or otherwise of hilar and/or mediastinal nodes]. The presence of metastatic disease [M stage] and supraclavicular nodal involvement [N3] were however recorded.

**Table II. Prognostic factors recorded in the Peter MacCallum Lung Cancer database**

| |
|---|
| Age |
| Sex |
| Histology |
| Smoking history |
| Duration of symptoms |
| Symptoms/signs of locoregional disease |
| Symptoms/signs of metastatic disease |
| Malaise |
| Performance status [ECOG] |
| Weight loss [three months before diagnosis] |
| Paraneoplastic syndrome |
| Pleural effusion |
| Pericardial effusion |
| Superior vena caval obstruction |
| Location of primary [laterality, apical or otherwise] |
| Cervical node involvement |
| Sites of distant metastases [bone, brain, liver, adrenal, lung, kidney, skin] |
| Spinal cord compression |

The omission of TN stage from the design of the database was not an oversight but a deliberate decision based on our experience of the considerable variation in staging procedures from patient to patient. For the majority of patients with poor performance status or known metastatic disease, TN status is irrelevant from a management point of view, and its prognostic influence is subsumed by the more powerful effect of the other factors. Hence such patients are likely to have had the extent of their locoregional disease assessed by a chest X-ray, a technique with low sensitivity for the detection of hilar and mediastinal lymphadenopathy or extent of the primary. At the other end of the spectrum are those patients who have not only had a thoracic CT scan but who have gone on to have histopathologic staging at thoracotomy. If a standard staging protocol had been applied to all patients there might have been some justification for assigning a TNM stage in every case, but staging procedures varied from the minimal to the exhaustive depending on performance status, clinically evident extent of disease etc. The more thoroughly patients are staged the better the prognosis of patients within a given TNM category - the so-called Will Rogers phenomenon[25]

- with the result that variations in staging protocol can be associated with changes in survival that are mistakenly attributed to treatment effects. In any event a major revision of the staging system was published in 1986, during the period of data collection, and so any analysis of the data involving TNM stage would have required two separate analyses according to whether staging was based on the old system or on Mountain's revision [26].

We did give consideration to recording the size of the primary tumour, a potential prognostic factor in patients treated with radiotherapy [17]. Interestingly the TNM system makes only one reference to tumour size: T1 must be 3 cm or less but T2 – 4 can be *any* size. In retrospect, information on tumour size may have been extremely valuable, particularly in a group of patients treated predominantly by radiotherapy, but at the time a number of difficulties were foreseen and in the end it was removed from the draft. These difficulties included: (a) distinguishing tumour from adjacent collapse, consolidation or pleural fluid; (b) defining the medial limit of tumour extension into the mediastinum, particularly in patients staged by chest x-ray without CT scan; and (c) differences in measurements depending on whether they were made in a vertical [chest x-ray] or horizontal [chest x-ray and CT scan] plane. Finally, we assumed that in the large group of patients who already had distant metastatic disease any relevance of primary tumour size would be largely overshadowed by the prognostic influence of metastatic site and total disease burden.

The first patient was added to the database on 9/1/84 and the last on 23/3/90. When the database was closed to new patients it contained information on a total of 4123 patients in 68 fields stored on Microsoft Access 97 ®.

**1.3.2. Patient characteristics.**

Table III provides a list of demographic characteristics for all patients in the database. Patients were classified as smokers if they had ever been regular smokers for any period of their life, for whatever duration and no matter how long before the diagnosis of lung cancer. Not all patients had a histologic diagnosis, but in only a small proportion was the diagnosis based on clinical grounds alone. A disappointingly large proportion of patients [15.3%] did not have their performance status recorded, usually because of poor compliance by the clinician completing the data forms. Metastatic disease was said not to be present if the patient had no symptoms or physical signs of metastases, or if there was no evidence of spread of disease after the completion of staging at PMCI. Involvement of cervical lymph nodes was not classified as metastatic disease, although it had been designated as such [M1] prior to the 1986 revision[26].

Approximately three quarters of the patients were male and the median age of the group was 66.2 years. The women had a younger median age than the men [64.7 versus 66.6 years]. A significantly greater proportion of the females were under the age of 50 compared with the males [9.25% vs 5.58%, $p < 0.01$]. There are two possible explanations for this observation. Because smoking became socially acceptable and more prevalent among women at a later time in comparison with male smoking habits, then the cohort of females who have lung cancer resulting from smoking will be younger than the male cohort, assuming equal susceptibility of the sexes to the carcinogenic effects of tobacco smoke. Alternatively, the differences observed may be due to an increased susceptibility of women to carcinogens, such that they have to smoke less than men as measured by pack-years to achieve the same level of risk. Although the findings from various studies designed to address the question of whether women are more susceptible are not consistent, the results of a recent and well conducted case control study suggest they are.[27]

**Table III. Characteristics of All Patients**

| | | Number | % |
|---|---|---|---|
| Sex | Male | 3172 | 76.9 |
| | Female | 951 | 23.1 |
| Age | Median | 66 yrs | |
| | Range | 29 – 92 yrs | |
| Histology | Squamous cell | 1555 | 37.7 |
| | Adenocarcinoma | 818 | 19.8 |
| | Alveolar cell | 6 | 0.1 |
| | Small cell anaplastic | 623 | 15.1 |
| | Large cell Undifferentiated | 634 | 15.4 |
| | Unspecified | 344 | 8.3 |
| | Mixed histology | 65 | 1.6 |
| | Other | 35 | 0.8 |
| | Unknown | 43 | 1.0 |
| Smoking hsitory | Smoked | 3929 | 95.3 |
| | Never smoked | 140 | 3.4 |
| | Unknown | 54 | 1.3 |
| Previous treatment | Surgery | 474 | 11.5 |
| | Chemotherapy | 447 | 10.8 |
| | Radiotherapy | 84 | 2.0 |
| | Other | 99 | 2.4 |
| Performance status (ECOG) | 0 | 302 | 7.3 |
| | 1 | 1636 | 39.7 |
| | 2 | 895 | 21.7 |
| | 3 | 491 | 11.9 |
| | 4 | 170 | 4.1 |
| | Unknown | 629 | 15.3 |
| Weight loss | None | 1635 | 39.7 |
| | <10% | 1304 | 31.6 |
| | >10% | 827 | 20.1 |
| | Known but amount unspecified | 175 | 4.2 |
| | Unknown | 182 | 4.4 |
| Metastatic disease | Absent | 2086 | 50.6 |

The most common histologic subtype was squamous cell carcinoma [37.7%]. There were 3007 patients with NSCLC [squamous cell carcinoma, adenocarcinoma, and large cell undifferentiated carcinoma, but excluding patients with unspecified carcinoma] forming 72.9% of the total. The vast majority were or had been smokers. There were marked differences in the relative frequency of squamous cell carcinoma and adenocarcinoma between the sexes [Table IV]; these differences were statistically highly significant [$p < 0.0001$].

**Table IV. Distribution of histology according to sex**

| Histology | Male [n =3172] | [%] | Female [n = 951] | [%] |
|---|---|---|---|---|
| Squamous cell | 1308 | [41.2] | 247 | [26.0] |
| Adenocarcinoma | 567 | [17.9] | 251 | [26.4] |
| Small cell | 444 | [14.0] | 179 | [18.8] |
| Large cell undifferentiated | 478 | [15.1] | 156 | [16.4] |
| Carcinoma unspecified | 262 | [8.3] | 82 | [8.6] |

A smoking history was more common in patients with squamous cell carcinoma, and least common in women with adenocarcinoma [Table V].

**Table V. Proportion of patients with a smoking history according to sex and histology.**

| | Male | Female |
|---|---|---|
| Squamous cell carcinoma | 1284/1308 [98.1%] | 234/247 [94.4%] |
| Adenocarcinoma | 536/567 [94.7%] | 206/251 [82.1%] |
| Small cell | 436/444 [98.2%] | 168/179 [93.9%] |
| Large cell undifferentiated | 466/478 [97.5%] | 136/158 [87.2%] |
| Carcinoma unspecified | 255/262 [97.3%] | 66/82 [80.5%] |

The reasons for the differences in distribution of histologic type between the sexes are unclear, but may be related in part to evolving shifts in the pathology of lung cancer which have been observed in the United States. There, squamous cell carcinoma has been replaced by adenocarcinoma as the most frequent histologic type for both sexes[28]. This change has been attributed to changes in smoking habits and in particular the use of filtered cigarettes

which may permit deeper inhalation of carcinogens into the lung periphery where adenocarcinoma is more likely to develop [29, 30]. Unlike the US experience, squamous histology was still predominant among men in the PMCI database. In contrast adenocarcinoma was more common in women, who, forming a younger cohort, are more likely to reflect recently reported US trends in smoking habits and histologic distribution. Table VI shows the frequency of squamous cell carcinoma and adenocarcinoma according to age and sex.

**Table VI. Distribution of histology according to age and sex**

| Sex | Male | | | |
|---|---|---|---|---|
| Age cohort | <50 | 50 - 59 | 60 - 69 | >70 |
| Number | 177 | 626 | 1270 | 1099 |
| SCC | 37 | 227 | 515 | 529 |
| | [20.9%] | [36.6%] | [40.6%] | [48.1%] |
| Adenoca | 57 | 136 | 219 | 155 |
| | [32.2%] | [21.7%] | [17.2%] | [14.1%] |

| Sex | Female | | | |
|---|---|---|---|---|
| Age cohort | <50 | 50 - 59 | 60 - 69 | >70 |
| Number | 80 | 199 | 397 | 267 |
| SCC | 12 | 39 | 114 | 82 |
| | [13.6%] | [19.6%] | [28.7%] | [30.7%] |
| Adenoca | 42 | 60 | 81 | 68 |
| | [47.7%] | [30.1%] | [20.4%] | [25.5%] |

There is a clear increase in the proportion of patients with squamous cell carcinoma with increasing age in both sexes and a corresponding decline in the proportion of patients with adenocarcinoma. These data are also consistent with an increasing incidence of adenocarcinoma, being first observed in the youngest cohorts of patients, which suggests that with the passage of time adenocarcinoma may become the most common histology in men as well.

Of all the common lung cancer histologies the association between smoking and adenocarcinoma is the weakest, an observation from our own data [Table V] as well as

elsewhere[28], Even so, smoking remains the major cause of adenocarcinoma of the lung[30] and the vast majority of our patients with adenocarcinoma [90.7%] had a smoking history.

Whatever the underlying explanation, the changing histologic distribution of lung cancer may well have implications for the future management of patients with NSCLC, particularly in relation to the value of local therapies. Table VII shows the proportion of patients in each major histologic category who were free of symptoms or signs of distant metastatic disease after evaluation following initial presentation at PMCI.

**Table VII. Proportion of patients metastasis-free according to histology**

| Histology | Total | Number free of metastases | % |
|---|---|---|---|
| SCC | 1555 | 1003 | 64.5 |
| Adenocarcinoma | 818 | 327 | 40.0 |
| Small cell | 623 | 245 | 39.3 |
| Large cell undifferentiated | 634 | 287 | 45.2 |
| Unspecified | 344 | 149 | 43.3 |

A significantly larger proportion of patients with squamous cell carcinoma was metastasis-free compared with other histologic subtypes. It follows that a greater proportion of patients with SCC is in a position to benefit from local therapies, and that unless effective systemic therapies are found the majority of patients with non-squamous histologies will be incurable at diagnosis. The greater propensity for non-squamous tumours to recur was also evident in a Lung Cancer Study Group analysis of recurrences in 572 patients who had resection of early stage [T1N0M0] disease[31]. In this study 11% of the patients with SCC developed a recurrence compared with 24% of patients with nonsquamous tumours [$p<0.001$]. The brain was more frequently a site of first recurrence in the nonsquamous group. A significantly greater rate of freedom from distant metastasis among patients with squamous histology was also seen in a group of 370 patients having resection for stage I NSCLC at the Mayo Clinic[32]. If the proportion of patients with SCC continues to decline so may the overall importance of local therapies.

**1.3.3 Survival analysis.**

In 1990 we analysed the survival of patients with non-metastatic NSCLC to see if there was a relationship between radiotherapy dose and survival as suggested by the results of RTOG 73-01[12]. If no relationship were evident, the higher doses and more protracted treatments used in our radical group of patients could not be justified; on the other hand, if there were a correlation between higher doses and longer survival, we could be reassured that our current policy was appropriate. Thus, although this was not a randomised trial, the results of the analysis might at least provide us with guidance for the future management of our patients, since better evidence beyond RTOG 73-01 for a radiotherapy dose – survival relationship in NSCLC was simply not available.

The following strict eligibility criteria were used for this analysis.

(a) The patient was first seen at PMCI for their lung cancer between January 1984 and March 1990 and their details recorded in the database.

(b) The diagnosis was established by histology or cytology.

(c) The tumour type was coded as squamous cell, adenocarcinoma or large cell undifferentiated. Patients coded as the following histologies were ineligible: alveolar cell, small cell anaplastic, carcinoma unspecified and mixed histology.

(d) No previous surgery or radiotherapy or chemotherapy.

(e) No symptoms or signs of metastatic disease.

(f) No pleural effusion.

(g) No pericardial effusion.

(h) Primary site coded as being involved.

(i) No recurrent locoregional disease coded.

(j) No cervical lymph node metastases coded.

(k) No distant metastases coded after clinical examination or staging investigations at PMCI.

(l) No spinal cord compression coded.

(m) Planned treatment coded as radiotherapy with no surgery or chemotherapy planned.

A total of 920 patients met the eligibility criteria. The patient characteristics are given in Table VIII. There are no remarkable features of the study population.

**Table VIII. Characteristics of 920 patients with non-metastatic NSCLC planned for radiotherapy**

| | | Number | % |
|---|---|---|---|
| Sex | Male | 737 | 80.1 |
| | Female | 183 | 19.9 |
| Age | Median | 68.4 years | |
| | Range | 29.8 – 88.9 years | |
| Histology | Squamous cell | 605 | 65.8 |
| | Adenocarcinoma | 152 | 16.5 |
| | Large cell undifferentiated | 163 | 17.7 |
| Smoking history | Never smoked | 19 | 2.1 |
| | Smoked | 896 | 97.4 |
| | Unknown | 5 | 0.5 |
| Symptoms of local disease | Absent | 69 | 7.5 |
| | Present | 843 | 91.6 |
| | Unknown/equivocal | 8 | 0.9 |
| Malaise | Absent | 633 | 96.6 |
| | Present | 255 | 27.7 |
| | Unknown | 32 | 3.4 |
| Paraneoplastic syndrome | Absent | 889 | 96.6 |
| | Present | 27 | 2.9 |
| | Unknown | 4 | 0.4 |
| Superior vena cava obstruction | Absent | 875 | 95.1 |
| | Present | 44 | 4.8 |
| | Equivocal | 1 | 0.1 |
| Weight loss | None | 379 | 41.2 |
| | <10% in 3 months | 280 | 30.4 |
| | >10% in 3 months | 205 | 22.3 |
| | Unspecified amount | 35 | 2.8 |
| | Unknown | 21 | 2.3 |
| Performance status [ECOG] | Grade 0 | 48 | 5.2 |
| | Grade 1 | 439 | 47.7 |
| | Grade 2 | 215 | 23.4 |
| | Grade 3 | 85 | 9.2 |
| | Grade 4 | 17 | 1.8 |
| | Unknown | 116 | 12.6 |
| Hemithorax involvement | Right | 517 | 56.2 |
| | Left | 376 | 40.9 |
| | Both | 27 | 2.9 |

The majority of patients were male smokers, squamous cell carcinoma was the most frequent histology and the right hemithorax was more often involved than the left. Most patients had symptomatic disease and performance status ECOG one or two. Performance status was not documented in a disappointingly large proportion of patients [12.6%]. The majority had noted some loss of weight. Paraneoplastic syndromes and superior vena caval [SVC] obstruction were uncommon. The case records of one patient with an adenocarcinoma, a 13 year survivor, were reviewed in February 2000, and it appears that she may have had metastatic breast cancer, but she has been left in the analysis which was based on 'intention to treat'.

**Treatment policies.** Forty nine different dose/fractionation schedules were planned in the 920 patients. The numbers of patients assigned to each dose level are shown in Table IX. In spite of the large number of schedules prescribed, the majority of patients were prescribed treatment in a consistent manner according to the policies outlined in section 3.2. The most commonly prescribed dose was 20 Gy; followed by 60 Gy. There were three main categories of patients for whom an intermediate dose was planned: those for whom 30 Gy was prescribed, those for whom 36 Gy was prescribed, and a third group for whom 30 Gy was prescribed, and if they were tolerating treatment satisfactorily, the dose was to be taken to 36 Gy; they have been designated the 30 ? 36 Gy group in the table. Most patients were treated five days per week, but some were treated six days per week, and others three days per week. A small group of patients [n=5] for whom 60 Gy was prescribed were treated with an accelerated schedule, giving ten treatments per week. Since overall treatment time as well as dose may have an influence on outcome, its effect cannot be ignored, but in the analysis of the relationship between dose and survival, I have grouped those patients who were treated with the same total dose and the same dose per fraction together, provided treatment was prescribed for at least three days and no more than six days per week.

**Table IX. Planned radiotherapy dose for 920 patients with NSCLC**

| Planned dose | Number | % of 920 |
|---|---|---|
| No dose planned | 3 | 0.3 |
| <20 Gy | 11 | 1.2 |
| 20 Gy | 420 | 45.6 |
| 21-29 Gy | 7 | 0.8 |
| 30 Gy | 74 | 8.0 |
| 30 ? 36 Gy | 46 | 5.0 |
| 35 Gy | 1 | 0.1 |
| 36 Gy | 131 | 14.2 |
| 37-59 Gy | 14 | 1.5 |
| 60 Gy | 209 | 22.7 |
| >60 Gy | 4 | 0.4 |

Furthermore the patients in the intermediate dose range have been grouped together, designated the 30-36 Gy policy group. Since meaningful comparisons are only possible with the larger numbers of patients whose treatment was prescribed in a consistent manner according to the three standard policy groups the first analysis has been restricted to those groups.

All patients in the three main policy groups have been analysed on the basis of "intention to treat" to avoid an unfavourable bias against the lower dose group which may result from a survival analysis based on treatment actually received. For example, patients who die during treatment or are unable to complete the course because of a declining condition would be analysed in a lower dose group than intended, potentially decreasing the survival in the lower dose group while increasing that in the higher dose group. The "intention-to–treat" form of analysis parallels the technique used in randomised trials in which survival is measured from the date of randomisation and comparisons are made according to randomisation arm no matter what treatment the patients actually received[33].

The numbers of patients available for the analysis are shown in Table X. There were 868 patients allocated to one of the standard policy groups, or 94.3% of the total. This indicates good clinician adherence to the Lung Unit treatment policies as set out in section 1.2, enabling comparisons of three large patient groups in each of which the prescription was relatively homogeneous in terms of total dose, fraction size and treatment time.

**Table X. Numbers of patients in the three main policy groups**

| Policy | Dose per fraction | Number | % of 920 | % of 868 |
|---|---|---|---|---|
| 20 Gy | 4 Gy | 416 | 45.2 | 47.9 |
| 30-36 Gy | 3 Gy | 249 | 27.0 | 28.7 |
| 60 Gy | 2 Gy | 203 | 22.0 | 23.3 |

The doses have not been adjusted for biological equivalence in view of the high $\alpha/\beta$ ratio associated with NSCLC. The demographic characteristics and distribution of major prognostic factors in the patients allocated to the three main policy groups are shown in Table XI. The groups appear similar in terms of sex, age, histology and smoking history. However, there are greater proportions of patients with poor prognostic factors such as poor performance status and weight loss in the groups allocated to 20 Gy and 30-36 Gy, as might be expected. Similarly, locoregional symptoms and malaise, both of which are closely related to performance status, were more common in patients in the two lower dose groups. The long-term survivor with adenocarcinoma who may have had metastatic breast cancer is included in the analysis in the 30-36 Gy group.

**Table XI. Patient characteristics of the three main policy groups**

| Characteristic | | | 20 Gy group, [% of 416] | 30-36 Gy group, [% of 249] | 60 Gy group. [% of 203] |
|---|---|---|---|---|---|
| Sex: | Male | | 334 [80.3] | 202 [81.1] | 157 [77.3] |
| | Female | | 82 [19.7] | 47 [18.9] | 46 [22.7] |
| Age: | Median | | 70.0 yrs | 68.4 yrs | 65.4 yrs |
| | Range | | 40.9-88.9 yrs | 41.7-87.3 yrs | 29.8-81.5 yrs |
| Histology: | SCC | | 262 [63.0] | 170 [68.3] | 138 [68.0] |
| | Adenocarcinoma | | 69 [16.6] | 38 [15.3] | 38 [18.7] |
| | Large cell undiff. | | 85 [20.4] | 41 [16.5] | 27 [13.3] |
| Smoking history: | never | | 10 [2.4] | 5 [2.0] | 4 [ 2.0] |
| | smoked | | 402 [96.6] | 244 [98.0] | 198 [97.5] |
| | unknown | | 4 [1.0] | 0 [0] | 1 [0.5] |
| Locoregional symptoms | yes | | 402 [96.6] | 233 [93.6] | 159 [78.3] |
| | no | | 12 [2.9] | 15 [6.0] | 39 [19.2] |
| | equivocal | | 2 [0.5] | 1 [0.4] | 4 [2.0] |
| | unknown | | 0 [0] | 0 [0] | 1 [0.5] |
| Malaise: | yes | | 146 [35.1] | 75 [30.1] | 21 [10.3] |
| | no | | 248 [59.6] | 169 [67.9] | 179 [88.2] |
| | equivocal | | 1 [0.2] | 2 [0.8] | 0 [0] |
| | unknown | | 21 [5.0] | 3 [1.2] | 3 [1.5] |
| Paraneoplastic syndrome: | yes | | 13 [3.1] | 7 [2.8] | 4 [2.0] |
| | no | | 399 [95.9] | 242 [97.2] | 199 [98.0] |
| | equivocal | | 4 [1.0] | 0 [0] | 0 [0] |
| SVC obstruction: | yes | | 15 [3.6] | 22 [8.8] | 2 [1.0] |
| | no | | 400 [96.2] | 227 [91.2] | 201 [99.0] |
| | equivocal | | 1 [0.2] | 0 [0] | 0 [0] |
| Weight loss: | none | | 130 [31.3] | 93 [37.3] | 137 [67.5] |
| | < 10% | | 113 [27.2] | 102 [41.0] | 52 [25.6] |
| | > 10% | | 133 [32.0] | 50 [20.0] | 9 [4.4] |
| | unspecified | | 27 [6.4] | 3 [1.2] | 3 [1.4] |
| | unknown | | 13 [3.1] | 1 [0.4] | 2 [1.0] |
| ECOG PS: | 0 | | 2 [0.5] | 10 [4.0] | 34 [16.7] |
| | 1 | | 136 [32.7] | 149 [59.8] | 128 [63.1] |
| | 2 | | 136 [32.7] | 56 [22.5] | 14 [6.9] |
| | 3 | | 60 [14.4] | 15 [6.0] | 5 [2.5] |
| | 4 | | 9 [2.2] | 1 [0.4] | 2 [1.0] |
| | unknown | | 73 [17.5] | 18 [7.2] | 20 [9.9] |
| Location: | right hemithorax | | 218 [52.4] | 146 [58.6] | 121 [59.6] |
| | left hemithorax | | 188 [45.2] | 95 [38.2] | 75 [36.9] |
| | both | | 10 [2.4] | 8 [3.2] | 7 [3.4] |

The status of all patients was determined at 31/3/98, giving a minimum of eight years follow up from the closure of the database. At that time only 7 of the 868 patients [0.8] were still alive. Two patients were lost to follow up less than one year after presentation after going overseas. The distribution of patients according to status and treatment policy is shown in Table XII.

**Table XII. Status of all patients in the three policy groups as at 31/3/98**

| Status | 20 Gy | 30-36 Gy | 60 Gy |
|---|---|---|---|
| Alive | 1 | 3* | 3 |
| Lost to follow up | 0 | 1 | 1 |
| Dead | 415 | 245 | 199 |

* Includes one patient who may have had metastatic breast cancer.

Survival was measured from the date the person was first seen at PMCI to date of death from any cause. Patients who were still alive at their date of last contact had their survival censored at that date. No close-out date was used in the analysis. Seven patients have survived between 8.4 and 14.9 years following presentation, with last contact dates between June 1998 and August 1999. The latest reported death was in July 1997. Survival estimates were obtained using the Kaplan-Meier method and compared using the Cox proportional hazards model. Ninety-five per cent confidence intervals [95% CI] have been given for the main results. The Brookmeyer-Crowley method was used to estimate the 95% CI for the median survivals. All p-values are two-tailed.

The median survival for all 920 eligible patients and for patients in the three main policy groups is shown in Table XIII, and illustrated in Figures 4 and 5. The 95% CI have been given in brackets. The differences in median survival between the groups are highly significant, with longer survival associated with increasing dose. At two years the difference

in survival between the two lower dose groups is less marked and the confidence intervals overlap; but the estimated proportion of patients in the 60 Gy group alive at two years is still significantly greater than in the two lower dose groups. By five years estimated survival in the 60 Gy group is only six per cent and the differences in survival between the groups are small, although the confidence intervals for the 20 Gy group and the 60 Gy group do not overlap. This effect of time on the influence of treatment policy on survival will be examined in more detail later.

**Table XIII. Survival of all patients and for patients in the three main policy groups**

| | **All eligible patients** | | **20 Gy policy** | | **30 - 36 Gy policy** | | **60 Gy policy** | |
|---|---|---|---|---|---|---|---|---|
| **Number of patients** | 920 | | 416 | | 249 | | 203 | |
| **Median survival (months)** | 8.6 | (7.9 - 9.1) | 6.0 | (5.6 - 6.5) | 9.4 | (7.7 – 10.5) | 14.8 | (12.5-16.9) |
| **Estimated % surviving:** | | | | | | | | |
| 6 months | 63 | (60 - 67) | 50 | (45 - 55) | 68 | (62 - 74) | 87 | (82 - 91) |
| 1 year | 36 | (33 - 39) | 25 | (21 - 29) | 37 | (31 - 43) | 59 | (52 - 66) |
| 2 years | 13 | (11 - 15) | 8 | (5 - 10) | 12 | (8 - 16) | 27 | (21 - 33) |
| 3 years | 6 | (5 – 8) | 4 | (2 - 6) | 6 | (3 - 9) | 13 | (8 - 18) |
| 4 years | 4 | (2 – 5) | 1 | (0.3 - 2.6) | 4 | (1 - 6) | 8 | (5 - 12) |
| 5 years | 3 | (2 - 4) | 1 | (0.3 - 2.6) | 3 | (1 - 5) | 6 | (3 - 10) |
| 10 years | 0.9 | (0.3 - 1.5) | 0.2 | (0.0 - 0.7) | 1.2 | (0.0 - 2.6) | 1.5 | (0.0 -3.2) |

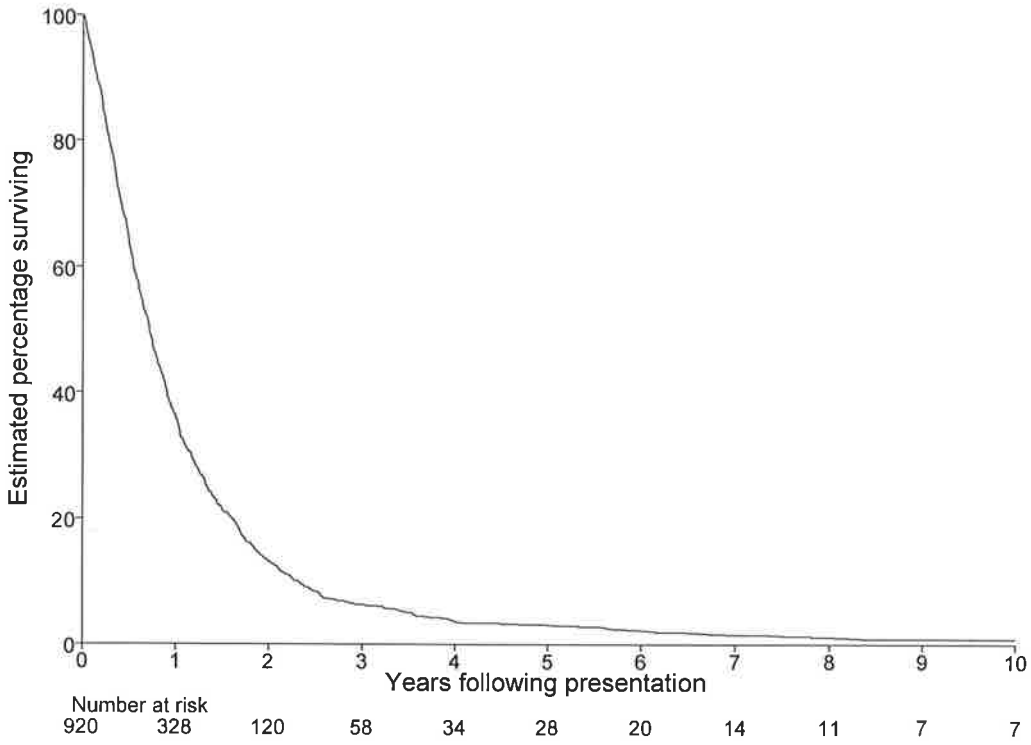


**Figure 4. Overall survival for all 920 eligible patients**

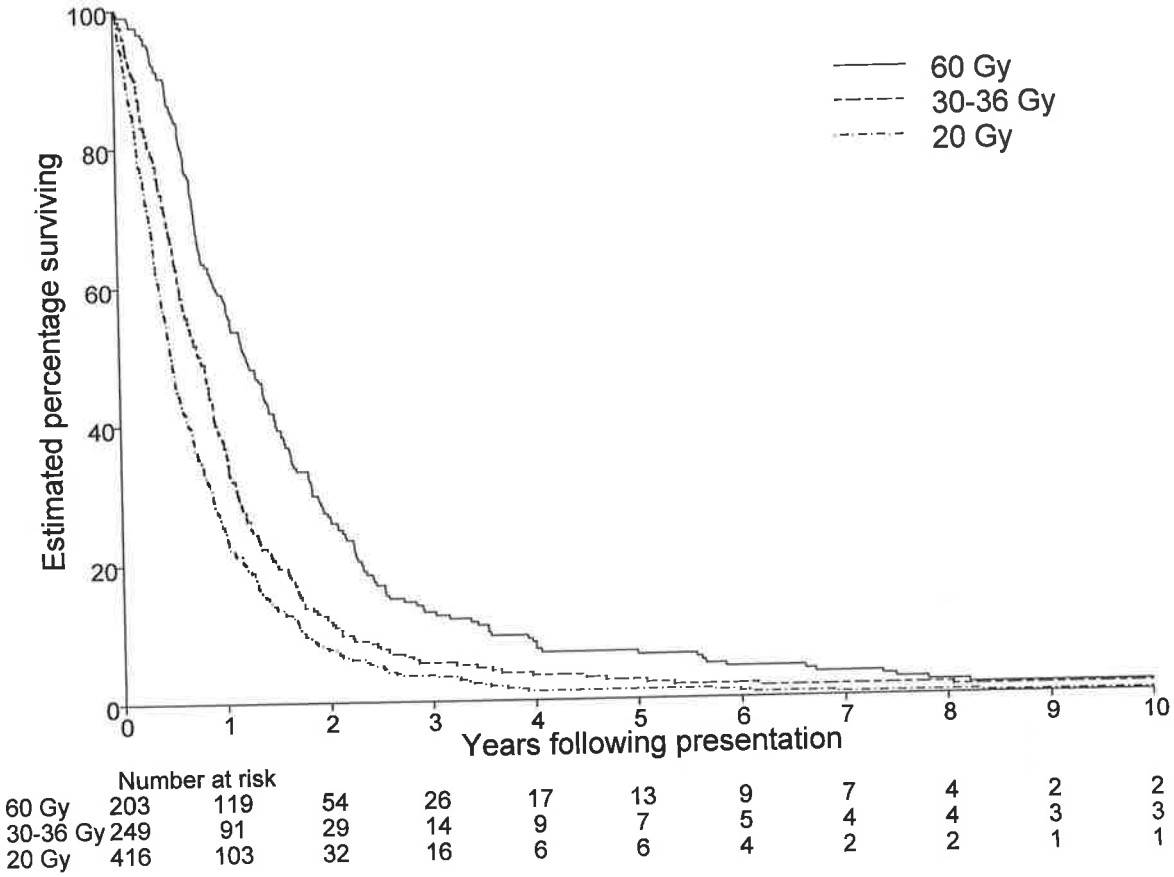


**Figure 5. Overall survival by policy group**

These differences in survival may have been due to patient selection, in which patients with adverse prognostic characteristics were treated with short palliative courses and the more robust patients were treated over a longer period to a higher dose, and therefore not related to the dose policy at all. We therefore examined the influence of other possible prognostic factors on survival, and having established the major prognostic factors, we adjusted for their effect to determine if treatment policy was still associated with differences in survival. If patient selection alone had determined survival, after adjustment for the influence of the major prognostic factors, the influence of treatment policy should have disappeared.

The prognostic influence of each of the factors has been tested in a unifactor analysis both for the 920 eligible patients and for the subset of 868 patients who were treated according to one of the three main policy groups. Patients with equivocal or unknown results for a given factor were excluded from the summary of that factor. The results are shown in Table XIV.

**Table XIV. Prognostic significance of individual factors**

| | | All patients | | | In main policy groups | | |
|---|---|---|---|---|---|---|---|
| **Factor** | **Group** | **No.** | **HR** | **P-value** | **No.** | **HR** | **P-value** |
| Sex | male | 737 | 1.00 | | 693 | 1.00 | |
| | female | 183 | 0.86 | 0.074 | 175 | 0.89 | 0.16 |
| Age | < 50 | 29 | 1.00 | | 24 | 1.00 | |
| | 50 - 59 | 146 | 1.12 | | 130 | 1.20 | |
| | 60 - 69 | 366 | 1.27 | | 348 | 1.34 | |
| | 70 - 79 | 335 | 1.29 | | 323 | 1.37 | |
| | ≥ 80 | 44 | 2.00 | 0.019 | 43 | 2.11 | 0.021 |
| | per decade | | 1.12 | 0.0028 | | 1.13 | 0.0025 |
| Histology | SCC | 605 | 1.00 | | 570 | 1.00 | |
| | adenocarcinoma | 152 | 1.02 | | 145 | 1.00 | |
| | large cell | 163 | 1.12 | 0.42 | 153 | 1.13 | 0.40 |
| Smoking history | never smoked | 19 | 1.00 | | 19 | 1.00 | |
| | smoked | 896 | 0.72 | 0.18 | 844 | 0.71 | 0.16 |
| Locoregional symptoms | no | 69 | 1.00 | | 66 | 1.00 | |
| | yes | 843 | 1.48 | 0.0011 | 794 | 1.53 | 0.0006 |
| Malaise | no | 633 | 1.00 | | 596 | 1.00 | |
| | yes | 255 | 1.40 | < 0.0001 | 242 | 1.36 | 0.0001 |
| Paraneoplastic syndrome | no | 889 | 1.00 | | 840 | 1.00 | |
| | yes | 27 | 1.92 | 0.030 | 24 | 1.75 | 0.014 |
| SVC obstruction | no | 875 | 1.00 | | 828 | 1.00 | |
| | yes | 44 | 1.57 | 0.0067 | 39 | 1.47 | 0.027 |
| Weight loss | none | 379 | 1.00 | | 360 | 1.00 | |
| | <10% | 280 | 1.57 | | 267 | 1.58 | |
| | > 10% | 205 | 1.69 | | 192 | 1.68 | |
| | unknown | 35 | 1.55 | < 0.0001 | 33 | 1.52 | < 0.0001 |
| | none | 379 | 1.00 | | 360 | 1.00 | |
| | some | 520 | 1.61 | < 0.0001 | 492 | 1.61 | < 0.0001 |
| ECOG PS [all patients] | 0 | 48 | 1.00 | | 46 | 1.00 | |
| | 1 | 439 | 1.59 | | 413 | 1.66 | |
| | 2 | 215 | 2.31 | | 206 | 2.39 | |
| | 3 | 85 | 3.15 | | 80 | 3.28 | |
| | 4 | 17 | 9.27 | | 12 | 7.08 | |
| | unknown amount | 116 | 2.16 | < 0.0001 | 111 | 2.20 | < 0.0001 |

**Table XIV [continued]**

| | | | All patients | | | In main policy groups | | |
|---|---|---|---|---|---|---|---|---|
| **Factor** | **Group** | | **No.** | **HR** | **P-value** | **No.** | **HR** | **P-value** |
| ECOG PS | | 0 | 48 | 1.00 | | 46 | 1.00 | |
| [excluding | | 1 | 439 | 1.59 | | 413 | 1.66 | |
| unknowns] | | 2 | 215 | 2.30 | | 206 | 2.39 | |
| | | 3 | 85 | 3.15 | | 80 | 3.28 | |
| | | 4 | 17 | 9.30 | < 0.0001 | 12 | 7.10 | < 0.0001 |
| | | per grade | | 1.50 | < 0.0001 | | 1.48 | < 0.0001 |
| Hemithorax | | left | 517 | 1.00 | | 485 | 1.00 | |
| | | right | 376 | 1.02 | | 358 | 1.04 | |
| | | both | 27 | 1.38 | 0.29 | 25 | 1.31 | 0.42 |
| | | unilateral | 893 | 1.00 | | 843 | 1.00 | |
| | | bilateral | 27 | 1.37 | 0.12 | 25 | 1.29 | 0.23 |

The prognostic significance of individual factors has been summarised using hazard ratios [HR] representing the death rate for a given group relative to a baseline group.

The most significant adverse factors in the complete data set were increasing ECOG performance status [$p < 0.0001$], any weight loss [$p < 0.0001$], malaise [$p < 0.0001$], the presence of locoregional symptoms [$p = 0.0011$], increasing age [$p = 0.0028$], superior vena caval obstruction [$p = 0.0067$], and paraneoplastic syndrome [ $p = 0.030$]. All of these factors remained significant when the analysis was restricted to patients treated in one of the three main policy groups. Females had a lower death rate than males, but this was not statistically significant. There appeared to be no influence of histology on survival. When all the factors in Table XIV were studied in a multifactor analysis in the subset of the 770 patients [84% of the 920] for whom the data was complete [no missing or equivocal information], only three were significant at the 0.05 level: ECOG performance status [$p < 0.0001$], weight loss [ $p < 0.0001$] and age [$p < 0.027$] [Table XV].

**Table XV. Jointly significant factors associated with overall survival**

| Factor | HR | 95% CI | P-value |
|---|---|---|---|
| ECOG performance status (per increasing grade) | 1.38 | 1.26 - 1.52 | < 0.0001 |
| Weight loss (some vs none) | 1.39 | 1.19 - 1.63 | < 0.0001 |
| Age (per increasing decade) | 1.10 | 1.01 - 1.20 | 0.027 |

After adjusting for the effect of performance status, weight loss and age, the significance of the remaining factors is shown in Table XVI. As expected, the presence of locoregional symptoms, and malaise are closely linked to performance status, and they lose their significance when the effect of performance status is taken into account.

**Table XVI. Factors not associated with survival after adjustment for the effect of performance status, weight loss and age**

| Factor | P-value |
|---|---|
| Sex | 0.19 |
| Histology | 0.14 |
| Adenocarcinoma (vs SCC) | 0.21 |
| Large cell (vs SCC) | 0.060 |
| Smoking history | 0.77 |
| Locoregional symptoms | 0.51 |
| Malaise | 0.49 |
| Paraneoplastic syndrome | 0.086 |
| SVC obstruction | 0.18 |
| Hemithorax (unilateral vs bilateral) | 0.18 |

A further multifactor analysis was performed using the characteristics that had been listed by the IASLC consensus group as definite or possible prognostic factors[11] and which had also been recorded in our database. Of the three IASLC 'definite' prognostic factors we did not have information on UICC stage, but we did have performance status and weight loss; and of the 'possible' prognostic factors, we had recorded sex, histology and age. There were 795 patients with full data on all these factors; the results are shown in Table XVII.

**Table XVII. Joint significance of IASLC 'definite' and 'possible' prognostic factors**

| Factor | Group | HR | 95% CI | P-value |
|---|---|---|---|---|
| ECOG performance status (per increasing grade) | Definite | 1.35 | 1.23 - 1.49 | < 0.0001 |
| Weight loss (some vs none) | Definite | 1.40 | 1.20 - 1.63 | < 0.0001 |
| Age (per increasing decade) | Possible | 1.11 | 1.02 - 1.20 | 0.017 |
| Histology | Possible | | | 0.061 |
| Adenocarcinoma (vs SCC) | | 1.17 | 0.96 - 1.43 | 0.13 |
| Large cell (vs SCC) | | 1.23 | 1.02 - 1.49 | 0.035 |
| Sex (female vs male) | Possible | 0.85 | 0.72 - 1.02 | 0.079 |

Again, ECOG performance status, weight loss and age were significant. When histology was considered as a single factor it was not significant [p = 0.061], but it did appear that large cell undifferentiated carcinoma was associated with a worse prognosis than squamous cell carcinoma. The IASLC group had classified squamous cell carcinoma as a possible favourable characteristic but in early stage disease only. Females had a lower death rate than males, but this was not statistically significant [p = 0.079]. Thus our observations were in general agreement with the IASLC consensus.

There was a highly significant survival difference between the three treatment policy groups [p < 0.0001] both on unifactor analysis [Table XVIII] and when adjusting for performance status and weight loss [Table XIX]. When the IASLC 'definite' and 'possible' prognostic factors that were available were included in the model, the treatment policy remained highly significant [p < 0.0001] [Table XX]. The 30-36 Gy policy was associated with an estimated 16% [95% CI : 0.4% - 29%, p = 0.044] reduction in the death rate relative to the 20 Gy policy group, whereas the 60 Gy policy was associated with an estimated 38% [95% CI : 24% - 49%, p < 0.0001] reduction in the death rate relative to the 20 Gy policy group.

**Table XVIII. Significance of treatment policy***

| Policy group | HR | 95% CI | P-value |
|---|---|---|---|
| 30 - 36 Gy (vs 20 Gy) | 0.74 | 0.63 - 0.86 | 0.0001 |
| 60 Gy (vs 20 Gy) | 0.48 | 0.40 - 0.57 | < 0.0001 |
| per increasing dose group | 0.70 | 0.64 - 0.76 | < 0.0001 |

* Based on 868 patients treated according to one of the 3 main treatment policies.

**Table XIX Significance of treatment policy adjusting for performance status and weight loss***

| Policy group | HR | 95% CI | P-value |
|---|---|---|---|
| 30 - 36 Gy (vs 20 Gy) | 0.81 | 0.68 - 0.96 | 0.013 |
| 60 Gy (vs 20 Gy) | 0.59 | 0.48 - 0.71 | < 0.0001 |
| per increasing dose group | 0.77 | 0.70 - 0.85 | < 0.0001 |

* Based on 868 patients treated according to one of the 3 main treatment policies.

**Table XX. Significance of treatment policy adjusting for performance status, weight loss, age, histology and sex***

| Policy group | HR | 95% CI | P-value |
|---|---|---|---|
| 30 - 36 Gy (vs 20 Gy) | 0.84 | 0.71 - 0.996 | 0.044 |
| 60 Gy (vs 20 Gy) | 0.62 | 0.51 - 0.76 | < 0.0001 |
| per increasing dose group | 0.79 | 0.72 - 0.87 | < 0.0001 |

* Based on 868 patients treated according to one of the 3 main policies.

The joint significance of the 'definite' and 'possible' prognostic factors adjusting for treatment policy [in a model stratified by this factor] is shown in Table XXI. Only the definite prognostic factors [ECOG performance status and weight loss] remained significant in this analysis.

**Table XXI. Joint significance of "definite" and "possible" prognostic factors adjusting for treatment policy***

| Factor | HR | 95% CI | P-value |
|---|---|---|---|
| ECOG performance status (per increasing grade) | 1.26 | 1.14 – 1.40 | < 0.0001 |
| Weight loss (some vs none) | 1.33 | 1.13 – 1.56 | 0.0007 |
| Age (per increasing decade) | 1.06 | 0.97 – 1.16 | 0.22 |
| Histology | | | 0.22+ |
| Adenocarcinoma (vs SCC) | 1.14 | 0.93 – 1.40 | 0.20 |
| Large cell (vs SCC) | 1.16 | 0.95 – 1.41 | 0.15 |
| Sex (female vs male) | 0.89 | 0.74 – 1.06 | 0.19 |

* Based on 751 patients with no missing data or equivocal results and treated according to one of the 3 main policies.

\+ Significance of histology (adenocarcinoma vs large cell vs SCC) as a single factor.

Previously we had noted the declining influence of treatment policy over time so that by five years the differences between the policy groups were no longer significant. Examination of the survival curves in Figure 5 reveals an initial shoulder associated with the 60 Gy curve not evident on the other curves. This might reflect the influence of patient selection or earlier diagnosis rather than treatment on survival. If that were the case the early survival advantage conferred by better prognostic characteristics and/or earlier diagnosis in the 60 Gy group should gradually disappear [assuming treatment is ineffective and there is no reduction in the rate of cancer progression] and the survival curves of the three policy groups should become parallel.

In order to test whether the survival advantage associated with higher doses diminishes with increasing time a further analysis was performed in which the risk of death was determined for four time intervals after presentation, and adjusting for performance status and weight loss. The relative death rates are expressed as hazard ratios [relative to the 20 Gy group]. The number of patients 'at risk' at the beginning of each interval has been included The results are shown in Table XXII.

**Table XXII. Time-dependence of prognostic significance of treatment policy, adjusting for performance status and weight loss**

| Policy Group | Months From Presentation | No. pts. | HR | 95% CI |
|---|---|---|---|---|
| 30 - 36 Gy (vs 20 Gy) | $\leq$ 6 months | 249 | 0.65 | 0.49 – 0.85 |
| | > 6 months - $\leq$ 12 months | 168 | 0.95 | 0.70 – 1.30 |
| | > 12 months - $\leq$ 24 months | 91 | 1.06 | 0.74 – 1.52 |
| | > 24 months | 29 | 0.72 | 0.40 – 1.31 |
| 60 Gy (vs 20 Gy) | $\leq$ 6 months | 203 | 0.28 | 0.18 – 0.43 |
| | > 6 months - $\leq$ 12 months | 176 | 0.68 | 0.47 – 0.96 |
| | > 12 months - $\leq$ 24 months | 119 | 0.81 | 0.56 – 1.18 |
| | > 24 months | 54 | 0.83 | 0.49 – 1.41 |

The reduction in death rate associated with the higher doses diminished with increasing time, and the test for time-dependence of the prognostic significance of the policy groups was highly significant [$p = 0.0007$]. This observation does not invalidate the conclusion that the higher dose treatment policies are associated with a statistically significant increase in survival duration. In the proportional hazards model with different hazard ratios in the four chosen time intervals, policy group was still a highly significant prognostic factor [$p < 0.0001$]. It is interesting to note that the effect of performance status also diminishes with increasing time [$p < 0.0001$], but not the effect of weight loss [$p = 0.45$]. The hazard ratios associated with these factors in the four time selected intervals are given in Table XXIII. The data in this table are based on all patients treated according to one of the three treatment policy groups, and with known performance status and no missing weight loss data.

**Table XXIII. Time-dependence of prognostic significance of performance status and weight loss, adjusting for treatment policy**

| Policy Group | Months From Presentation | No. pts. | HR | 95% CI |
|---|---|---|---|---|
| ECOG performance status (per increasing grade) | ≤ 6 months | 751 | 1.63 | 1.39 – 1.92 |
| | > 6 months - ≤ 12 months | 481 | 1.17 | 0.95 – 1.44 |
| | > 12 months - ≤ 24 months | 276 | 0.93 | 0.74 – 1.16 |
| | > 24 months | 105 | 1.18 | 0.88 – 1.57 |
| Weight loss (none vs some) | ≤ 6 months | 751 | 1.32 | 1.01 – 1.74 |
| | > 6 months - ≤ 12 months | 481 | 1.33 | 0.98 – 1.80 |
| | > 12 months - ≤ 24 months | 276 | 1.60 | 1.15 – 2.24 |
| | > 24 months | 105 | 0.95 | 0.58 – 1.55 |
| ECOG performance status | over all time periods | 751 | 1.26 | 1.14 – 1.40 |
| Weight loss | over all time periods | 751 | 1.31 | 1.11 – 1.54 |

In parallel with the finding that the reduction in death rate associated with the higher dose treatment policies diminishes with increasing time, had the comparison of the treatment policies been confined to the 552 patients who survived six months from presentation, the survival differences would not have been significant between the groups [p = 0.057] with hazard ratios of 0.95 [95% CI: 0.76 - 1.18] and 0.77 [95% CI: 0.61 – 0.96] for the 30-36 Gy group and the 60 Gy group respectively relative to the 20 Gy group. However the test for trend between the three groups would still have been significant [ p = 0.024]. Had the comparison been confined to the 313 patients who survived 12 months from presentation, the survival differences would not have been significant at all (p = 0.47) with hazard ratios of 0.95 (95% CI: 0.70 – 1.30) and 0.84 (95% CI: 0.62 – 1.13) for the 30-36 Gy group and the 60 Gy group respectively relative to the 20 Gy group. The test for trend between the three groups would also have been non-significant (p = 0.23). The estimates of the hazard ratios are still less than one, but they are closer to one than the estimates based on the whole data set and are

based on smaller numbers, thus leading to larger standard errors, wider confidence intervals and less power to detect a given difference.

Thus far the survival of patients has been measured from time of presentation at PMCI, which was generally the time at which the treatment policy was formulated. However there were 11 patients [8 in the 20 Gy group, 2 in the 30-36 Gy group and 1 in the 60 Gy group] who never commenced treatment. Patients in the 60 Gy group were more likely to start at a later time after presentation than the lower dose groups because of the greater complexity of the planning process in the radically treated patients [Table XXIV]. Note, the date of presentation at the PMCI was recorded only in months and years in the database. The day of presentation was arbitrarily set to be the 16$^{th}$ day of the month; however, where this led to a date which was after the date of radiotherapy (which was recorded in full in the database), the date of presentation was set back to the date of radiotherapy. This means that the number of days from presentation to commencement of radiotherapy is not only estimated, but is biased towards lower numbers.

**Table XXIV. Days between presentation and commencement of radiotherapy according to policy group**

| Estimated days to commencement of radiotherapy | 20 Gy n = 408 | | 30 – 36 Gy n = 247 | | 60 Gy n = 202 | |
|---|---|---|---|---|---|---|
| Median | 8 | | 11 | | 18 | |
| Range | 0 - 183 | | 0 - 64 | | 0 - 68 | |
| | **n** | **%** | **n** | **%** | **n** | **%** |
| ≤ 7 | 200 | 49 | 99 | 40 | 45 | 22 |
| 8 – 14 | 95 | 23 | 50 | 20 | 26 | 13 |
| 15 – 21 | 58 | 14 | 50 | 20 | 44 | 22 |
| 22 – 28 | 26 | 6 | 28 | 11 | 39 | 19 |
| 29 – 35 | 9 | 2 | 9 | 4 | 23 | 11 |
| 36 – 42 | 11 | 3 | 8 | 3 | 12 | 6 |
| ≥ 43 | 9 | 2 | 3 | 1 | 13 | 6 |

The survival analysis was repeated excluding the 11 patients who never started treatment and measuring survival from the date of commencement of radiotherapy. The results are shown in Table XXV and Figure 6. The estimated hazard ratios from the Cox proportional hazards model stratified by ECOG performance status and weight loss are summarised in Table XXVI. These are virtually identical to the values from the analysis based on all patients with one of the selected policies and with survival time measured from the date of presentation.

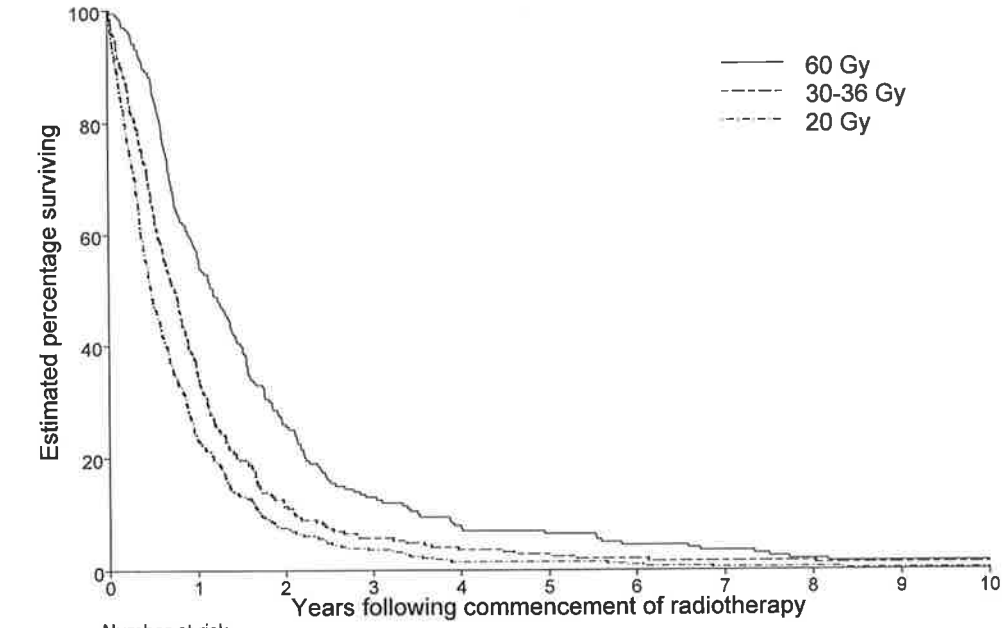


**Figure 6. Survival by policy group following commencement of radiotherapy**

**Table XXV. Survival of the three main policy groups measured from commencement of radiotherapy**

| | 20 Gy policy | | 30 - 36 Gy policy | | 60 Gy policy | |
|---|---|---|---|---|---|---|
| Number of patients | 408 | | 247 | | 202 | |
| Median survival (months) | 5.7 | (5.1 – 6.7) | 9.0 | (7.5 – 9.9) | 14.2 | (11.9 – 16.6) |
| Esimated % surviving: | | | | | | |
| 6 months | 49 | (44 – 53) | 65 | (59 – 71) | 85 | (80 – 90) |
| 1 year | 23 | (19 – 27) | 35 | (29 – 41) | 56 | (49 – 63) |
| 2 years | 8 | ( 5 – 10) | 11 | ( 7 – 15) | 26 | (20 – 32) |
| 3 years | 4 | ( 2 – 6) | 6 | ( 3 – 9) | 13 | ( 8 – 18) |
| 4 years | 1.5 | (0.3 – 2.6) | 4 | ( 1 – 6) | 7 | ( 4 – 11) |
| 5 years | 1.5 | (0.3 – 2.6) | 2.9 | (0.8 – 4.9) | 6 | ( 3 – 10) |
| 10 years | 0.2 | (0.0 – 0.7) | 1.2 | (0.0 – 2.6) | 1.5 | (0.0 – 3.1) |

**Table XXVI. Significance of treatment policy adjusting for performance status and weight loss, measuring survival from commencement of radiotherapy**

| Policy group | HR | 95% CI | P-value |
|---|---|---|---|
| 30 - 36 Gy (vs 20 Gy) | 0.81 | 0.68 – 0.96 | 0.013 |
| 60 Gy (vs 20 Gy) | 0.59 | 0.49 – 0.72 | < 0.0001 |
| per increasing dose group | 0.77 | 0.70 – 0.85 | < 0.0001 |

### 1.3.4 Discussion.

These results have confirmed the importance of performance status and weight loss as major independent prognostic factors in patients with NSCLC. Any weight loss - whether greater or less than 10% - appeared to be an adverse prognostic factor. Increasing age and large cell anaplastic histology also appeared to be adverse prognostic factors, but of much less importance. These observations are not new. What is however new is the observation that higher doses of thoracic radiotherapy were associated with a highly significant prolongation in survival compared with lower doses, and this advantage was still clearly present after

adjusting for the influence on survival of the most important prognostic factors. The survival benefit was most marked within the two years after treatment, but by five years the differences between the groups were small, with the estimated survival in the 60 Gy group being six per cent [95% CI: 3 – 10] compared with one per cent [95% CI 0.3 – 2.6] in the 20 Gy group, and three per cent [ 95% CI: 1 – 5] in the 30 – 36 Gy group. Cure [however that is defined] was therefore extremely unlikely in any of the groups and the benefits of higher doses were seen in the short term, best characterised by the median and two year survivals. It follows that if five year survival figures alone are used as a measure of therapeutic effect [as is often the case in surgically treated populations] there is a risk that important treatment benefits may go undetected.

Our observations are in line with the results of RTOG 73-01[13] which had revealed a non-significant early survival advantage for patients who were randomised to receive 50 or 60 Gy. The two year survival for those patients was 19% compared with 27% for our 60 Gy group. At five years the survival of all four arms in 73-01 was the same - six per cent - regardless of dose. In comparing the survival data of 73-01 and our own data, it must be borne in mind that the patients of 73-01 were managed without the benefit of CT staging and CT-assisted treatment planning, which were standard practice in our 60 Gy group.

We thus felt vindicated in our choice of policy, based as it was on 73-01, because the survival differences between the dose groups remained even after allowance had been made for the adverse effects of poor performance status and weight loss which were more common in the lower dose groups. It was our interpretation that choice of dose had an effect over and above the obvious influence of patient selection. In the absence of better evidence from randomised studies we could see no reason to change our policy of giving higher doses of radiotherapy to patients with NSCLC who had good performance status, no history of weight loss and no

evidence of distant metastases. If our analysis had shown a detrimental effect of the higher dose policy, or if the outcomes between groups had been similar once patient selection factors had been taken into account, we may have concluded that further studies in the form of a randomised trial similar to 73-01 employing modern planning and treatment techniques were necessary to establish the superiority of higher doses. However, there seems nothing equivocal about the estimated 38% [95% CI: 24% - 49%, $p < 0.0001$] reduction in death rate that was associated with the 60 Gy policy compared with the 20 Gy policy, after adjusting for all available definite and possible prognostic factors. That a dose-response relationship may exist was suggested by the observation that the death rate of the 30 –36 Gy group was intermediate between that of the 20 Gy and 60 Gy groups [16% reduction in death rate relative to the 20 Gy group, after adjusting for prognostic factors].

An earlier analysis of this study was published in the *International Journal of Radiation Oncology Biology Physics* in 1993[34]. The study population was slightly different in that it did not include the small group of patients that were registered on the database after 31/12/89, but it did include 23 patients with mixed NSCLC histology. The results of the earlier analysis are very similar to the present study, with reductions in death rates relative to the 20 Gy group of 21% [95% CI: 7% - 33%, $p = 0.006$] and 47% [95% CI: 35% - 56%, $p < 0.0001$] associated with the 30 – 36 Gy and 60 Gy groups respectively, after adjusting for the influence of performance status and weight loss. The 30 – 36 Gy policy group was further subdivided into three subgroups according to planned dose: 30 Gy, 36 Gy, and 30?36 Gy. There was no survival benefit associated with the 30 Gy policy compared with 20 Gy after adjusting for the two major prognostic factors [relative death rate 0.98; 95% CI: 0.76 – 1.27, $p = 0.87$], but there was with the 36 Gy policy [relative death rate 0.71; 95% CI: 0.57 – 0.88, $p = 0.0013$]. The 30?36 Gy group had a survival intermediate between the other two groups [ relative death rate 0.80; 95% CI: 0.58 – 1.10, $p = 0.15$]. These data do not fit with a linear dose-response

model because of the apparent equivalence of 20 and 30 Gy. They might however fit with a sigmoid shaped dose response relationship in which doses of 20 –30 Gy are located either below the threshold for a detectable effect or on the shallow initial part of the curve, and their effects are therefore indistinguishable whereas doses of 36 and 60 Gy lie on the steep part of the curve and so their differential effects are more obvious.

An abstract of this paper was published together with comments by the editor in the 1994 edition of Mosby's Year Book of Oncology[35]. The accompanying commentary by Glatstein contained the following paragraph:

'This paper from Australia simply demonstrates that increasing the dose, as well as the number of fractions, does improve the survival of a fairly large group of patients who have NSCLC. The authors go to some trouble to try to demonstrate that this is not a function of patient selection, although that is always going to be a question when they have treated only approximately 25% of the total patient load that they have seen. Even so, hopefully in the future, for patients who do not have metastatic disease, the issue of dose will be accepted as important enough to justify what the Australians refer to as "radical therapy" '.

If we accept that higher doses improve survival why did we not treat all patients with limited disease radically to 60 Gy regardless of performance status and other prognostic factors? Patients in the lower dose groups were more likely to have adverse prognostic characteristics and the majority of such patients are simply not fit enough to cope with a protracted course of treatment associated with significant toxicity including fatigue and oesophagitis. Similarly, we do not recommend surgery – in spite of its potential benefits - to all patients with limited NSCLC, unless they are fit enough to undergo thoracotomy and resection.

We acknowledged in our original publication that there may have been unrecognised prognostic factors which influenced the choice of treatment policy and therefore survival but were not recorded in our database, and that they, and not the dose of radiotherapy, were what accounted for the survival differences observed[34]. Apart from the possible influence of tumour size, TNM staging and serious co-morbidities [which were not recorded] we are unable to say what other prognostic factors may have influenced choice of policy.

These shortcomings were criticised by Macbeth and Gregor in a letter to the *International Journal of Radiation Oncology Biology Physics*[36], which has been quoted in full below.

'We are surprised that Ball and his colleagues can be so confident in their conclusion that the longer survival in their group of patients with non-small cell lung cancer can largely be attributed to the higher dose of radiotherapy. They gloss over the "possible influence of tumor size and TNM staging (which were not recorded)" without any further discussion. They state that the patients who received 60 Gy were selected on the basis of tumor size ("primary tumor less than 6 cm in maximum diameter"), which implies that those who were treated with palliative doses almost certainly had disease that was more bulky. The radically treated group of patients were also intensively staged by bone scan, computed tomography (CT) of chest and upper abdomen and, for some histologies, CT brain scan. It is not clear whether the other patients were staged in this way, but it seems unlikely that they were.

'The group treated with lower radiation doses almost certainly included patients with more advanced local disease (probably including bulky nodal disease) and some subclinical metastases. These factors might of themselves account for the observed survival differences, because it is well known from surgical series what important prognostic factors they are. It is also not clear how many of those given 60 Gy were inoperable because of tumor extent or because of age and intercurrent medical problems. These constitute two rather different

groups which may have different outcomes. This report, therefore, does not offer credible evidence to justify the use of radical radiotherapy in inoperable non-small cell lung cancer, and until a proper, modern, randomised study is carried out, we will continue to be treating on the basis of hunch and tradition.'

We were asked to respond to their criticism in the same edition and the text of our response[37] is as follows:

'In their opening sentence, Macbeth and Gregor have paraphrased our conclusion in such a way that it no longer represents either what we wrote or the manner in which it was written. We cautiously concluded that our data "support the hypothesis that the increased survival ..... with higher dose radiotherapy is not due purely to patient selection" and that based on our results "we see no reason to change our policy of offering high dose thoracic irradiation to selected patients with inoperable NSCLC confirmed to the primary site and mediastinum".

'While we accept that the patients treated with lower radiation doses may have had more advanced local disease than those treated with higher radiation doses, some of the influence of a difference in stage of disease would have been accounted for already in the multivariate analyses adjusting for performance status and weight loss. Even though there were considerable differences in the distribution of these two factors in the patients treated with 60 Gy and those treated with 20 Gy, the relative death rate for these two groups of patients only changed from a value of 0.44 (95% confidence interval (CI): 0.37-0.52, $p<0.0001$) in the univariate analysis to 0.53 (CI: 0.44-0.65, $p<0.0001$) after adjusting for these two major prognostic factors. It is difficult to believe that further adjustment by inclusion of stage would have altered the relative death rate to the extent that it was no longer significant (upper limit of the confidence interval greater than 1).

'Your correspondents also attribute prognostic significance to the intensity of staging, implying that more vigorous investigation in the lower dose groups may have produced a sufficiently large stage shift to alter our results by excluding patients with subclinical metastases. We are unable to say what percentage of our patients who had no symptoms or signs of metastatic disease might have had a positive result on multiorgan scanning, but in a study of patients being worked up for surgical resection it was only 3%[38].

'In his book "Intellectuals", Paul Johnson alleges that there is no evidence that Karl Marx ever set foot inside a factory; this did not however deter Marx from telling the world how it should be changed to improve the lot of the working classes. We on the other hand have been inside the factory; we have carefully documented and analyzed out observations and prefer to use the best information from our own practice as the basis for the future management of our patients rather than leaving them to the fate of "hunch and tradition"'.

And there the debate ended. It is significant that their own randomised study [along the lines suggested by Macbeth and Gregor in their final sentence] was closed prematurely because of poor recruitment[39]. In this study, conducted in Glasgow and Copenhagen, 117 eligible patients were randomised to one of three arms: A – radical radiotherapy, 50 Gy in 20 daily fractions; B – chemotherapy plus radical radiotherapy, consisting of two cycles of cisplatin 100 mg/m$^2$ intravenously [iv] day 1 and vindesine 3 mg/m$^2$ iv days 1 and 8 at three weekly intervals before radiotherapy as in arm A; and C – control, in which patients were given palliative radiotherapy as appropriate to relieve symptoms, no more than 30 Gy. Chemotherapy was not used in the control arm. The eligibility criteria and patient demographics are not clearly spelled out in the paper, but the majority [66%] had an ECOG performance status of one and 77% had lost less than 10% of body weight. TNM staging is not mentioned at all. Although median survival was longer in the two treatment arms, the differences were not statistically

significant: A, 53 weeks [95% CI: 32 - 59 weeks]; B, 52 weeks [95% CI: 35 – 73 weeks]; and C, 34 weeks [95 % CI: 22 - 57 weeks]. At two years survival was 20% in the treatment arms and 15 % in the control arm. The authors argued that the trial failed for two reasons: only a small proportion [10-15%] of lung cancer patients meet the criteria for high-dose irradiation; but the principle reason was the prejudice of referring physicians against aggressive treatment, particularly chemotherapy. The possibility that there was physician and patient prejudice against the control arm was not mentioned. So, in spite of arguing that the question of the value of high dose radiotherapy will remain unanswered until 'a proper , modern, randomised study is carried out' Macbeth and Gregor found in practice that they could not do the very study that they were to subsequently advocate! It is possible that their trial might have been more successful if there had been no chemotherapy arm, but there is no indication that they have gone on to plan or perform a study with a design more acceptable to their referring clinicians.

One other randomised trial purporting to test the influence of radiotherapy on survival had been published in 1990 by the Southeastern Cancer Study Group [SECSG] in the United States with the provocative title 'Thoracic radiotherapy does not prolong survival in patients with locally advanced unresectable non-small cell lung cancer'[40], but it was really a comparison between radiotherapy and chemotherapy rather than 'best supportive care'. This study did not have a control arm because few investigators were willing to randomise patients to 'no treatment'. Instead, patients were randomised to single agent vindesine, considered at the time to be one of the most active agents against NSCLC. The other two arms were radiotherapy alone, 60 Gy in 6.5 weeks; and combined chemotherapy/radiotherapy in which vindesine was given 3 $mg/m^2$ iv weekly for six weeks simultaneously with the same radiotherapy and continued fortnightly for six months in responding and stable patients. Patients with disease progression while on vindesine therapy or thoracic radiotherapy alone

were crossed over to thoracic radiotherapy and vindesine therapy, respectively. Eligibility criteria included stage I - III disease [including supraclavicular nodes] and performance status [Karnofsky] > 50%. Weight loss did not exclude patients: approximately 30% of patients in each arm had > 10% weight loss, and approximately 20% had performance status of 50-70%. Thus of the 319 patients randomised there were substantial numbers with adverse prognostic characteristics. Forty seven patients were crossed over from vindesine to radiotherapy, and 29 patients were crossed over from radiotherapy to vindesine.

Survival was notably poor in all groups, indicative of the poor pre-treatment prognostic characteristics of many of the patients. The median survival for patients randomised to radiotherapy alone was 8.6 months, to vindesine alone 10.1 months and to combined therapy 8.6 months [p = 0.58]. Five year survival ranged from 1 – 3%. Interpretation of this result is complicated by the cross-over nature of the study design and the inclusion of a large number of patients who would have been regarded as suitable only for palliative treatment in many centres. In contrast, the median survival of our 60 Gy group was 14.8 months, 72% longer than the SECSG's 60 Gy arm. This is a striking difference – for NSCLC – and is almost certainly a consequence of patient selection, although it is possible that poor radiotherapy technique may also have contributed to the short survival. The authors' bold claim encapsulated in the title of their paper might be more believable had they achieved a similar outcome with more carefully selected patients and a study design which included a control arm and which did not mandate crossover.

At most the SECSG and West Scotland/ Danish studies can only be regarded as inconclusive: the former flawed by poor study design and excessively broad eligibility criteria; the latter suggesting an advantage for patients randomised to radical radiotherapy, but underpowered to detect a statistically significant effect.

In addition to the studies examining the influence of radiotherapy on survival, there have been a number of published randomised trials which have examined the effect of dose although survival has not always been the primary endpoint. These studies have been summarised in Table XXVII. Only one of the studies – that of the Medical Research Council[45] - has shown a survival advantage in favour of the higher dose; the remainder showed no differences and none revealed a deleterious effect of higher dose on survival. These outcomes should not be surprising: any survival benefit of the higher dose could have been masked by inclusion of patients with adverse prognostic features such as small cell histology[41], non-ambulatory performance status[41, 42, 43, 44], pleural effusion[43], supraclavicular node involvement[42, 43], or distant metastases[44]. Furthermore, the differences in dose between the arms were small, and even in an homogeneous population it might be expected that very large numbers of patients might be required to demonstrate a survival advantage resulting from a 10 Gy increase in dose.

**Table XXVII. Randomised trials of different doses in lung cancer**

| Author, year, ref. | Number | Dose [Gy] | Split | Median survival [months] | Significance |
|---|---|---|---|---|---|
| Petrovich 1981 [41] | 343# | 42 | no | 8.8 | NS |
| | | 50 | no | 8.8 | |
| Sealy 1982 [42] | 269 | 40 | yes | 7.1 | NS |
| | | 50 | yes | 8.5 | |
| Simpson 1985 [43] | 409 | 30 | no | 6.4 | NS |
| | | 40 | yes | 6.2 | |
| | | 40 | no | 6.9 | |
| MRC 1991 [44] | 369 | 17 | yes | 5.9 | NS |
| | | 30 | no | 5.8 | |
| MRC 1996 [45] | 509 | 17 | yes | 7 | P = 0.03 |
| | | 39 | no | 9 | |

Legend: MRC - Medical Research Council Lung Cancer Working Party; # - all histologies

The trial reported by the Medical Research Council's Lung Working Party[45] was not handicapped to the same degree as the earlier studies by the inclusion of patients with adverse prognostic characteristics, although 24% of patients did have non-ambulatory performance status, and the number of patients [if any] with supraclavicular lymph node involvement or pleural effusion was not reported. The 22 Gy difference [uncorrected for fraction size] in dose between the arms [39 Gy in 13 fractions versus 17 Gy in 2 fractions] was the largest in any of the studies reported in Table XXVII. The finding of a small survival advantage in favour of patients randomised to have 39 Gy [hazard ratio = 0.82; 95% CI: 0.69 - 0.99; p = 0.03] therefore represents some of the most important evidence in support of a dose-survival relationship. The survival advantage was associated with a reduction in local recurrence – although this was not statistically significant – *and* a reduction in distant metastases [hazard ratio = 0.69; 95% CI: 0.55 – 0.86], suggesting that improving local control has an effect on the incidence of distant metastases, similar to the Halstedian model of breast cancer[46].

Building on our own study, and using a similar analytical strategy, Schaafsma and Coy examined the survival of 129 patients with NSCLC on whom data including TNM staging had been prospectively collected as part of a cost-effectiveness study in British Columbia[47]. Patients were divided into three groups according to radiotherapy dose; a 'no treatment' option in which patients either received no primary treatment or low dose palliative treatment [less than 30 Gy in one to six fractions]; a high dose palliative group in which the dose was 30-50 Gy in 10-20 fractions with palliative intent; and a radical radiotherapy group, in which the dose was 50 Gy in 20 or more fractions, with curative intent. The basis for allocating patients to a particular policy was not described; however 26% of patients in the 'no-treatment' group had distant metasases as did 11% of patients in the high dose palliative group.An initial analysis showed that the survival of the patients having no treatment or low

dose palliation was the same, holding everything else constant. However, the median survivals of the no-treatment, high dose palliative and radical groups were 123, 266, and 651 days respectively. When the treatment variables were fitted to a Cox proportional hazards model containing the prognostic factors examined by ourselves *plus* TNM stage and tumour size, the improved survival of the high dose palliative and radical groups were statistically significant individually [p = 0.0388 and p = 0.0001 respectively] and jointly [p = 0.0004]. The authors calculated that the death rates of of the high dose palliative and radical radiotherpy patients were 53% and 24%, respectively, of what they would have been had these patients not received treatment. They concluded that 'Despite the differences in variable definitions, the number of prognostic variables in the model, and patient sample, our estimates of the survival benefit attributable to treatment are qualitatively similar to those reported by Ball *et al.*' It is of interest that Schaafsma and Coy found TNM staging, tumour size, tumour histology [adenocarcinoma had a 92% higher death rate than other histologies] and weight loss to be independent and statistically significant prognostis factors, but Karnofsky performance status was only marginally so [p = 0.0735]. In their final paragraph, they say: 'our prospective analysis illustrates how the Cox proportional hazards model with covariates can be used to estimate treatment effects on survival when a randomised clinical trial cannot be conducted for ethical reasons'.

It seems unlikely that further evidence will become available – particularly of a randomised nature – to support the existence of a dose-survival relationship for NSCLC up to 60 Gy. Consensus is not evidence, but if there is widespread agreement among clinicians on their preferred management strategy for loco-regional non-metastatic disease, there will be negligible incentive to study the question further. For example, 58 international lung cancer 'experts' were surveyed in 1996 and asked their treatment recommendation for a 77 year old man with a T2N0 adenocarcinoma of the left lower lobe[48]. The patient was not fit for surgery

on medical grounds. Curative radiotherapy was recommended by 75.8% of respondents, and combined radiotherapy and chemotherapy by 17.2 %. Only 5.2% recommended a policy of 'wait and see'. The responses of a group of Australian lung cancer clinicians, predominantly thoracic physicians, who were surveyed about the same case, indicated a higher level of scepticism. Curative radiotherapy was recommended by only 49.8% of respondents, combined radiotherapy and chemotherapy by 7.0% and 'wait and see' by 24.7%[48].

Acceptance [at an international level] of what evidence there is for a beneficial survival effect of radical radiotherapy, in particular the randomised studies of the RTOG[14] and the MRC[45], and the non-randomised studies from British Columbia[47] and ourselves [previously published[36] and this thesis], though imperfect, has been underlined by the consistent choice of radiotherapy [60 Gy] as the standard therapy control arm in those randomised trials which have shaped the modern non-surgical management of NSCLC. These studies will be described in detail in Part II of this thesis.

# PART II.

## Treatment intensification for non-small cell lung cancer.

## 2.1 Introduction and background

The next generation of studies of radical radiotherapy for locoregional NSCLC after RTOG 73-01 involved a variety of different strategies, but nearly all were were based on the principle of treatment intensification either by dose escalation beyond 60 Gy in six weeks, or by the addition of chemotherapy. The various strategies can be classified according to aim and method:

[i] Improved local control

[a] dose escalation -hyperfractionation

-conformal therapy with standard fractionation

[b] radiosensitisation - concurrent chemotherapy

[c] induction chemotherapy

[d] reduction of overall treatment time.

[ii] Reduction in incidence of metastatic disease.

[a] an intended benefit of [i-c]

[b] an incidental benefit of [i-b]

We shall consider each of these strategies one by one

### 2.1.1 Hyperfractionation

Hyperfractionation refers to the delivery of radiotherapy using fraction sizes smaller than 1.8 to 2 Gy and administering multiple treatments per day so that there is no change in overall treatment time. The theoretical basis for hyperfactionation is that smaller doses per fraction are less damaging to late-reacting normal tissues. Provided there is no corresponding reduction in tumour sensitivity, it may be possible to improve the therapeutic ratio by increasing total dose without an increased risk of complications in late-reacting tissues[49]. It is

well established that the opposite approach - hypofractionation [the use of a small number of large dose fractions] – is associated with an increased risk of late effects in relation to the acute reactions. For example, in a series of patients with early laryngeal cancer treated with radiotherapy at PMCI, I and several colleagues had been able to show a lower rate of tumour control *and* a greater risk of delayed treatment-related complications in patients whose course was hypofractionated [7 x 6 Gy, once per week] compared with those patients receiving conventional fractionation [30 x 2 Gy, 5 days per week][50].

If conventional fractionation is safer, could further sparing of late reacting tissues be achieved using doses per fraction less than 1.8 Gy? In 1983 the RTOG embarked on a dose escalation study using hyperfractionated radiotherapy [RTOG 83-11][51]. The study design was unusual for a dose escalation trial: patients were initially randomised to one of three dose levels: 60.0 Gy, 64.8 Gy, and 69.6 Gy. Furthermore, a pilot study involving 125 patients had already demonstrated the feasibility of dose escalation with hyperfractionation to 74.4 Gy[52]. Daily doses of 2.4 Gy were given in two fractions of 1.2 Gy separated by 4 to 8 hours, 5 days per week. When the risks of grade 3 or greater reactions were found acceptable, the lowest total dose was discontinued and a fourth dose level, 74.4 Gy was added; the highest dose evaluated was 79.2 Gy. It could be argued that the starting dose was unnecessarily conservative, since the toxicities in the highest dose arm of 73-01 [60 Gy conventional fractionation] had hardly been dose-limiting. The absence of a definition for 'acceptable toxicities' perhaps explains the large accrual - 848 patients - with no significant differences being found between arms in respect to either acute or late toxicities, or survival. Thus, although 83-11 demonstrated the feasibility and safety of giving up to 79.2 Gy, it provided no evidence that the higher doses achieved with hyperfractionation improved the outcome. It did however place significant additional demands on the patients who had to attend for treatment on 66 occasions if they were randomised to the highest dose level.

In an attempt to explain the observed absence of a dose-survival relationship in 83-11, Cox et al performed a subset analysis, examining the survival of those patients with the most favourable pre-treatment characteristics: stage III disease, Karnofsky performance status 70-100 and less than 6% weight loss. When this was done, patients randomized to 69.6 Gy had a better survival than patients randomized to the two lower dose groups [p=0.02]; but beyond 69.6 Gy there was no additional survival advantage[51]. The possibility that prolongation of overall treatment time had offset any advantage of the higher dose was investigated in a further analysis published separately[53]. Interruptions to treatment were indeed increasingly common with increasing dose, and any prolongation of time was associated with shortened survival. Multivariate analysis revealed that the effect of treatment delay on survival was confined to patients who received total doses of $\geq$69.6 Gy.

The conclusions that can be drawn from RTOG 83-11 are limited because of the absence of a 60 Gy conventional fractionation control arm and the dependence of the main findings on subset analysis; but the results suggested that hyperfractionated radiotherapy at a dose of 69.6 Gy was at least worthy of further investigation and so it became one of the investigational arms of the next RTOG study, 88-08, to be described in detail below.

### 2.1.2 Dose escalation using conformal therapy with standard fractionation.

If a dose-response relationship for NSCLC exists for standard fractionation up to 60 Gy, it is logical to hypothesize that higher doses may improve local control and survival further still. The chief factor limiting the dose of radiotherapy to any tumour is the tolerance of the adjacent normal tissues which may be incidentally irradiated. The aim of increasing the precision of dose delivery exclusively to the tumour has therefore always been a high research priority in radiotherapeutic physics. The development of computer software programs which

enable three dimensional [3D] visualisation of the tumour and its relationship to the surrounding normal structures has significantly improved our ability to increase tumour dose while limiting the dose to surrounding normal tissues. The use of multiple beams in different planes and the customised shielding of normal tissues on all beams can create a dose envelope which conforms more closely to the shape of the tumour and irradiates less normal tissue than can be achieved with simple arrangements using two dimensional planning[54, 55].

The feasibility of dose escalation beyond 60 Gy using 3D planning techniques has now been well established by groups in St Louis[56] and at the University of Michigan[57]. The Michigan group have achieved doses as high as 102.9 Gy given as 2.1 Gy daily fractions to limited volumes with acceptable pulmonary toxicity [M. K. Martel, personal communication]. As none of the 3D dose escalation studies has progressed beyond the phase I level meaningful comparative survival data are not available at the time of writing, but preliminary analysis of local progression-free survival suggests that doses above 70 Gy may be more effective than lower doses[58].

There are numerous issues yet to be resolved before high dose conformal therapy is ready for phase III testing. Can clinically negative draining lymph nodes be safely excluded from the target volume? Can breath-holding or respiratory gating techniques be used to immobilise the tumour during treatment to minimise the size of the planning target volume [PTV]? What doses can be safely given with concurrent chemotherapy? Even though it is much more labour intensive than conventional planning and delivery techniques, the principle of high dose conformal therapy is nevertheless appealing, especially as the Michigan group have used modelling techniques to calculate that doses of the order of 84 Gy may be required to achieve 50% local progression-free survival at 30 months[58].

### 2.1.3 Radiosensitisation using concurrent chemotherapy.

The notion that the cytotoxicity of ionizing radiation might be enhanced by the concurrent administration of a chemical modifier has long been attractive to radiation oncologists, particularly if the increased cytotoxicity is confined to or expressed to a greater degree in malignant cells compared with normal tissue. An obvious choice is the nitroimidazoles, a group of agents that selectively sensitise hypoxic tumour cells which are known to be relatively radioresistant compared with fully oxygenated cells. Clinical experience with most of these agents has however been disappointing, and they have not found a permanent place in standard radiotherapy practice[59].

**Cisplatin.** Cisplatin, which had been discovered in 1965, is an important cytotoxic agent in its own right. In addition, it was found to produce radiosensitisation [i.e. an increase in cell lethality greater than the added effects of each agent used singly] of hypoxic mammalian cells in 1977 by Douple and Richmond[60], suggesting a rationale for combined platinum-radiotherapy[61]. How radiosensitisation occurs is unclear, but suggested mechanisms have included an increase in the yield of free radicals, reduction of levels of endogenous radioprotectors and inhibition of repair of sublethal and potentially lethal damage[61]. Subsequent preclinical studies revealed that in most cases the supra-additive effects of the combination was greatest when the cisplatin was given a short time before irradiation[62]. In normal tissues, on the other hand, most data suggested that the increase in damage is merely additive and the result of independent cell killing[62]. In studies on the RIF-1 tumour implanted in mice, the greatest supra-additivity was seen when cisplatin was given immediately before irradiation, daily for five consecutive days; this schedule also produced the greatest gain in therapeutic ratio[63]. Thus, the experimental work stongly suggested that combined therapy held prospects of improving the treatment outcomes, by causing proportionately more cell killing in neoplastic than in normal tissues.

The feasibility of administering cisplatin with radical radiotherapy in patients with NSCLC was first demonstrated in a phase I study at the Netherlands Cancer Institute conducted by Schaake-Koning and colleagues[64]. Patients were treated with radiotherapy to 55 Gy in 20 fractions, with a two week break after the first phase, given as 30 Gy in 10 fractions in two weeks. After the break, a further 25 Gy in 10 fractions was administered. Cisplatin was given on the first day of radiotherapy in each week of treatment. The dose was increased progressively in cohorts of three patients from 10 mg/m$^2$ per week to 35 mg/m$^2$ at which level dose-limiting toxicity in the form of intractable nausea and vomiting was reached. The maximum tolerated dose [MTD] was therefore taken to be 30 mg/m$^2$ per week. Other acute and late toxicities were acceptable. Nine patients [45%] achieved a histologically proven complete response. As a result this regimen was taken forward into a randomised trial of the European Organisation for Research and Treatment of Cancer [EORTC].

At first the trial was described as 'randomised phase II' and patients were randomised to one of three arms: radiotherapy alone, 55 Gy in 20 fractions in six weeks with a two week break; the same radiotherapy with weekly cisplatin 30 mg/m$^2$ as in the dose-finding study; and a third arm in which the cisplatin was given daily immediately before each fraction of radiotherapy at a dose of 6 mg/m$^2$. Eligibility included inoperable stage I, II or III disease, performance status ECOG $\leq 2$ and weight loss $< 15\%$. The results with 100 patients enrolled were published in 1990 with an announcement that the study would continue as a phase III trial although accrual had closed by the time of publication[65]. The phase II study not only established the feasibility of giving low dose daily cisplatin, but also revealed a survival advantage favouring daily cisplatin which was of borderline statistical significance [$p = 0.056$]. The final report with 331 patients enrolled appeared in *The New England Journal of Medicine* and it confirmed that combined therapy was associated with better local control and

longer survival compared with radiotherapy alone[66]. At 12 months the estimated survival of patients randomised to daily cisplatin was 54% compared with 46% for patients randomised to radiotherapy alone; at two years the corresponding figures were 26% and 13% respectively [p = 0.009]. The survival of patients randomised to weekly cisplatin was not significantly different to that of patients randomised to radiotherapy alone [p = 0.36]. Global comparison of all three treatment groups showed that survival improved when cisplatin was combined with radiotherapy [p = 0.054]. The time to local recurrence was significantly longer in the groups given cisplatin [p = 0.015], especially when it was given daily [p = 0.003]. There was however no difference between groups in time to distant metastasis. There were no differences in acute or delayed toxicities between the groups. Multivariate analysis of prognostic factors indicated that weight loss, performance status and the type of treatment all had a significant association with survival; interestingly, location of the tumour in the upper lobes approached significance, but there was no mention of an influence of TNM stage. The outcomes observed were therefore as might have been predicted from the preclinical studies: cisplatin is a radiosensitizer [because it influenced local control rather than metastatic spread]; the radiosensitizing effect appeared to be confined to the tumour and not the normal tissues; and it was most effective if given as frequently as possible, before irradiation.

In spite of the impressive differences of the EORTC study, there has been a puzzling reluctance on the part of many clinicians to accept the result and it seems to have had little influence on practice. One reason for this may have been the prior publication in 1990 of a study by the Cancer and Leukemia Group B [CALGB], which showed a survival advantage for patients with inoperable NSCLC who were given cisplatin-based chemotherapy *before* radiotherapy[67]. Another reason may have been the failure of three other randomised trials of concurrent cisplatin and radiotherapy to confirm the EORTC result, although in only one of these was the cisplatin given daily.

In 1988 Soresi and colleagues in Milan had reported a study in which 95 patients with NSCLC were randomised to radiotherapy [50 Gy] with or without weekly cisplatin 15 mg/m$^2$. This revealed a survival advantage for patients randomised to the combination [median survival 16 months versus 11 months for patients randomised to radiotherapy alone], but with limited patient numbers this did not achieve statistical significance [p = 0.18][68].

The North-Eastern Italian Oncology Group[69] reported no difference in survival between patients with NSCLC randomised to radiotherapy alone [45 Gy in 15 fractions] or to the same radiotherapy plus daily cisplatin, 6 mg/m$^2$. The poor survival in both arms - median survival approximately 10 months – may be a reflection of the broad inclusion criteria [patients with supraclavicular node involvement and poor performance status – minimum Karnofsky 60 – were eligible] and the low dose of radiotherapy prescribed. The inclusion of patients with poor prognostic characteristics and the inadequacy of the radiotherapy ensured that the trial was going to be underpowered in comparison with the EORTC study, even though the cisplatin was administered in an identical manner – but for three weeks, not four.

The third study, by the Hoosier Oncology Group, randomised 240 patients to 60-65 Gy radiotherapy with or without cisplatin given as 70 mg/m$^2$ every three weeks, commencing on the first day of radiotherapy[70]. There was a trend to improved progression-free survival with combined chemoradiotherapy [p = 0.054] more marked in patients with non-squamous histology [p = 0.027], but there was no difference in overall survival. Again, median survivals were disappointing for combined treatment [43 weeks] and radiotherapy alone [46 weeks], especially as the study population included a small number of patients with inoperable stage I or II disease. Although patients with Karnofsky scores as low as 50 were eligible, there were no differences in survival when the outcomes for good performance status patients were compared.

How do we reconcile what appear to be conflicting results? It should be emphasised that in none of the three inconclusive studies was the most effective investigational treatment arm of the EORTC trial duplicated; and in two of the studies[68, 70] there was a suggestion of a benefit of combined therapy, but the numbers of patients may have been too small to allow detection of a statistically significant effect. The clinicians who have not adopted the daily cisplatin combined approach could argue that the EORTC study has demonstrated an effect of combined modality treatment, but judging by the results of the other studies it is probably small, and may not justify the additional cost, inconvenience and toxicity that daily administration of cisplatin entails. We do not have the evidence to say that their line of argument is right or wrong, but if survival, local control and absence of enhanced radiation toxicity are the endpoints by which a treatment is judged, the EORTC trial ranks as a landmark study providing the best available evidence for a clinical radiosensitising effect of cisplatin in NSCLC.

**Carboplatin.** Clinical evaluation of the second generation platinum complex, carboplatin, began in the early 1980's, with the expectation that higher levels of platinum could be achieved because it was less toxic than cisplatin without the dose-limiting gastrointestinal and renal toxicities[71]. Preclinical studies did indeed confirm that carboplatin could enhance radiation-induced cell killing in bacteria[71] although in oxic RIF1 cells in culture it was only a modest radiosensitiser producing an enhancement ratio [DER] of 1.2 [ratio of dose of radiation alone versus dose of radiation with carboplatin to achieve a survival of 3%][72]. It was however an extremely potent inhibitor of repair of sublethal damage[72]. Any benefit of this latter effect would clearly only be evident if the radiotherapy were given as a series of fractions, rather than as a single dose.

Skov and MacPhail studied the interaction of both cisplatin and carboplatin with radiation in hypoxic Chinese hamster V79 cells, and found higher DER's at lower doses of radiation, which are closer to those used clinically[73]. For example, the DER at 80% survival was 2.0 after incubation with carboplatin for an hour before irradiation; at 2% survival the DER was 1.2. A comparable dose of cisplatin also achieved a DER of 2.0 at 80% survival. The enhancement of cell kill in V79 cells disappeared when they were irradiated in oxic conditions with a DER of 1.0 for both cis- and carboplatin at 80% survival.

The importance of timing drug administration and radiation was investigated by Schwachofer and colleagues in a series of experiments using multicellular spheroids derived from the human tongue squamous cell carcinoma line HN-1[74]. The authors regarded spheroids as a more realistic in vitro model than monolayer cultures. Using the dose to induce growth delay 10 days as the endpoint, the DER's were maximal for both cis- and carboplatin if they were present at the time of irradiation, and split doses were used, with values of 3.9 and 3.2 respectively. There was no enhancement if the spheroids were exposed to drug, and then washed, 24 hours before irradiation. The DER's were much lower [1.2-1.5] if the drugs were administered after irradiation. Carboplatin produced similar results to cisplatin, but in the doses used it was less effective in producing growth delay or cure.

Two human small cell lung cancer cell lines, one sensitive to, the other resistant to cisplatin cytotoxicity, were studied by Groen and colleagues for evidence of cis- and carboplatin radiation enhancement[75]. The cells were irradiated under oxic conditions with single doses, and enhancement ratios calculated for a survival of 75%. Pre-treatment incubation with drug for 24 hours produced the largest DER's, with values of 1.36 for cisplatin and 1.21 for carboplatin at the lowest concentration of drug tested. Enhancement with both drugs was also

observed in the cisplatin-resistant line. The DER's varied with the concentration and duration of exposure to drug, but cisplatin consistently showed higher DER's than carboplatin.

It seems reasonable then to draw the following conclusions from the limited pre-clinical data:

[a] carboplatin enhances radiation-induced cell killing in a variety of cell lines;

[b] the greatest effects are seen when the drug is present at the time of irradiation, when the cells are hypoxic, and when the radiation dose is fractionated;

[c] the effects are similar to cisplatin, but of a slightly lower magnitude;

[d] sensitivity to cisplatin may not be a pre-requisite for enhancement to occur.

Based on these observations, carboplatin seemed an appropriate drug to test as a clinical radiosensitiser. Although not appearing to have the same efficacy of cisplatin, it was much less toxic, and there was the possibility that there might be better patient compliance with prospects of giving higher doses - which could conceivably compensate for any theoretical reduction in radiosensitisation. It was an idea that I and my colleagues would explore further in the randomised trial to be reported in detail later in this thesis.

**2.1.4 Induction chemotherapy.** The observation that cisplatin chemotherapy was more likely to produce responses in NSCLC patients with good performance status encouraged the CALGB to devise a trial [8433] in which chemotherapy was given before radical radiotherapy[67]. This might have two effects: [a] in responding patients the cytoreduction would leave fewer clonogens for the radiotherapy to sterilize, increasing the probability of local cure; and [b] the chemotherapy might destroy clinically inapparent micrometastases. By giving the chemotherapy at the outset, the micrometasases would not have an opportunity to grow unchecked while the six week course of radiotherapy was being administered. The term 'neoadjuvant' was therefore used to describe this approach. The CALGB study, published in

1990 in *The New England Journal of Medicine* was a landmark, because for the first time since the 1966 report of the VA study by Wolf and colleagues[8], a survival benefit for a non-surgical therapeutic intervention had been unequivocally demonstrated in patients with NSCLC.

In this trial patients with stage III NSCLC, performance status ECOG 0 or 1, less than 5% weight loss, and no supraclavicular nodes or pleural effusion were randomised to two cycles of chemotherapy with cisplatin and vinblastine followed by radiotherapy 60 Gy in 30 fractions in six weeks, or to radiotherapy alone. Between 1984 and 1987, 180 patients were enrolled, at which time an interim analysis revealed a survival advantage in favour of the patients randomised to induction chemotherapy. The median survival of the 78 eligible patients having chemotherapy was 13.8 months compared with 9.7 months for 77 patients having radiotherapy alone [p = 0.0066]. A later report confirmed the benefit of induction chemotherapy with seven-year follow-up[76]. At five years survival in the combined modality group was 17% compared with 6% for patients randomised to radiotherapy alone. A five year survival of 17% in patients with stage III disease would have been respectable had the treatment been surgery[19]. There was a high incidence of disease progression both locally and at distant sites in both groups, and it was not clear whether the improved survival was a consequence of better local control or a reduction in incidence of distant metatasis.

An effect of induction chemotherapy on rate of distant metastasis was however clearly evident in the preliminary report of a randomised trial published by Arriagada and colleagues in 1991[77]. In this study, patients with inoperable NSCLC [but excluding adenocarcinoma] were randomised to arm A, radiotherapy alone [65 Gy in 26 fractions] or arm B, the same radiotherapy following induction chemotherapy consisting of three monthly cycles of a combination of vindesine, cyclophosphamide, cisplatin and lomustine. The eligibility criteria

allowed for randomisation of patients with stage I and II as well as stage III disease [including involvement of supraclavicular nodes], with a minimum performance status of >50%. Three hundred and fifty three patients were randomised, and evaluation of local control was rigorous, requiring bronchoscopic histological confirmation of complete response. The median survival of patients randomised to arm A was 10 months compared with 12 months for arm B [p = 0.08]. Local control at one year was only 17% for arm A and 15% for arm B. However the relative risk of metastasis was 2.0 for the radiotherapy arm compared with the combination [p = 0.02]. A subsequent publication with updated results indicated that the survival difference between the arms had become statistically significant at p = 0.02 with 14% of patients in arm A alive at two years compared with 21% in arm B[78].

The French study thus indicated that local control was extremely poor in spite of a dose of 65Gy, and that the only effect of giving chemotherapy and radiotherapy in sequence was to reduce the incidence of distant metastasis. Induction therapy did not appear to tackle the problem of local failure, which presumably contributed to a significant number of patient deaths.

A similar lack of influence of induction chemotherapy on local control was observed in an analysis of patterns of failure in an intergroup trial which had been designed to confirm the results of CALGB 8433[79]. This study [RTOG 8808] was first reported by Sause and colleagues in 1995[80] and updated in 2000[81]. The study had an almost identical design to CALGB 8433, with the two original treatment arms plus the addition of a third arm, the hyperfractionated 69.6 Gy schedule from RTOG 83-11[51]. Eligibility criteria included Karnofsky performance status > 70%, weight loss < 5% in the previous three months, and stage II – III disease. There were 458 eligible patients, 95% of whom had stage III disease. The differences in survival between treatment arms, although statistically significant, were not

as pronounced as in Dillman et al's report of long-term follow-up[76]. The median survival of patients randomised to induction chemotherapy was 13.2 months compared with 11.4 months for those randomised to radiotherapy alone [p = 0.04][81]. Patients randomised to hyperfractionated radiotherapy had an intermediate result with a median survival of 12 months, not significantly better than for conventionally fractionated radiotherapy. Five year survivals were: standard radiotherapy alone, 5%; induction chemotherapy, 8%; hyperfractionated radiotherapy, 6%. The benefit of induction chemotherapy was most noticeable in patients under the age of 60.

An analysis of patterns of failure[79] revealed a reduction in the incidence of distant metastasis in patients randomised to induction chemotherapy, as in the French study, and there was no effect of chemotherapy on local control. Paradoxically, the reduction in metastatic disease, confined to patients with squamous cell carcinoma, was not associated with a survival advantage; patients with non-squamous histology had no chemotherapy-associated reduction in distant metasasis, but did have a better survival. The authors were therefore unable to explain the precise reason for the better survival in patients randomised to induction chemotherapy, but with such small differences in survival between the arms to start with, it would be difficult to detect any further differences in smaller subsets. Furthermore, an analysis of the rates of failure, rather than the absolute incidence, would have been more informative since virtually every patient failed at some time; however, in contrast to the EORTC study[66] actuarial rates were not reported.

Cisplatin-based induction chemotherapy before radiotherapy was associated with longer survival compared with radiotherapy alone in two other large trials, one conducted by the Swedish Lung Cancer Study Group [number randomised: 302][82] and the other by Cullen and colleagues in Britain [n = 446][83]. The differences were less marked than in the earlier studies,

with the median survivals in the Swedish study 10.5 months and 11.0 months for the radiotherapy and combined arms respectively [p = 0.11]. At five years survival was 1.4% and 3% respectively. Because more patients with unfavourable characteristics were randomised to the combined treatment arm, multivariate Cox analysis did show a favourable effect of the addition of chemotherapy on survival that was statistically significant [p = 0.045]. There was a trend to fewer distant metastases in the combined treatment group [p = 0.10]. As in the French study[77], local control was poor: 10% in the combined treatment group and 5% in the radiotherapy group [p = 0.08]. The survival difference was not statistically significant in the British study, the median being 11.7 months for combined modality treatment and 9.7 months for radiotherapy alone [p = 0.14][83]. Patterns of failure were not reported in this study.

A meta-analysis of 22 trials involving 3033 patients comparing radical radiotherapy versus radical radiotherapy plus chemotherapy was performed by The Non-Small Cell Lung Cancer Cooperative Group and reported in the *British Medical Journal* in 1995[84]. The results showed a significant overall benefit of chemotherapy, with a 10% reduction in risk of death [p = 0.006], corresponding with absolute benefits of 3% at two years and 2% at five years. Trials using cisplatin-based chemotherapy provided the strongest evidence in favour of chemotherapy, with a 13% reduction in risk of death [p = 0.005], equivalent to an absolute benefit of 4% at two years and 2% at five years. In most of the trials included in the meta-analysis, the chemotherapy was given before radiotherapy and in only one study was the chemotherapy [cyclophosphamide] given concurrently with radiotherapy.

Based on these studies of induction chemotherapy and the meta-analysis, we can conclude that there is a small survival benefit associated with the addition of cisplatin based-chemotherapy and that this may be a consequence of a reduction in risk of distant metasasis; it does not appear to be a result of improved local control. The magnitude of the benefit,

particularly as measured by five year survival, may not be as great as suggested by the result of CALGB 8433[67].

A slight or absent effect of induction chemotherapy on local control has been observed at other sites, including cancer of the head and neck[85], cancer of the cervix[86] and cancer of the bladder[87], even though the chemotherapy can cause substantial reduction in the size of the cancer before radiotherapy. The explanation for this is unclear, but it is possible that any benefit of chemotherapeutic cytoreduction is offset by accelerated repopulation of the remaining clonogens, and that the increase in overall treatment time required to deliver two or three cycles of chemotherapy is largely wasted. The importance of overall treatment time and its effect on outcome will be discussed in more detail in the next section, but it is sufficient to say that the use of concomitant chemotherapy and radiotherapy appears to be more effective than sequential treatment, at least in head and neck cancer[85] and cancer of the cervix[88]. In NSCLC there is now one published trial[89] in which induction chemotherapy has been compared with concomitant administration of chemotherapy and radiotherapy, and a second study which has appeared only in abstract form at the time of writing[94].

The West Japan Lung Cancer Group[89] randomised 320 patients with stage III NSCLC and ECOG performance status 0-2 to receive two cycles of chemotherapy [mitomycin C 8 mg/m$^2$ day 1, vindesine 3 mg/m$^2$ days 1 and 8, and cisplatin 80 mg/m$^2$ day 1] four weeks apart either preceding or concurrently with radiotherapy [56 Gy in 28 fractions]. Patients with involvement of supraclavicular nodes were eligible. The patients randomised to concurrent treatment were given split course radiotherapy, with a 10 day break introduced after 28 Gy. Those randomised to sequential treatment had no planned break in radiotherapy. There was a statistically significant survival advantage [$p = 0.04$] for patients randomised to concurrent treatment with median and five year survivals of 16.5 months and 15.8% respectively

compared with 13.3 months and 8.9% for the sequential group. If patients with supraclavicular node involvement were excluded from the analysis, five year survivals were 17.9% for the concurrent group and 7.1% for the sequential [p = 0.018]. There were more local relapses in patients having sequential therapy [39.3% versus 32.7%] but this was not statistically significant [p = 0.273]. There were more brain relapses in patients randomised to concurrent treatment, perhaps reflecting the increased risk associated with longer survival as is seen in patients with small cell lung cancer[90]. The patterns of failure failed to explain the survival advantage, as in the intergroup study[79], probably the result of the small size of the subgroups and the incidence of failure being reported as an absolute rather than time dependent phenomenon. It is likely that the benefit was multifactorial, and that improved local control was contributory.

One of the major criticisms levelled at the concurrent approach is the concern that there will be an increase in treatment related toxicity which may require a chemotherapy dose reduction. This in turn may lead to loss of efficacy of the systemic effect of the chemotherapy against subclinical disease. The frequency of myelosuppression was greater on the concurrent arm in the West Japan study, but there were, surprisingly, no significant differences between arms in relation to other toxicities, including oesophagitis and pulmonary toxicity. The use of split course radiotherapy may have ameliorated the risk of these toxicities in the concurrent arm, because there was no additional need for dose reduction in this group. We can infer from this that the systemic effects of chemotherapy were not compromised by the concurrent approach.

If we accept the result of the West Japan study, how do we explain it? We do not know the comparative rates of local and distant relapse between the arms, although we do know that while overall relapse rates were similar in both arms, there were fewer local failures in patients having concurrent treatment. This occurred *even though those patients received split*

*course radiotherapy* which, for reasons to be explained below, we would regard as inferior to the continuous course given to the sequential group.

There are three theoretical reasons why the concurrent approach might improve survival, and they all relate to improvement in local control. They are: cisplatin radiosensitisation; exploitation of non-cross resistant treatment modalities; and reduction in overall treatment time.

Both preclinical[62] and clinical studies[66] have shown that cisplatin radiosensitisation is greatest when cisplatin is given shortly before irradiation, and the more often it is given, the greater the probability of local control. It seems unlikely that cisplatin given weeks before irradiation [as in induction therapy] is likely to have any significant radiosensitising effect.

Drug resistance, both intrinsic and acquired, is thought to be an important reason why some cancers, initially responsive to cytotoxic chemotherapy, subsequently begin to grow in spite of continued treatment. The chance of clones which are intrinsically chemoresistant to agent A proliferating during treatment may be reduced by the simultaneous administration of additional cytotoxic agents which, having a different mechanism of action, kill those cells resistant to A while they are few in number. This hypothesis, an extension of the one developed originally by Goldie and Coldman[91], provides the rationale for combination chemotherapy not only of cancer, but also of microbial infections. Lack of cross-resistance between radiotherapy and cytotoxic drugs is something we observe regularly in clinical practice, when patients are referred for radiotherapy which then produces responses even after their cancer has progressed in spite of chemotherapy. To maximize cell kill, therefore, it is logical to administer both radiation and chemotherapy simultaneously.

Finally, there was a difference in the overall treatment time between the arms in the West Japan study. The total time to deliver the induction therapy program was 13 weeks, the concurrent program a little over 7 weeks. For reasons that are made clear in section 2.1.6, prolongation of overall treatment time is detrimental to local control, and this probably applies to combined modality treatments as well as to radiotherapy used alone[92].

Although one meta-analysis showed that the magnitude of benefit was similar whether platinum-based chemotherapy was administered sequentially or concurrently with radiotherapy[93], the West Japan study is the only published randomised trial in which the two approaches have been compared directly. The results of a randomised trial comparing sequential and concurrent chemotherapy/radiotherapy conducted by the RTOG [9410] have been presented in abstract form[94], and although the survival differences bordered on statistical significance, they favoured patients randomised to concurrent treatment [median survivals: sequential arm 14.6 months, concurrent arm 17.0 months, $p = 0.08$].

The available evidence therefore supports the concurrent approach, in spite of its greater toxicity. The observations from these studies also support the argument that any survival advantages are due to the combination of radiotherapy and chemotherapy, and are not due solely [as suggested by some sceptics] to chemotherapy alone. They are thus in keeping with the results of an earlier randomised trial, also conducted in Japan, which demonstrated superior long-term [but not median] survival in patients randomised to have sequential chemotherapy and radiotherapy compared with chemotherapy alone[95].

### 2.1.5 Reduction in overall treatment time.

The concept of accelerated repopulation during treatment was first introduced by Withers and colleagues in 1988[96], and it has since become one of the cornerstones of modern clinical

radiobiology. Although the phenomenon was originally identified using local control data from patients who had received radiotherapy for oropharyngeal cancer, there is now evidence to suggest that accelerated repopulation occurs in NSCLC as well[97]. Cox and colleagues had shown a reduction in survival associated with treatment interruptions on RTOG 83-11[53] [see section 2.1.1]. Using this data – and recognising that the end point was survival and not local control – Fowler and Chappell have estimated that the loss of survival to be on average 1.7% per day of delay[97]. They advocated limitation of overall treatment times after calculating that clonogenic doubling times may accelerate to 3 – 3.5 days after 3 or 4 weeks of treatment. With conventionally fractionated radiotherapy, a substantial proportion of dose delivered beyond four weeks may theoretically be wasted as the amount of cell killing is offset by accelerated repopulation of the remaining clonogens. A similar phenomenon may also occur in association with other treatment modalities and so explain the minimal effect of induction chemotherapy on ultimate local control in spite of evidence of an initial reduction in tumour size in patients with head and neck cancer[92].

The challenge, in reducing overall treatment time to four weeks or less, is to give a radical dose without increasing the risk of late effects which will result if fraction size is increased. To keep the dose per fraction at 2 Gy, and still deliver 60 Gy, it is therefore necessary to give 2 or 3 treatments per day, or to treat more than 5 days per week. This is termed accelerated fractionation, as opposed to hyperfractionation. Fears that pure acceleration without total dose reduction might produce unacceptable toxicity led some investigators to reduce the dose per fraction to less than 2 Gy, increasing the number of fractions even further but still enabling a high total dose. This mixture of reduced treatment time *plus* increased number of fractions at less than 2 Gy per fraction is thus termed hyperfractionated accelerated radiotherapy [HART], and if given continuously seven days a week without interruption, continuous HART [CHART][98].

The schedule with which the CHART acronym has become most closely associated was first developed and tested in the late 1980's at the Mount Vernon Hospital in London in patients with cancers of the head and neck and bronchus. Initially, 38 patients were treated with 36 fractions of 1.4 Gy to a total dose of 50.4 Gy in 12 days[99]. The treatments were given at 8 a.m., 2 p.m., and 8 p.m. on 7 days per week. When the early tolerance was noted to be acceptable, the dose per fraction was increased to 1.5 Gy, so that the total dose was 54 Gy. The first phase target volume included the primary tumour with a margin and the regional lymphatic drainage. After 30 treatments, the target volume was reduced and only the known areas of involvement were treated for the last 6 fractions. The acute reactions, specifically oesophagitis, were noted to be more intense than with conventional radiotherapy, as might have been predicted[100]. Although it was anticipated that the late reactions would be less because of the incorporation of hyperfractionation, two cases of radiation myelopathy were observed in the first 206 patients, both in individuals who had been treated for cancer of the head and neck[101]. The dose originally allowed on the spinal cord [44 Gy] was therefore reduced in subsequent patients to a maximum of 39 Gy.

The survival of 75 patients with locally advanced NSCLC treated with CHART on the pilot study - 60% at one year and 40% at two years - was sufficiently encouraging in comparison with historical controls[102] that a randomised multicentre trial of CHART versus conventional radiotherapy was undertaken. Between 1990 and 1995, 563 patients with inoperable NSCLC were randomised in a 3:2 ratio to CHART or conventional radiotherapy, 60 Gy in 30 fractions over 6 weeks. Patients with inoperable stage I and II were eligible, and all patients had to have a performance status of ECOG 0 or 1. The results have been reported as interim[103], final[104] and long term analyses[105]. Survival favoured patients randomised to CHART, with a 22% reduction in risk of death, equivalent to an absolute improvement in 2 year survival from 20

to 29% [p = 0.008]. The median survival of patients randomised to CHART was 16.5 months, compared with 13 months for patients randomised to conventional fractionation. Subset analysis revealed that the survival advantage was confined to patients with squamous cell carcinoma, who constituted the bulk [72%] of the study population. The beneficial effect of CHART was mediated through improved local control. Dysphagia occurred earlier and was more severe in the CHART group, but it settled satisfactorily in both arms. There were no cases of radiation myelopathy, but more patients on the CHART arm developed pneumonitis; there were 3 deaths in each arm thought to be a consequence of radiation lung injury.

There was intense interest in the outcome of the CHART study – reflected in the large number of ensuing publications in high profile journals - even though its implementation would be beyond the resources of most departments. But here at least was proof of principle: cellular repopulation is a cause of failure to achieve local control, and reduction in overall treatment time can counteract the effect of repopulation. Further, the CHART trial provided further evidence that local control is important for survival in NSCLC, and that survival can be improved by radiotherapeutic means alone, as argued in part I of this thesis.

In their 1999 report[105], Saunders and colleagues compared the level of benefit achieved by CHART with that of cisplatin-based chemotherapy as reported in the 1995 meta-analysis[84]. CHART was associated with a 22% reduction in risk of death versus 13% for combined cisplatin and radiotherapy. Yet the influence of these results on clinical practice has been negligible, and the reality is that CHART has not been implemented as routine treatment for inoperable NSCLC[106]. There are at least two reasons why this has occurred, in spite of what is strong evidence in favour of a survival advantage. The first is the impracticality of the schedule, requiring long departmental hours, and inefficient use of resources particularly on weekends. It is possible that the schedule could be modified to make it easier to implement

without sacrificing the principle of keeping overall treatment time short and without any loss of effect[107]. But that would still leave the question unanswered: how do the benefits of CHART compare with the "best of the rest", namely conventional radiotherapy combined with concomitant platinum-based chemotherapy[89]? The only randomised study to have directly compared concurrent platinum-based chemotherapy and radiotherapy with a shortened overall treatment time was one designed and conducted by myself with colleagues in Australia, and a detailed analysis of that work forms the next section of this thesis.

## 2.2 A pilot study of concurrent carboplatin chemotherapy and conventional and accelerated radiotherapy for NSCLC.

In 1987, based on the preclinical observations summarised in section 2.1.3 above, my medical oncology colleagues Dr Jim Bishop and Dr Ian Olver and I developed a protocol to test the feasibility of giving radiotherapy and carboplatin concurrently with radical radiotherapy in patients with inoperable NSCLC. We had had considerable experience with carboplatin in the treatment of small cell lung cancer, and were among the earliest groups to report on its clinical efficacy and toxicity in combination with etoposide[108] and with etoposide, cyclophosphamide and vincristine[109]. In these studies we had observed that in combination, carboplatin was extremely well tolerated with nausea and vomiting absent or mild in over 50% of patients, and with minimal mucosal and renal toxicity. The major toxicities were neutropaenia and thrombocytopaenia, but the reduced gastrointestinal toxicity gave carboplatin a particular advantage over cisplatin, since 5-HT3 receptor antagonists such as ondansetron were not available at that time. In both studies three cycles of chemotherapy were given, and those patients with limited disease who achieved a complete or partial response were then given radiotherapy to the primary site and regional lymph nodes to a total dose of 50 Gy in 25 fractions over five weeks[110]. Chemotherapy was not given concurrently

with radiotherapy, and there was no suggestion that the sequential administration of carboplatin-based chemotherapy and high dose radiotherapy was associated with any increase in acute or late toxicity.

### 2.2.1 Study design.

To investigate the toxicity associated with the concurrent administration of carboplatin and high dose radiotherapy [60 Gy], we chose a similar dose schedule to that used in the small cell cancer studies. In both the two-drug and four-drug regimens, carboplatin was given as 100 mg/m$^2$ on days 1, 2 and 3, and the cycle repeated on day 28[107, 108]. Although grade 3 and 4 neutropaenia – the major toxicity – was seen in 63% and 74% of patients in the two-drug and four-drug studies respectively, we felt that neutopenia was likely to be less severe when carboplatin was given as a single agent, and therefore a dose reduction was not indicated. So, in combination with radiotherapy, carboplatin was given as 70 mg/m$^2$ daily on the first five days of radiotherapy and the cycle repeated in week five. This increased the number of days on which drug and radiation were given together, which may have been important for radiosensitisation. If the first cohort of three patients treated at the level of 70 mg/m$^2$ daily for five days experienced no grade 3 or 4 toxicity, and were able to complete treatment as planned, a second cohort of three patients would be given a higher dose at 80 mg/m$^2$ daily for five days.

Because we were also interested in the possibility that shortened treatment time might also improve local control and survival, we extended the pilot study further. Once the maximum tolerated dose of carboplatin given concomitantly with conventionally fractionated radiotherapy was established, a second cohort of patients was treated with accelerated fractionation, in which radiotherapy was given as 60 Gy in 30 fractions over three weeks, and carboplatin 70 mg/m$^2$ was given daily concurrently with radiotherapy on days 1 to 5. By

keeping the dose and number of fractions constant, we hoped to be able to examine the effect of a single treatment variable – overall time – on outcome. Because of the shortened treatment time, it was not possible to administer a second course of carboplatin, but we reasoned that some radiosensitisation may have been possible for ten fractions as in the first cohort because some drug given before the morning radiotherapy fraction may still have been present when the afternoon treatment was administered.

The results of this study, which provided the foundation for the randomised trial to follow, were published in 1991[111]. We anticipated that oesophagitis might be a significant toxicity, but the toxicity scale used for the study, that of the WHO[112], did not have a scale for oesophagitis, and so we modified the WHO scale for stomatitis [Table XXVIII].

**Table XXVIII. Modified scale for oesophagitis[111]**

| Grade | |
|---|---|
| 0 | No pain on swallowing |
| 1 | Mild pain, normal diet, no medication |
| 2 | Pain, requires medication to eat solids |
| 3 | Pain such that liquid diet only is possible |
| 4 | Severe pain – alimentation not possible |

The values in this modified scale are approximately one grade higher than in more recently adopted scales[113], and they therefore overestimate the toxicities observed. However the same scale has been used consistently in this study and in the randomised trial to be described below, and the modification needs to be borne in mind throughout.

As this was a phase I study, the following dose modification rules were incorporated in the protocol. (a) "If grade 4 toxicity is encountered following the first course of carboplatin in any patients, the subsequent course of carboplatin will be reduced by 50%." (b) "If WHO grade 4

toxicity occurs, a further 3 patients will be studied at either 50% or 75% carboplatin dose depending on the site of toxicity encountered. If no severe toxicity occurs, a further 3 patients will be studied." (c) "If, on day 29, myelosuppression persists from course 1 with neutrophils $<1.5 \times 10^9$/l and/or platelets $< 100 \times 10^9$/l, the second carboplatin course can be deferred for one week."

**2.2.2 Results.**

Thirteen patients with inoperable biopsy-proven NSCLC confined to the primary site and mediastinum and maximum performance status of ECOG 1 were entered on the study. The first group of six patients was enrolled between March and June 1987; they were treated with conventionally fractionated radiotherapy and two cycles of carboplatin as described above. Radiotherapy was given as 60 Gy in 30 fractions over six weeks to the primary site and adjacent hilum and mediastinum, whether involved or not. Treatment planning was CT-based and corrections were made for tissue inhomogeneities. The first phase of treatment [40 Gy] was given via anterior and posterior parallel opposed beams and the second phase was given with opposed oblique beams to avoid the spinal cord, the dose to which did not exceed 45 Gy. Carboplatin was given as a one hour intravenous infusion 70 mg/m$^2$ per day for five days and followed by radiotherapy 30 to 60 minutes later during the first and fifth weeks of radiotherapy. Because of the toxicities encountered, the planned carboplatin dose escalation was not possible.

The second group of seven patients was treated between May and October 1988. These patients were treated with twice daily fractions of 2 Gy to a total dose of 60 Gy in three weeks. A minimum of four hours was specified between treatments, but in practice the interval was more often 6 to 8 hours. Tumour response and toxicity were documented according to the WHO criteria[112] [except oesophagitis]. All patients gave informed consent and the protocol was approved by the Ethics Committee of the Peter MacCallum Cancer Institute.

Patient characteristics of the two groups are listed in Table XXIX.

**Table XXIX. Characteristics of patients enrolled in the pilot study of concurrent carboplatin with conventional and accelerated radiotherapy**

| Characteristic | Group I [conventional fractionation] | Group II [accelerated fractionation] |
|---|---|---|
| Number | 6 | 7 |
| Sex: male/female | 5/1 | 3/4 |
| Median age [years] | 60 | 66 |
| [range] | [50 - 67] | [45 – 75] |
| Histology: | | |
| Squamous cell carcinoma | 5 | 4 |
| Adenocarcinoma | 1 | 1 |
| Large cell anaplastic | 0 | 2 |
| Performance status: | | |
| ECOG 0 | 2 | 2 |
| ECOG 1 | 4 | 5 |
| Stage I | 1 | 0 |
| Stage IIIA | 5 | 6 |
| Stage IIIB | 0 | 1 |

Ten of the 13 patients completed treatment as planned. In the conventionally fractionated group, two patients did not receive the second cycle of carboplatin because of grade 3 neutropenia [0.5 - 0.99 x $10^9$/l] persisting at week 5 of radiotherapy. In the accelerated group one patient received only 54 Gy in 27 fractions because she was neutropaenic and febrile at

the time her last three fractions were scheduled. The toxicities for both conventionally and accelerated fractionated groups are shown in Tables XXX and XXXI respectively. In patients receiving conventional fractionation, the worst oesophageal toxicity [grade 2] occurred in only one patient.

**Table XXX. Toxicity of carboplatin/ conventional radiotherapy**

| | Number of patients – worst toxicity | | | | |
|---|---|---|---|---|---|
| | **Grade 0** | **Grade 1** | **Grade 2** | **Grade 3** | **Grade 4** |
| Haemoglobin | 2 | 4 | 0 | 0 | 0 |
| White cell count | 4 | 0 | 0 | 2 | 0 |
| Platelets | 3 | 2 | 1 | 0 | 0 |
| Nausea and vomiting | 1 | 0 | 3 | 1 | 0 |
| Oesophagitis | 0 | 5 | 1 | 0 | 0 |

**Table XXXI. Toxicity of carboplatin/ accelerated radiotherapy**

| | Number of patients – worst toxicity | | | | |
|---|---|---|---|---|---|
| | **Grade 0** | **Grade 1** | **Grade 2** | **Grade 3** | **Grade 4** |
| Haemoglobin | 4 | 2 | 1 | 0 | 0 |
| White cell count | 4 | 2 | 0 | 1 | 0 |
| Platelets | 6 | 0 | 1 | 0 | 0 |
| Nausea and vomiting | 1 | 3 | 3 | 0 | 0 |
| Oesophagitis | 0 | 0 | 4 | 2 | 1 |

In the accelerated fractionation group, all patients developed at least grade 2 oesophagitis, with two patients experiencing grade 3 symptoms. One patient required nasogastric feeding for two weeks [grade 4]. In Figure 7 the duration of oesophagitis in the accelerated group has been plotted according to grade, including maximum, minimum and average grade experienced at any time; the average duration of symptomatic oesophagitis was 21 weeks.

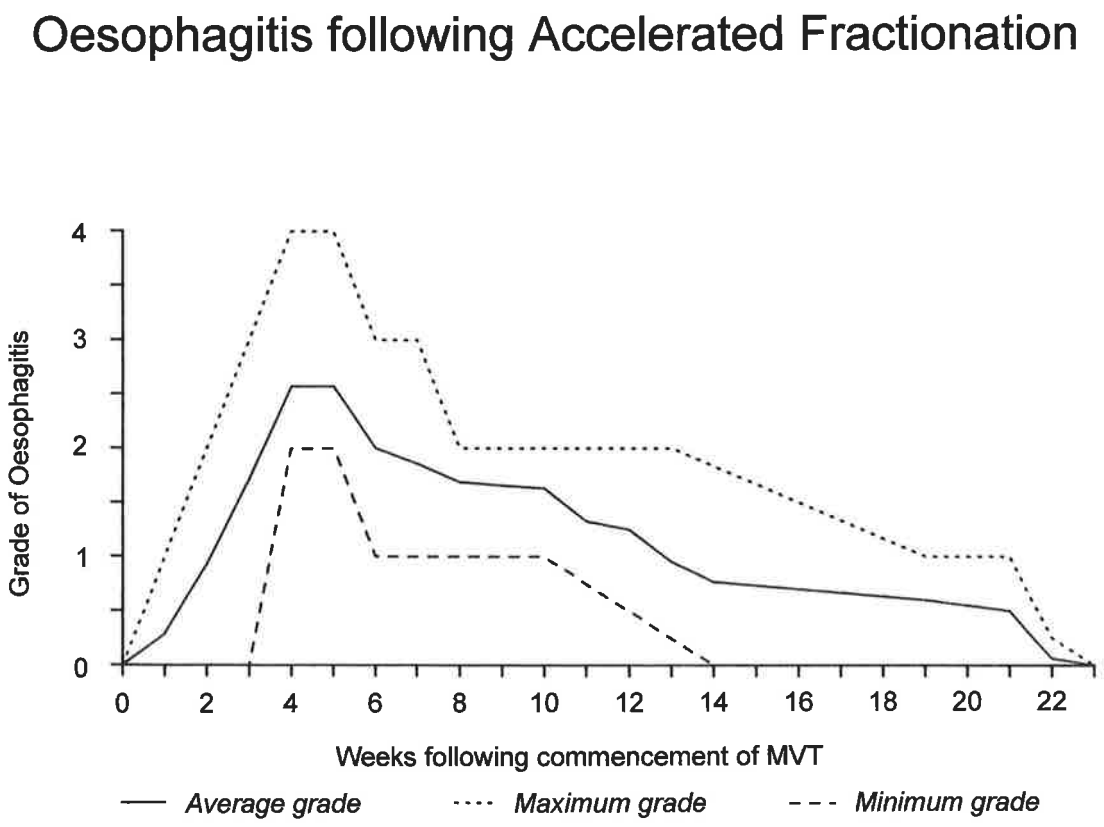


**Figure 7. Grade of oesophagitis according to duration in patients receiving combined carboplatin/accelerated radiotherapy.**

Another patient who had resumed a normal diet and was free of dysphagia developed acute oesophageal obstruction at 23 weeks requiring dilatation, but his swallowing returned to normal, and no other cases of oesophageal stricture were observed with a minimum 14 months follow up. No cases of radiation pneumonitis were observed but one patient in the conventionally fractionated group developed L'Hermitte's sign which persisted for three weeks five months after radiotherapy. There were no treatment related deaths.

No patient achieved a complete response, but four of six patients in the conventionally fractionated group and four of seven in the accelerated group achieved partial responses, giving an overall response rate of 62%.

**2.2.3 Discussion.**

In this study we established the maximum tolerated dose of carboplatin given concurrently with 60 Gy of conventionally fractionated radiotherapy to be 70 mg/m$^2$ per day for five days during weeks one and five. It was not possible to dose escalate to 80 mg/m$^2$ as planned because two patients were unable to have their second cycle of carboplatin as a result of persisting neutropaenia. Although inability to administer the second cycle of chemotherapy was not specified as a dose limiting toxicity in the protocol, it was clear that with three out of six patients experiencing grade 3 toxicity at the starting dose level, we had reached the upper limit of safety, and so this treatment schedule was taken into the phase III study. The major toxicity observed in the patients treated with accelerated radiotherapy was oesophagitis, which was both more severe and more prolonged than in patients treated with conventional fractionation. In spite of this, the accelerated schedule also appeared safe, as the dysphagia scale we used gave an overestimate of the toxicity, and no long term sequelae were observed. We felt therefore that there was no contraindication to taking this accelerated schedule into phase III evaluation.

## 2.3 A randomised study of conventional and accelerated radiotherapy with and without concurrent carboplatin as treatment for inoperable non-small cell lung cancer.

### 2.3.1 Study design and rationale.

Having established the feasibility of giving carboplatin concomitantly with both accelerated and conventionally fractionated radical radiotherapy, we were faced with the problem of how to design a trial in which not one but two promising treatment approaches [shortened treatment time and chemoradiation] could be compared. Since information on the superiority of combined cisplatin-based chemotherapy and radiotherapy was not available at that time, the control arm had to be conventionally fractionated radiotherapy, 60 Gy in 30 fractions administered over six weeks [R6]. The investigational arms had to incorporate both shortened treatment time and chemoradiation, thus the second arm was accelerated radiotherapy, 60 Gy in 30 fractions given in three weeks [R3]. There was no reduction in fraction size, nor reduction in overall dose; it was to be a pure test of the effect of shortening overall treatment time, unconfounded by adjustment of other treatment variables, which may have made the outcome uninterpretable. The third arm was the chemoradiation arm, identical to that in the phase I study, consisting of the same radiotherapy as for R6, with carboplatin 70 mg/m$^2$ given daily for five days during weeks one and five of radiotherapy [R6C]. We could have left the design as a three arm comparison, but there was the tantalizing thought that if both altering the fractionation *and* giving concomitant carboplatin improved outcome, acting through differing mechanisms, then a treatment arm in which both accelerated fractionation and chemotherapy were used might give the best result of all. We thus devised a fourth arm, again identical to one used in the phase I study, in which patients would be given accelerated radiotherapy as in R3, plus a course of carboplatin 70 mg/m$^2$ daily for five days during the first week of radiotherapy [R3C]. Clearly, so many comparisons would require large numbers

if statistically robust conclusions were to be drawn, but the final trial design had the advantage of being a 2 x 2 factorial design, whereby comparisons could be made not only by treatment arm, but also by treatment factor. Thus, it would be possible to collapse R6 and R6C together, and compare their outcomes with those of R3 and R3C combined, to determine the influence of shortened treatment time. Similarly, R6 and R3 could be collapsed and compared with the combination of R6C and R3C to determine the influence of chemotherapy. Such comparisons might increase the power of the trial without increasing the total number of patients enrolled, but there was a risk that the lesser amount of carboplatin given in R3C [one cycle, compared with two cycles in R6C] might obscure the magnitude of the benefit of carboplatin [if there were one] in the factorial comparison of carboplatin versus no carboplatin. The carboplatin was given primarily as a radiosensitiser, and we reasoned that if it were given before the first treatment of the day, some of the drug might still be present at the time of administration of the second fraction of radiation six hours later. Studies on patients with small cell lung cancer treated in our own Institute revealed that carboplatin has a mean plasma half life of only 105 minutes [SD = $\pm$ 30 minutes], which varies according to renal function[114]; but whether it is bound drug or plasma levels which are important for radiosensitisation is not clear. The experiments of Kalchofer and colleagues[74] revealed that if the drug were given 24 hours before irradiation, there was no sensitisation, suggesting that cellular binding of the drug is limited or negligible. If the degree of radiosensitisation is dependent on plasma levels at the time of irradiation, we would have to conclude, knowing what we do of the pharmacokinetics of carboplatin, that the effect should be less for the radiotherapy dose given later in the day, at least 7 hours [as many as four half-lives] after the drug had been infused. These possibilities would need to be taken into account when interpreting the results.

The treatments were to be compared both by arm and factor for the following endpoints: efficacy, as judged by response, time to disease progression and survival; and toxicity.

### 2.3.2 The protocol.

A copy of the final protocol is attached as Appendix B. The case report forms for the trial are attached as Appendix C. Although the major endpoints of this study were survival and toxicity, we also asked patients to complete, before and after treatment, a simple quality of life questionnaire devised in-house. In collaboration with Dr Ron Borland of the Anti-Cancer Council of Victoria, we asked patients to complete a life orientation test[115] before and after treatment. This was designed to measure patient optimism, and to examine its effect on quality of life, and survival; and to examine the effect of treatment on optimism. These two aspects of the study will not be dealt with further in this thesis.

**Statistical considerations.** The initial intent was to randomise a total of 200 patients, 50 in each arm. It was estimated that if there were no interaction between the treatment factors [accelerated fractionation and carboplatin], the study had a probability of detecting a change in response rates from 60% to 80% associated with a given factor when tested at a significance level 0.05 using a two-tailed test. A 60% increase in the median survival could be detected if the data are analysed when 72% of the patients had died. Accrual would be closed in one or more of the arms if unacceptable toxicity is experienced or if the arm [or factor] is associated with significantly inferior results when tested at the 0.01 level of significance. The protocol stated: 'At the completion of accrual of 200 patients the data will be carefully analysed and consideration may be given to extending the trial if necessary.'

**Eligibility criteria.** To be eligible for the study, patients had to satisfy the following criteria:

1. Histologically or cytologically proven non-small cell carcinoma of the lung;

2. ECOG performance status of 0 or 1;

3. No extension of disease beyond primary site and mediastinum. Disease stages I - III eligible, excepting patients with pleural effusions or cervical lymph node involvement. The patients with stage I or II disease were either inoperable for medical reasons or had refused surgery.

4. Clinically evident disease present. Measurable or evaluable disease preferred.

5. Granulocyte count at least 1.5 x $10^9$/L.

6. Platelet count at least 100 x $10^9$/L.

7. Weight loss less than 10%.

8. Patients with renal impairment [creatinine clearance 0.4-0.8 ml/sec] are eligible but the dose of carboplatin to be reduced. Patients with a creatinine clearance of $< 0.4$ ml/sec are ineligible.

9. Written informed consent. A copy of the consent form is to be found with the protocol in Appendix B. The protocol was approved by the institutional ethics committees of all the hospitals participating in the study.

**Pre-treatment work-up.** All patients had a history and physical examination, full blood count and differential, urea and electrolytes, urinary creatinine clearance and liver function tests. Staging investigations included chest x-ray, CT scan of thorax and upper abdomen and radioisotope bone scan. Spirometry was performed, but bronchoscopy was not mandatory.

**Randomisation.** Patients who satisfied the eligibility criteria were stratified by treating institution, performance status [ECOG 0 or 1] and histology [squamous or non-squamous] and then randomised to one of four arms: R6, R3, R6C or R3C. The randomisation was adaptive biased coin with a bias of $5^n$:1 in favour of each arm with fewer patients already allocated, where n is the difference between the number of patients already allocated to that

arm and the number allocated to the arm with the most patients. The clinicians were unaware of the treatment to which the next patient would be randomised.

**Treatment.** All patients were given radiotherapy, 60 Gy in 30 fractions. Treatment was planned in the same way for all patients. Both conventional simulator films and planning CT images of the chest were obtained. The primary tumor, involved nodes and nodal regions deemed to be at risk were outlined with a 1.5 – 2.0 cm margin on the CT images using a computer treatment planning system. At Peter MacCallum, where most of the patients were treated, the system used was Theraplan which enabled 2.5D reconstruction. The usual target volume extended to cover ipsilateral hilar and mediastinal nodes to the level of the sternal notch, even in patients with peripherally situated stage I tumours. There was no attempt to routinely cover uninvolved contralateral mediastinal or hilar nodes. The subcarinal area was treated if involved or if the primary was located in the lower lobes or right middle lobe. The supraclavicular nodes were not electively treated, and supraclavicular involvement was an eligibility exclusion. In the dose calculation, corrections were made for tissue inhomogeneities. The dose was prescribed to the isodose line that ensured that the variation in dose within the target volume in the central plane was no greater than $\pm$ 5% of the prescription.

All patients were treated with a linear accelerator with an energy of 6 MV or greater. The target volume was treated to 40 Gy in 20 fractions using anterior and posterior parallel opposed beams. The remainder of the dose [20 Gy in 10 fractions] was given using a parallel opposed pair of oblique or lateral beams, angled so as to avoid spinal cord. Occasionally, the change in technique was implemented at a lower dose, 36 or 38 Gy, to avoid excessive cord dose in situations where the target volume was particularly close to the spinal cord, which then received such a high proportion of the dose from the oblique beams that the maximum

cord dose specified in the protocol [45 Gy] would have been exceeded had the change been made at 40 Gy. The target volume remained the same throughout treatment; no reductions were made. Those nodal stations that were electively irradiated were thus treated to the same dose as the primary and involved nodes. An example of a treatment plan [for a patient randomised to R6C] is shown in Figure 3.

Patients who were randomised to R6 were treated with anterior and posterior beams to 40 Gy, and then treated with obliques. The total dose was 60 Gy in 30 fractions over six weeks. Those randomised to R6C were treated with oblique beams in the weeks in which chemotherapy was given before radiotherapy; this was to avoid any potential sensitisation of the spinal cord by carboplatin. This was a precautionary measure only; we had no evidence that concomitant carboplatin administration lowered the tolerance of the spinal cord to radiation injury. As for R6, treatment duration was 6 weeks. In patients randomised to R3 or R3C treatment was given twice a day and the minimum interval between treatments was set at 6 hours. The total treatment time was therefore 3 weeks. For 2 weeks of the treatment, oblique or lateral beams were used once per day so that the spinal cord was included in the treated volume for only one fraction per day; thus minimising the risk of dose accumulation resulting from incomplete repair. As in R6C, the treatment administered immediately following the infusion of carboplatin in R3C was via obliques, and the afternoon treatment was given with anterior and posterior beams.

All patients were required to have weekly check films, but central review of radiotherapy treatment plans was not performed.

In patients randomised to the chemotherapy arms, carboplatin 70 mg/m$^2$ was given in 500 ml of normal saline infused over a period of one hour on days 1 to 5 of radiotherapy, which was

given 30–60 minutes after completion of the infusion. Patients randomised to R6C were given a second course of carboplatin on days 29-33 at the same dose and timing as for the first course provided the neutrophil count was $\geq$ 1.5 x $10^9$/l and the platelet count was $\geq$ 100 x $10^9$/l. If myelosuppression below those levels was present on day 29, the second course was to be deferred for a week. If grade 4 toxicity was encountered following the first course of carboplatin, the dose for the second course was to be reduced by 50 %. Doses were to be modified if patients had renal impairment as indicated by a low creatinine clearance or high serum creatinine.

**Toxicity.** Most toxicities were graded according to the standard WHO criteria[112], excepting oesophagitis, which was graded according to the scale in Table XXVIII. Patients were seen and had toxicity assessed weekly during treatment and thereafter every 4 weeks for at least 4 months until toxicities resolved.

**Response criteria.** Responses were assessed based on CT scans taken 6 weeks after the completion of treatment using the WHO criteria for response[112]. A complete response [CR] was defined as the disappearance of all known disease lasting at least 4 weeks. A partial response [PR] required a reduction of at least 50 % in the size of the tumor for at least 4 weeks. Progressive disease [PD] was defined as an increase of 25 % or more in the size of the tumor and stable disease [SD] as no change or < 50% reduction or < 25% increase. If a patient achieved CR or PR on only one assessment, this was accepted as the response to treatment, provided the patient survived at least another 4 weeks without relapse.

**2.3.3 Statistical methods.**

All statistical analyses were performed by Dr Jennifer Smith with my advice and direction.

All patients were analysed according to their randomised treatment arm ["intention-to-treat"], except for the toxicity analysis. Percentages have been rounded off to the nearest whole number. If a date were known only to the nearest month, it was taken to be the 16$^{th}$ of the month.

The Pearson chi-square test was used for comparisons of dichotomous prognostic factors between arms [sex, performance status, histology, weight loss] and the Kruskal - Wallis test for comparisons of continuous or ordinal variables [age, stage][116]. Response rates were calculated as percentages of all randomised patients with 95% confidence intervals, and were compared using the Pearson chi-square test [comparing 4 arms] or the Fisher exact test [comparing 2 arms or factors][116].

A close-out date for overall survival and time to progression was used to avoid possible bias introduced by earlier reporting of deaths than of survivors. All patients were followed to a close-out date of 6$^{th}$ January 1998. The status of each patient on the close-out date was taken to be his or her final status. The median potential follow-up time from the date of randomisation to the close-out date was 5.1 years for all patients with a range of 2.6 to 8.8 years.

Overall and progression free survival were measured from the date of randomisation. For overall survival, deaths from any cause were counted as events and surviving patients were censored at the close-out date. For progression free survival, progression at any site or death from any cause was counted as an event and patients surviving without progression were

censored at the close-out date. The Kaplan-Meier product-limit method was used to estimate overall survival or progression free survival. Ninety-five per cent confidence intervals for median survival were estimated using the Brookmeyer-Crowley method and comparisons of survival between subgroups of patients were carried out using the Mantel-Cox log rank test[117].

Sites of first progression ["in-field" versus "out-of-field"] were analysed according to competing risks analysis. The cumulative incidences according to various failure types were estimated according to the method described by Kalbfleisch and Prentice[118].

Three patients who were not treated and one patient who received only 6 Gy were not assessed for toxicity and so they were omitted from the toxicity analysis. Acute toxicities were defined as those toxicities occurring within 90 days of commencing radiotherapy. For each patient the worst grade of each toxicity achieved within 90 days of commencing radiotherapy is provided. Percentages were calculated based on the number of patients with known values. The Wilcoxon rank sum test with exact calculation of P values was used to compare worst grades of acute toxicities of the treatment factors or arms, omitting patients with unknown values. The duration of oesophagitis was measured from the date on which the oesophagitis was first recorded until the date when it permanently returned to grade 0. The duration of oesophagitis for 200 patients who received more than 6 Gy of radiotherapy was estimated using the Kaplan-Meier product-limit method. Twenty-one patients who never developed oesophagitis were included in the graph with a duration of 0 days. For 150 patients oesophagitis had resolved by the close-out date. For 29 patients oesophagitis had not returned to grade 0 when they were last assessed and their duration of oesophagitis was censored at that date or the close-out date whichever was the earlier. The Mantel-Cox log rank test was used to compare the duration of oesophagitis between sub groups.

### 2.3.4 Accrual.

Altogether 208 patients were randomised on the trial. Four patients were deemed to be ineligible. Two patients, one randomised to R6C and the other to R3 were found to have pleural effusions before randomisation. A third patient, randomised to R3, was found to have a pleural effusion the day after randomisation. The fourth patient, randomised to R6C, was found to have cervical node involvement 3 days after randomisation. All four patients were given non-protocol radiotherapy after exclusion from the trial. This left 204 patients available for analysis. One patient was randomised to R6C by the Statistical Centre, but the randomisation arm was recorded as R3C by the data manager, and the patient was therefore treated on that arm. As the patient was treated according to intent, the patient's data have been analysed as if he had been randomised to R3C.

The first patient was entered on the trial on 3rd April 1989 and the last on 16th May 1995. The study commenced with two participating institutions, and three other centres joined subsequently. The institutions, the accrual periods and numbers of eligible patients randomised are shown in Table XXXII. Newcastle suspended participation in 1989 after accruing five patients because of toxicity concerns based on one episode of fatal haemoptysis, but following a change in personnel began to accrue again in 1994. The number of patients randomised according to treatment arm is shown in Table XXXIII.

**Table XXXII. Participating Institutions and Accrual**

| Institution | First patient | Last patient | Eligible |
|---|---|---|---|
| Peter MacCallum Cancer Institute | 3 / 4 / 89 | 16 / 5 / 95 | 156 |
| Royal Adelaide Hospital | 18 / 6 / 91 | 30 / 9 / 94 | 23 |
| Queensland Radium Institute | 16 / 10 / 92 | 12 / 4 / 95 | 15 |
| Mater Misericordiae Hospital, Newcastle | 9 / 5 / 89 | 6 / 10 / 89 | 5 |
| | 11 / 5 /94 | 3 / 3 / 95 | 3 |
| Geelong Hospital | 23 / 12 / 93 | 9 / 2 / 95 | 2 |

**Table XXXIII. Number of patients per arm**

| Arm | Number |
|---|---|
| R6 | 53 |
| R3 | 46 |
| R6C | 54 |
| R3C | 51 |
| Total | 204 |

### 2.3.5 Results.

The results of this study were first published as an interim analysis of toxicity experienced by the first 100 patients randomised in the *International Journal of Radiation Oncology Biology Physics* in 1995[119], and the final results were published in *Radiotherapy and Oncology* in 1999[120] with an accompanying editorial by Baumann[121]. Some further analyses were published in a letter to the editor of *Radiotherapy and Oncology* in 2001[122]. The results are presented in somewhat greater detail in this thesis.

### 2.3.6 Interim analysis.

In the 1995 toxicity analysis, the acute and late toxicities were analysed by treatment arm , but survival was only reported for the whole group as the trial was ongoing. An independent data monitoring committee had not been established at the outset and so a judgment had to be made by a committee consisting of the the two chief investigators [myself and Dr Bishop] and the Director of the Statistical Centre [Dr Jane Matthews] regarding the safety of the treatment and whether any differences between treatment arms or factors were large enough to justify early closure. The survival data were not made available to any of the other investigators, but since none of the arms or factors was associated with significantly inferior survival when tested at the 0.01 level of significance, it was decided that, provided that the results of the toxicity analysis were acceptable, continued accrual to the planned number of 200 patients was justifiable. Although the toxicities experienced by patients randomised to the three

experimental arms were greater than those for patients receiving conventional radiotherapy, they were not deemed to be excessive[119]. Patients randomised to receive carboplatin had significantly more neutropenia and thrombocyotpenia than those randomised to radiotherapy alone, but there were no deaths from neutropaenic sepsis or neutropaenia related infections. The major toxicity was oesophagitis, which was more severe and more prolonged in patients who had accelerated radiotherapy, with or without carboplatin. The median duration of oesophagitis for the four treatment arms is shown in Table XXXIV. A multivariate analysis of factors influencing the duration of oesophagitis, including treatment [carboplatin versus no carboplatin, accelerated versus conventional radotherapy] and length of treatment field revealed that the only factor influencing the duration of oesophagitis was accelerated radiotherapy.

**Table XXXIV. Duration of oesophagitis by treatment arm. Interim analysis[119]**

| Treatment arm | Number | Median duration in months [95% CI] | Estimated percentage with oesophagitis at 4 months |
|---|---|---|---|
| R6 | 23 | 1.4 [0.7 – 2.0] | 5% |
| R3 | 26 | 3.2 [2.8 – 5.4] | 48% |
| R6C | 24 | 1.6 [1.3 – 2.4] | 5% |
| R3C | 23 | 2.4 [1.6 – 4.3] | 32% |

Seven patients had ongoing symptoms of dysphagia thought to be due to a stricture. These individuals had oesophagoscopies and dilatations for what was more often consequential ulceration rather than chronic fibrous stricture. Six of the 7 had received accelerated radiotherapy on arm R3, and the other had been treated on arm R6C. One patient had been retreated for recurrence with a second course of thoracic radiotherapy 15 months after being treated on R3, required a dilatation for dysphagia 7 months after retreatment and died of a malignant tracheo-oesophageal fistula 3 months after dilatation; disease rather than treatment was more likely responsible for his symptoms. One patient required a second dilatation and

subsequently developed a laryngo-oesophageal fistula at the upper level of the radiation field, dying three months later. Biopsies of the fistula revealed no evidence of malignancy. This appeared to be the only death directly attributable to treatment.

In regard to pulmonary toxicity, there were no significant differences between treatment arms. The only instances of grade 4 pulmonary toxicity [life-threatening dyspnoea] occurred in 1 patient treated on R3 and 2 patients treated on R3C; one of these patients died of chronic pulmonary sepsis superimposed on lung fibrosis without evidence of active cancer. There were no instances of spinal cord injury, but one patient treated on R6 developed transient l'Hermitte's sign.

The interim analysis therefore reinforced the findings of the phase I study[111] that the experimental regimens were safe. There appeared to be at most only 2 treatment related deaths in the first 100 patients, and although they did occur in patients treated on the experimental arms, that could have happened by chance alone. The oesophageal toxicity was more severe in the experimental arms, but not significantly so in patients receiving carboplatin. Although oesophageal symptoms were more prolonged in patients receiving accelerated radiotherapy, in the majority of patients they had resolved by 4 months. The increased toxicity might prove to be acceptable should the accelerated regimens result in improved local control and longer survival. Thus we had no reason to close the trial based on either the interim survival or toxicity data.

### 2.3.7 Final analysis.

The survival of all 204 eligible patients was analysed using the 6th January 1998 as the close-out date. The status of each patient on that date was taken to be his or her final status. The

median potential follow-up time from the date of randomisation to the close-out date was 5.1 years for all patients, with a range of 2.6 to 8.8 years.

The patient characteristics at randomisation are shown in Table XXXV The majority of patients [76%] were randomised and treated at the Peter MacCallum Cancer Institute. Twenty three per cent of patients were female. The youngest patient was 40 and the oldest 79. The median age was in the seventh decade. Most patients [67%] had a performance status of ECOG 1. There were no patients with a performance status higher than one. Squamous cell carcinoma was the most common histology [64%]. The majority [68%] had no weight loss; none had weight loss greater than 10% in the previous three months. There were 36 patients [18%] with stage I disease, 8 [4%] with stage II , 100 [49%] with stage IIIA and 59 [29%] with stage IIIB. The primary tumor size ranged from 1 cm to 11 cm; in 57 patients [28%], the tumor size was not measurable. There were no significant differences in the distribution of pre-treatment prognostic characteristics between treatment arms, including sex [$p = 0.76$], age [$p = 0.21$], performance status [$p = 0.83$], histology [$p = 0.94$], weight loss [$p = 0.53$] or overall stage [$p = 0.53$].

**Table XXXV. Patient characteristics at randomisation**

| | | Without carboplatin | | | | With carbopolatin | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | R6 | (53) | R3 | (46) | R6C | (54) | R3C | (51) |
| | | No. | % | No. | % | No. | % | No. | % |
| **Hospital** | PMCI | 40 | 75 | 37 | 80 | 39 | 72 | 40 | 78 |
| | Royal Adelaide Hospital | 6 | 11 | 4 | 9 | 7 | 13 | 6 | 12 |
| | Queensland Radium Institute | 4 | 8 | 4 | 9 | 5 | 9 | 2 | 4 |
| | Mate Misericordiae, Newcastle | 2 | 4 | 1 | 2 | 2 | 4 | 3 | 6 |
| | Geelong Hospital | 1 | 2 | 0 | 0 | 1 | 2 | 0 | 0 |
| **Sex** | male | 42 | 79 | 34 | 74 | 44 | 81 | 38 | 75 |
| | female | 11 | 21 | 12 | 26 | 10 | 19 | 13 | 25 |
| **Age at last birthday** | median | 62 | | 65 | | 68 | | 66 | |
| | Range | 42-77 | | 40 – 78 | | 47 – 79 | | 46 – 77 | |
| Distribution: | 40 - 49 | 5 | 9 | 3 | 7 | 1 | 2 | 3 | 6 |
| | 50 – 59 | 16 | 30 | 8 | 17 | 9 | 17 | 10 | 20 |
| | 60 – 69 | 16 | 30 | 21 | 46 | 24 | 44 | 22 | 43 |
| | 70 – 79 | 16 | 30 | 14 | 30 | 20 | 37 | 16 | 31 |
| **ECOG Performance status** | 0 | 17 | 32 | 13 | 28 | 20 | 37 | 17 | 33 |
| | 1 | 36 | 68 | 33 | 72 | 34 | 63 | 34 | 67 |
| **Histology** | squamous | 34 | 64 | 29 | 63 | 36 | 67 | 31 | 61 |
| | non-squamous | 19 | 36 | 17 | 37 | 18 | 33 | 20 | 39 |
| **Diagnosis established by** | | | | | | | | | |
| | Sputum cytology | 3 | 6 | 5 | 11 | 4 | 7 | 5 | 10 |
| | Bronchoscopic cytology | 12 | 23 | 7 | 15 | 6 | 11 | 3 | 6 |
| | Bronchoscopic biopsy | 11 | 21 | 14 | 30 | 21 | 39 | 22 | 43 |
| | Node biopsy | 4 | 8 | 6 | 13 | 5 | 9 | 2 | 4 |
| | Needle biopsy of lung | 14 | 26 | 7 | 15 | 9 | 17 | 14 | 27 |
| | Open lung biopsy | 3 | 6 | 3 | 7 | 1 | 2 | 3 | 6 |
| | Mediastinoscopy | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 2 |
| | Combinations of above | 6 | 11 | 4 | 9 | 8 | 15 | 1 | 2 |
| **Weight loss in last 3 months** | none | 35 | 66 | 35 | 76 | 34 | 63 | 34 | 67 |
| | ≤10% | 18 | 34 | 11 | 24 | 20 | 37 | 17 | 33 |
| **T stage** | T1 | 5 | 10 | 8 | 17 | 6 | 11 | 7 | 14 |
| *(percentages of known values)* | T2 | 16 | 31 | 21 | 46 | 20 | 37 | 20 | 40 |
| | T3 | 16 | 31 | 9 | 20 | 15 | 28 | 11 | 22 |
| | T4 | 15 | 29 | 8 | 17 | 13 | 24 | 12 | 24 |
| | Unknown | 1 | | | | | | 1 | |
| **N stage** | N0 | 18 | 34 | 18 | 39 | 18 | 34 | 18 | 35 |
| *(percentages of known values)* | N1 | 3 | 6 | 3 | 7 | 6 | 11 | 4 | 8 |
| | N2 | 28 | 53 | 25 | 54 | 26 | 49 | 25 | 49 |
| | N3 | 4 | 8 | 0 | 0 | 3 | 6 | 4 | 8 |
| | Unknown | | | | | 1 | | | |

**Table XXXV. Patient characteristics at randomisation [continued]**

| | | | Without carboplatin | | | | With carbopolatin | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | R6 | (53) | R3 | (46) | R6C | (54) | R3C | (51) |
| | | | No. | % | No. | % | No. | % | No. | % |
| **Overall stage** (UICC 1987) | T1-2N0 | I | 10 | 19 | 9 | 20 | 8 | 15 | 9 | 18 |
| | T1-2N1 | II | 1 | 2 | 1 | 2 | 5 | 9 | 1 | 2 |
| | T1-2N2, T3-N0-2 | IIIA | 22 | 42 | 28 | 61 | 25 | 46 | 24 | 47 |
| | T1-4N3, T4N0-3 | IIIB | 19 | 36 | 8 | 17 | 16 | 30 | 16 | 31 |
| | T?N2 | III | 1 | 2 | 0 | 0 | 0 | 0 | 1 | 2 |
| **Months between and diagnosis randomisation** | median | | 0.66 | | 0.74 | | 0.67 | | 0.69 | |
| | range | | 0.07 – 2.60 | | 0.16- 2.27 | | 0.13 – 7.66 | | 0.20 – 31 | |
| | <1 | | 40 | 75 | 33 | 72 | 39 | 72 | 30 | 59 |
| | 1 - <2 | | 11 | 21 | 11 | 24 | 10 | 19 | 13 | 25 |
| | ≥2 | | 2 | 4 | 2 | 4 | 5 | 9 | 8 | 16 |
| **Initial sites of disease** | | | | | | | | | | |
| *(patients may have ≥1 primary)* | hilum | | 27 | 51 | 24 | 52 | 26 | 48 | 26 | 51 |
| | Lung parenchyma | | 47 | 89 | 43 | 93 | 48 | 89 | 45 | 88 |
| | Mediastinal nodes | | 34 | 58 | 24 | 52 | 32 | 59 | 28 | 55 |
| | Pleura | | 2 | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | R and L bronchi | | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 2 |
| | Chest wall | | 1 | 2 | 0 | 0 | 0 | 0 | 1 | 2 |
| | Mediastinum | | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Evaluability of disease** | measurable | | 36 | 68 | 31 | 67 | 36 | 67 | 36 | 71 |
| | evaluable | | 12 | 23 | 11 | 24 | 16 | 30 | 12 | 24 |
| *(using most evaluable site)* | Inevaluable | | 2 | 4 | 1 | 2 | 1 | 2 | 1 | 2 |
| | Unknown | | 3 | 6 | 3 | 7 | 1 | 2 | 2 | 4 |
| **Size of primary tumour on chest Xray or CT scan** (mm) | | | | | | | | | | |
| *(percentages of known values)* | Median | | 50 | | 43 | | 50 | | 50 | |
| | Range | | 23 – 90 | | 20 – 90 | | 18 – 100 | | 10 – 110 | |
| Distribution: | ≤30 | | 7 | 18 | 8 | 25 | 7 | 18 | 9 | 25 |
| | 31 – 60 | | 26 | 65 | 16 | 50 | 26 | 67 | 19 | 53 |
| | 61 – 90 | | 7 | 18 | 8 | 25 | 5 | 13 | 7 | 19 |
| | >90 | | 0 | 0 | 0 | 0 | 1 | 3 | 1 | 3 |
| | Unknown | | 13 | | 14 | | 15 | | 15 | |
| **FEV1** (L) | | | | | | | | | | |
| *(percentages of known values)* | Median | | 1.63 | | 1.64 | | 1.75 | | 1.59 | |
| | Range | | 0.80 – 2.86 | | 0.98 – 3.53 | | 0.77 – 3.55 | | 0.72 – 3.8 | |
| Distribution: | ≥3.0 | | 0 | 0 | 4 | 11 | 1 | 3 | 2 | 6 |
| | 2.0- 2.99 | | 13 | 34 | 7 | 20 | 15 | 38 | 7 | 19 |
| | 1.0 – 1.99 | | 23 | 61 | 23 | 66 | 20 | 50 | 22 | 61 |
| | ≤0.99 | | 2 | 5 | 1 | 3 | 4 | 10 | 5 | 14 |
| | Not recorded | | 15 | | 11 | | 14 | | 15 | |

Table XXXVI displays the results of laboratory tests conducted before treatment. Although most measurements were within the normal range, 17 [8%] patients were anaemic. Two patients with reduced creatinine clearance who were randomised to carboplatin were not given the dose specified according to the protocol: one had no dose reduction, and the other was given 50% of the specified dose, when the protocol had specified they both should have received 75% of the dose.

**Table XXXVI. Patient characteristics at randomisation [laboratory investigations].**

| *(latest test on, or prior to, date of commencing treatment; percentages of known values)* | | **Without carboplatin** | | | | **With carbopolatin** | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | **R6** | **(53)** | **R3** | **(46)** | **R6C** | **(54)** | **R3C** | **(51)** |
| | | **No.** | **%** | **No.** | **%** | **No.** | **%** | **No.** | **%** |
| Hæmoglobin (g/dL) | range | 9.0 - 17.0 | | 9.7 – 15.9 | | 9.7 – 16.8 | | 10.7 – 16.1 | |
| Distribution: | ≥11.0 | 47 | 89 | 41 | 91 | 49 | 91 | 48 | 96 |
| | 9.5 – 10.9 | 5 | 9 | 4 | 9 | 5 | 9 | 2 | 4 |
| | 8.0 – 9.4 | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Not recorded | | | 1 | | | | | |
| Platelet count ($10^9$/L) | range | 148 – 683 | | 176 – 765 | | 112 – 623 | | 83 – 826 | |
| Distribution: | ≥100 | 53 | 100 | 45 | 100 | 54 | 100 | 48 | 98 |
| | 75 – 99 | 0 | 0 | 0 | 0 | 0 | 0 | [a] 1 | 2 |
| | Not recorded | | | 1 | | | | 2 | |
| White cell count ($10^9$/L) | range | 5.9 – 25.9 | | 4.3 – 21.2 | | 4.9 – 20.0 | | 5.8 – 17.7 | |
| Distribution: | ≥4.00 | 53 | 100 | 45 | 100 | 54 | 400 | 50 | 100 |
| | Not recorded | | | 1 | | | | 1 | |
| Neutrophil count ($10^9$/L) | range | 2.70 – 16.00 | | 3.18 – 15.98 | | 3.10 – 14.00 | | 3.90 – 14.16 | |
| Distribution: | ≥2.00 | 53 | 100 | 45 | 100 | 53 | 100 | 50 | 100 |
| | Not recorded | | | 1 | | 1 | | 1 | |
| Creatinine (mmol/L) | range | 0.06 - 0.16 | | 0.05 – 0.13 | | 0.05 – 0.13 | | 0.05 – 0.14 | |
| Distribution: | ≤0.12 | 48 | 94 | 41 | 98 | 53 | 98 | 46 | 92 |
| | 0.13 – 0.18 | 3 | 6 | 1 | 2 | 1 | 2 | 4 | 8 |
| | Not recorded | 2 | | 4 | | | | 1 | |

**Table XXXVI. Patient characteristics at randomisation [continued]**

| *(latest test on, or prior to, date of commencing treatment; percentages of known values)* | | Without carboplatin | | | | With carbopolatin | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | R6 | (53) | R3 | (46) | R6C | (54) | R3C | (51) |
| | | No. | % | No. | % | No. | % | No. | % |
| Sodium (mmol/L) | range | 131 – 146 | | 134 – 149 | | 132 – 144 | | 130 – 147 | |
| Distribution: | ≥135 | 48 | 94 | 41 | 98 | 51 | 94 | 43 | 86 |
| | <135 | 3 | 6 | 1 | 2 | 3 | 6 | 7 | 14 |
| | Not recorded | 2 | | 4 | | | | 1 | |
| Bilirubin (μmol/L) | Range | 1 – 16 | | 3 – 15 | | 3 – 19 | | 2 – 14 | |
| Distribution: | ≤17 | 50 | 1000 | 43 | 1000 | 52 | 98 | 49 | 100 |
| | >17 | 0 | 0 | 0 | 0 | 1 | 2 | 0 | 0 |
| | Not recorded | 3 | | 3 | | 1 | | 2 | |
| Alkaline phosphate (U/L) | range | 36 – 272 | | 49 – 205 | | 57 – 220 | | 37 – 190 | |
| Distribution: | ≤120 | 41 | 82 | 30 | 70 | 43 | 81 | 36 | 73 |
| | >120 | 9 | 18 | 13 | 30 | 10 | 19 | 13 | 27 |
| | Not recorded | 3 | | 3 | | 1 | | 2 | |
| AST (U/L) | range | 5 – 68 | | 5 –37 | | 7 – 40 | | 5 – 47 | |
| Distribution: | ≤40 | 41 | 93 | 39 | 100 | 47 | 100 | 44 | 96 |
| | >40 | 3 | 7 | 0 | 0 | 0 | 0 | 2 | 4 |
| | Not recorded | 9 | | 7 | | 7 | | 5 | |
| Urinary creatinine clearance (ml/sec) | | | | | | | | | |
| *Carboplatin arms only* | range | | | | | 0.7 – 2.4 | | 0.6 – 3.1 | |
| Distribution: | ≥0.8 | | | | | 45 | 98 | 44 | 98 |
| | 0.6 – 0.79 | | | | | [b] 1 | 2 | [c] 1 | 2 |
| | Not recorded | | | | | 8 | | 6 | |

[a] QRI003 Platelet count was 106 x $10^9$/L at randomisation.

[b] PMC099 Patient given 50% of carboplatin dose on both courses (protocol specified 75% dose).

[c] PMC061 Patient given 100% of carboplatin dose (protocol specified 75% dose).

The treatment actually given according to randomisation arm is shown in Table XXXVII. Of the patients randomised to R6, 49 [92%] were treated according to protocol. Of the four patients not treated according to protocol, one changed his mind following randomisation to have surgery, which he had initially refused, and had no radiotherapy at all. Three patients received less than 60 Gy: two patients developed distant metastases and stopped treatment at 6 and 26 Gy and the third died during treatment after receiving 32 Gy. There were 8 patients in

whom treatment time was prolonged beyond the expected 40 -42 days: 4 patients in whom it was 44 days, 1 patient each 45, 46, 47 and 48 days.

All patients randomised to R3 received treatment as planned, except for five minor deviations: the overall treatment time was 23 days [expected treatment time was 19 to 21 days, depending on whether two or three weekends were included] in four patients and 24 days in one other.

Only 44 [82%] patients randomised to R6C completed treatment as planned. One patient withdrew consent and had no treatment. Two patients had less than 60 Gy: one died after receiving 56 Gy, and the second patient's treatment was terminated at 50 Gy when metastatic disease was detected. Four patients did not have the second cycle of carboplatin because of haematologic toxicity. Two patients required a carboplatin dose reduction during the first cycle, one having 50% of the dose because of diminished renal function, and the other receiving 86%; and two patients required a greater than 10% reduction during the second cycle. Seven patients had prolongation of treatment time, with durations of 44, 45, 45, 46, 46, 50 and 53 days, the two longest delays being one at the patient's request and the other an interruption for the repair of an abdominal aortic aneurysm. Ten patients had delays in the administration of the second cycle of carboplatin, and on one occasion, the carboplatin was given after radiotherapy, rather than before, as specified in the protocol. Two patients started their carboplatin in the second week of radiotherapy. Thus the predominant problem related to inability to administer the second cycle of carboplatin, as might have been predicted from the toxicities observed in the pilot study[111].

**Table XXXVII. Treatment**

| | | Without carboplatin | | | | With carbopolatin | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | R6 No. | (53) % | R3 No. | (46) % | R6C No. | (54) % | R3C No. | (51) % |
| **Treatment given** | protocol dose | 49 | 92 | 46 | 100 | 44 | 81 | 47 | 92 |
| | Reduced RT (<60Gy) | 3 | 6 | 0 | 0 | 1 | 2 | 0 | 0 |
| | Reduced CT (<90% in either course) | - | | - | | 7 | 13 | 2 | 4 |
| | Reduced both RT and CT | - | | - | | 1 | 2 | 1 | 2 |
| | None | 1 | 2 | 0 | 0 | 1 | 2 | 1 | 2 |
| **Field size ($cm^2$)** | median | 201 | | 196 | | 188 | | 194 | |
| | Range | 94 – 399 | | 104 – 360 | | 100 – 357 | | 83 – 390 | |
| **Length of field (mm)** | median | 140 | | 140 | | 140 | | 133 | |
| *(percentage of treated pts)* | range | 95 – 210 | | 80 – 200 | | 80 – 200 | | 90 – 190 | |
| Distribution: | ≤100 | 3 | 6 | 3 | 7 | 4 | 8 | 6 | 12 |
| | 101 – 120 | 11 | 21 | 9 | 20 | 10 | 19 | 11 | 22 |
| | 121 – 140 | 16 | 31 | 16 | 35 | 19 | 36 | 14 | 32 |
| | 141 – 160 | 12 | 23 | 14 | 30 | 14 | 26 | 11 | 22 |
| | 161 – 180 | 5 | 10 | 3 | 7 | 5 | 9 | 4 | 8 |
| | 181 – 200 | 3 | 6 | 1 | 2 | 0 | 0 | 2 | 4 |
| | >200 | 2 | 4 | 0 | 0 | 1 | 2 | 0 | 0 |
| | No treatment | 1 | | | | 1 | | 1 | |
| **Protocol violations** | | | | | | | | | |
| | No treatment received | 1 | | | | 1 | | 1 | |
| | Received less than 60Gy radiotherapy | 3 | | | | 2 | | 1 | |
| | Standard instead of acceleratcd RT | | | | | | | 1 | |
| | No carboplatin | | | | | | | 1 | |
| | No second course of carboplatin | | | | | 4 | | | |
| | CT dose reduction >10% in course 1 | | | | | 2 | | 2 | |
| | CT dose reduction>10% in course 2 only | | | | | 2 | | | |
| | RT break/delay | 8 | | 5 | | 7 | | 1 | |
| | CT break/delay | | | | | 10 | | | |
| | Incorrect RT fields | 1 | | 2 | | 2 | | 2 | |
| | Carboplatin given after RT on same day | | | | | 1 | | 14 | |
| | Carboplatin commenced after day 1 of RT | | | | | 2 | | 3 | |
| | Other error in treatment timing or dose | | | 1 | | | | 8 | |

Of the patients randomised to R3C, 47 [92%] completed treatment as planned. One patient had no treatment because of disease progression before it could be commenced. One patient withdrew consent, and was treated with conventional fractionation to a total dose of 58 Gy without carboplatin. Two patients were given 75% of the specified dose of carboplatin because of reduced creatinine clearance. Because of the difficulties associated with scheduling two radiotherapy treatments and an infusion of chemotherapy on the same day, it was often not possible to give the carboplatin before the first radiotherapy fraction; in fact 14 patients had their first dose of carboplatin after the first radiotherapy dose on day 1, rather than before. On three occasions, the first dose of carboplatin was given on the second radiotherapy day.

Radiotherapy was given by a different method to the two phase technique specified in the protocol in five patients. Single phase three field and four field techniques were used in two and three patients respectively. One patient's primary tumour was not included in the target volume because of misinterpretation of the original diagnostic scans, resulting in a geographic miss.

**Toxicity.** Three patients who were not treated and one patient who received only 6 Gy were not assessed for toxicity, and so they were omitted from the toxicity analysis. The haematologic toxicities are shown in Table XXXVIII.

Patients treated with carboplatin had significantly more haematologic toxicity than those treated with radfiotherapy alone. This was the case for anaemia, thrombocytopaenia, leukopaenia and neutropaenia. The degree of anaemia observed was mild, but it does raise the question of whether this may have partly offset any benefit that may have been associated with the administration of carboplatin. The effect was statistically significant in patients having two cycles of carboplatin [R6C], but not in patients having only one [R3C].

Thrombocytopaenia was mild and statistically significant only in patients having two cycles of carboplatin. Only four patients developed grade 3 thrombocytopaenia, and one grade 4. Neutropaenia was significantly worse in patients having one and two cycles of carboplatin, although it was more severe in those who had two cycles. Grade 3 neutropaenia was observed in nine per cent of patients on R6C, and grade 4 in four per cent. In comparison, only one patient [2%] on R3C developed grade 3 neutropaenia, and none developed grade 4. None of these findings is surprising, and could have been predicted from the pilot study results. Importantly, there were no deaths from sepsis during periods of neutropaenia.

**Table XXXVIII. Acute hæmatological toxicities**

(Percentages of known values are shown)

| | | Without carboplatin | | | | With carboplatin | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | R6 (51) | | R3 (46) | | R6C (53) | | R3C (50) | |
| | Grade | No. | % | No. | % | No. | % | No. | % |
| Hæmoglobin | 0 | 42 | 88 | 37 | 82 | 33 | 62 | 34 | 69 |
| | 1 | 4 | 8 | 6 | 13 | 16 | 30 | 14 | 29 |
| | 2 | 1 | 2 | 2 | 4 | 4 | 8 | 1 | 2 |
| | 3 | [a] 1 | 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Unknown | 3 | | 1 | | | | 1 | |

[a] PMC075 had grade 2 at randomisation.

*Hæmoglobin comparisons (* = statistically significant):*

| | | | |
|---|---|---|---|
| Radical RT | *vs* | Accelerated RT | P = 0.77 |
| No carboplatin | *vs* | Carboplatin | P = 0.0029* |
| Arm 1 | *vs* | Arm 2 | P = 0.54 |
| Arm 1 | *vs* | Arm 3 | P = 0.0053* |
| Arm 1 | *vs* | Arm 4 | P = 0.047 |

| | | Without carboplatin | | | | With carboplatin | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | R6 (51) | | R3 (46) | | R6C (53) | | R3C (50) | |
| | Grade | No. | % | No. | % | No. | % | No. | % |
| Platelet count | 0 | 48 | 100 | 45 | 100 | 39 | 74 | 43 | 88 |
| | 1 | 0 | 0 | 0 | 0 | 6 | 11 | 3 | 6 |
| | 2 | 0 | 0 | 0 | 0 | 5 | 9 | 1 | 2 |
| | 3 | 0 | 0 | 0 | 0 | 2 | 4 | 2 | 4 |
| | 4 | 0 | 0 | 0 | 0 | 1 | 2 | 0 | 0 |
| | Unknown | 3 | | 1 | | | | 1 | |

*Platelet count comparisons (* = statistically significant):*

| | | | |
|---|---|---|---|
| Radical RT | *vs* | Accelerated RT | P = 0.080 |
| No carboplatin | *vs* | Carboplatin | P < 0.0001* |
| Arm 1 | *vs* | Arm 2 | not done, all patients grade 0 |
| Arm 1 | *vs* | Arm 3 | P = 0.0001* |
| Arm 1 | *vs* | Arm 4 | P = 0.027 |

| | | Without carboplatin | | | | With carboplatin | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | R6 (51) | | R3 (46) | | R6C (53) | | R3C (50) | |
| | Grade | No. | % | No. | % | No. | % | No. | % |
| White cell count | 0 | 44 | 92 | 42 | 93 | 15 | 28 | 26 | 53 |
| | 1 | 4 | 8 | 3 | 7 | 18 | 34 | 10 | 20 |
| | 2 | 0 | 0 | 0 | 0 | 13 | 25 | 10 | 20 |
| | 3 | 0 | 0 | 0 | 0 | 7 | 13 | 3 | 6 |
| | Unknown | 3 | | 1 | | | | 1 | |

*White cell count comparisons (* = statistically significant):*

| | | | |
|---|---|---|---|
| Radical RT | *vs* | Accelerated RT | P = 0.047* |
| No carboplatin | *vs* | Carboplatin | P < 0.0001* |
| Arm 1 | *vs* | Arm 2 | P > 0.99 |
| Arm 1 | *vs* | Arm 3 | P < 0.0001* |
| Arm 1 | *vs* | Arm 4 | P < 0.0001* |

**Table XXXVIII. Acute hæmatological toxicities [continued]**

| | | Without carboplatin | | | | With carboplatin | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | R6 (51) | | R3 (46) | | R6C (53) | | R3C (50) | |
| | Grade | No. | % | No. | % | No. | % | No. | % |
| Neutrophil count | 0 | 46 | 96 | 43 | 96 | 29 | 55 | 37 | 76 |
| | 1 | 2 | 4 | 2 | 4 | 12 | 23 | 6 | 12 |
| | 2 | 0 | 0 | 0 | 0 | 5 | 9 | 5 | 10 |
| | 3 | 0 | 0 | 0 | 0 | 5 | 9 | 1 | 2 |
| | 4 | 0 | 0 | 0 | 0 | 2 | 4 | 0 | 0 |
| | Unknown | 3 | | 1 | | | | 1 | |

*Neutrophil count comparisons (* = statistically significant):*

| | | | |
|---|---|---|---|
| Radical RT | *vs* | Accelerated RT | P = 0.053 |
| No carboplatin | *vs* | Carboplatin | P < 0.0001* |
| Arm 1 | *vs* | Arm 2 | P > 0.99 |
| Arm 1 | *vs* | Arm 3 | P < 0.0001* |
| Arm 1 | *vs* | Arm 4 | P = 0.0042* |

Acute non-haematologic toxicities are shown in Table XXXIX. No patient developed alopecia, and there were no significant differences in nausea and vomiting between treatment arms. In regard to oesophagitis, patients treated with accelerated radiotherapy had significantly more severe oesophagitis. Although acute oesophageal symptoms were more severe in patients having carboplatin, the difference was not statistically significant.

Interestingly, there were no statistically significant differences in acute pulmonary toxicity between treatment arms, although three deaths attributed to pulmonary toxicity occurred in patients treatedwith the accelerated regimen. These were two patients who may have died of radiation pneumonitis [one R3, one R3C], and a third patient who died of chronic sepsis in a region of pulmonary radiation fibrosis [R3C].

**Table XXXIX. Acute non- hæmatological toxicities**
(Percentages of known values are shown)

| | | Without carboplatin | | | | With carboplatin | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | R6 (51) | | R3 (46) | | R6C (53) | | R3C (50) | |
| | Grade | No. | % | No. | % | No. | % | No. | % |
| **Alopecia** | 0 | 51 | 100 | 46 | 100 | 53 | 100 | 50 | 100 |
| **Nausea and vomiting** | 0 | 26 | 51 | 23 | 50 | 20 | 38 | 22 | 44 |
| | 1 | 14 | 27 | 11 | 24 | 20 | 38 | 19 | 38 |
| | 2 | 9 | 18 | 10 | 22 | 9 | 17 | 5 | 10 |
| | 3 | 2 | 4 | 2 | 4 | 3 | 6 | 4 | 8 |
| | 4 | 0 | 0 | 0 | 0 | 1 | 2 | 0 | 0 |

*Nausea and vomiting comparisons (* = statistically significant):*

| | | | |
|---|---|---|---|
| Radical RT | *vs* | Accelerated RT | P = 0.74 |
| No carboplatin | *vs* | Carboplatin | P = 0.34 |
| Arm 1 | *vs* | Arm 2 | P = 0.80 |
| Arm 1 | *vs* | Arm 3 | P = 0.24 |
| Arm 1 | *vs* | Arm 4 | P = 0.66 |

| | | | Without carboplatin | | | | With carboplatin | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | R6 (51) | | R3 (46) | | R6C (53) | | R3C (50) | |
| | | Grade | No. | % | No. | % | No. | % | No. | % |
| **Oesophagitis** | none | 0 | 10 | 20 | 1 | 2 | 8 | 15 | 2 | 4 |
| | soreness, no medication | 1 | 14 | 27 | 6 | 13 | 9 | 17 | 8 | 16 |
| | soreness, requests medication | 2 | 21 | 41 | 24 | 52 | 25 | 47 | 16 | 32 |
| | soreness, liquid diet only | 3 | 4 | 8 | 13 | 28 | 10 | 19 | 23 | 46 |
| | alimentation not possible | 4 | 2 | 4 | 2 | 4 | 1 | 2 | 1 | 2 |

*Oesophagitis comparisons (* = statistically significant):*

| | | | |
|---|---|---|---|
| Radical RT | *vs* | Accelerated RT | P < 0.0001* |
| No carboplatin | *vs* | Carboplatin | P = 0.13 |
| Arm 1 | *vs* | Arm 2 | P = 0.0002* |
| Arm 1 | *vs* | Arm 3 | P = 0.12 |
| Arm 1 | *vs* | Arm 4 | P = 0.0001* |

| | | Without carboplatin | | | | With carboplatin | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | R6 (51) | | R3 (46) | | R6C (53) | | R3C (50) | |
| | Grade | No. | % | No. | % | No. | % | No. | % |
| **Stomatitis** | 0 | 49 | 96 | 44 | 96 | 47 | 89 | 46 | 94 |
| | 1 | 2 | 4 | 1 | 2 | 6 | 11 | 2 | 4 |
| | 2 | 0 | 0 | 1 | 2 | 0 | 0 | 0 | 0 |
| | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 2 |
| | unknown | | | | | | | 1 | |
| **Pulmonary** | 0 | 36 | 71 | 33 | 72 | 41 | 77 | 36 | 73 |
| | 1 | 9 | 18 | 8 | 17 | 6 | 11 | 10 | 20 |
| | 2 | 2 | 4 | 4 | 9 | 4 | 8 | 2 | 4 |
| | 3 | 4 | 8 | 1 | 2 | 2 | 4 | 1 | 2 |
| | unknown | | | | | | | 1 | |

**Table XXXIX. Acute non- hæmatological toxicities [continued]**
(Percentages of known values are shown)

*Pulmonary toxicity comparisons (* = statistically significant):*

| | | | |
|---|---|---|---|
| Radical RT | *vs* | Accelerated RT | P = 0.98 |
| No carboplatin | *vs* | Carboplatin | P = 0.47 |
| Arm 1 | *vs* | Arm 2 | P = 0.85 |
| Arm 1 | *vs* | Arm 3 | P = 0.46 |
| Arm 1 | *vs* | Arm 4 | P = 0.64 |

| | | Without carboplatin | | | | With carboplatin | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | R6 (51) | | R3 (46) | | R6C (53) | | R3C (50) | |
| | Grade | No. | % | No. | % | No. | % | No. | % |
| **Renal (serum creatinine)** | 0 | 47 | 98 | 44 | 100 | 50 | 96 | 48 | 98 |
| *(graded using 0.12 mmol/L as upper limit* | 1 | a 1 | 2 | 0 | 0 | 2 | 4 | 1 | 2 |
| *of normal range)* | unknown | 3 | | 2 | | 1 | | 1 | |
| **Hepatic (AST)** | 0 | 41 | 95 | 39 | 95 | 43 | 91 | 43 | 98 |
| *(graded using 50 U/L as upper limit of* | 1 | 2 | 5 | 2 | 5 | 3 | 6 | 1 | 2 |
| *normal range)* | 2 | 0 | 0 | 0 | 0 | 1 | 2 | 0 | 0 |
| | unknown | 8 | | 5 | | 6 | | 6 | |
| **Cardiac** | 0 | 49 | 100 | 44 | 100 | 48 | 94 | 43 | 98 |
| | 1 | 0 | 0 | 0 | 0 | 1 | 2 | 0 | 0 |
| | 2 | 0 | 0 | 0 | 0 | 2 | 4 | 1 | 2 |
| | unknown | 2 | | 2 | | 2 | | 6 | |
| **Infection** | 0 | 45 | 92 | 43 | 96 | 42 | 84 | 42 | 93 |
| | 1 | 4 | 8 | 2 | 4 | 7 | 14 | 3 | 7 |
| | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 3 | 0 | 0 | 0 | 0 | 1 | 2 | 0 | 0 |
| | unknown | 2 | | 1 | | 3 | | 5 | |
| **Skin reaction** | 0 | 24 | 51 | 23 | 52 | 23 | 47 | 19 | 44 |
| | 1 | 14 | 30 | 16 | 36 | 18 | 37 | 21 | 49 |
| | 2 | 7 | 15 | 3 | 7 | 8 | 16 | 3 | 7 |
| | 3 | 2 | 4 | 2 | 5 | 0 | 0 | 0 | 0 |
| | unknown | 4 | | 2 | | 4 | | 7 | |

*Skin reaction comparisons (* = statistically significant):*

| | | | |
|---|---|---|---|
| Radical RT | *vs* | Accelerated RT | P = 0.65 |
| No carboplatin | *vs* | Carboplatin | P = 0.72 |
| Arm 1 | *vs* | Arm 2 | P = 0.69 |
| Arm 1 | *vs* | Arm 3 | P = 0.92 |
| Arm 1 | *vs* | Arm 4 | P = 0.95 |

The most problematic of the chronic toxicities related to dysphagia which persisted for a significantly longer period in patients who received accelerated radiotherapy. Initially we interpreted these symptoms to be due to fibrous strictures, and a number of patients were endoscoped with the intention of dilating the narrowed segment. Details of these cases are listed in Table XXXX. In two patients the problem developed after additional courses of palliative radiotherapy [30 Gy, conventionally fractionated] were administered for recurrent disease. In patients who had previously been treated with radical radiotherapy, we had demonstrated that this was relatively safe and effective[22], even though retreatment is still not practised in many departments.

**Table XXXX. Oesophageal stricture** (omitting three patients given no radiotherapy and one given only 6 Gy)

| | **Without carboplatin** | | | | **With carboplatin** | | | |
|---|---|---|---|---|---|---|---|---|
| | **R6 (51)** | | **R3 (46)** | | **R6C (53)** | | **R3C (50)** | |
| | **No.** | **%** | **No.** | **%** | **No.** | **%** | **No.** | **%** |
| Oesophageal stricture *(see details below)* | 1 | 2 | 6 | 13 | 3 | 6 | 2 | 4 |

| **Reg No** | **Arm** | **Commenced RT** | **1st dilation** | **Comments** |
|---|---|---|---|---|
| PMC096 | R6 | 9/3/93 | 16/3/94 | After additional 30Gy to chest |
| PMC004 | R3 | 29/5/89 | 3/5/91 | After additional 30Gy in Oct 90. Later in May 91, had oesophageal diversion for fistula |
| PMC027 | R3 | 24/7/90 | 25/1/91 | Second dilation 29/11/91 |
| PMC049 | R3 | 1/7/91 | 20/3/92 | Second dilation 29/1/93 |
| PMC072 | R3 | 8/6/90 | 31/7/92 | Second dilation 29/1/93. Death due to fistula 23/4/93 |
| PMC077 | R3 | 27/7/92 | 28/10/92 | |
| PMC083 | R3 | 21/9/92 | 23/2/93 | |
| PMC078 | R6C | 4/8/92 | 15/4/93 | Second dilation 23/7/93 |
| PMC092 | R6C | 5/1/93 | 20/7/93 | Second dilation 19/8/93 |
| PMC114 | R6C | 25/10/93 | 2/12/94 | |
| PMC060 | R3C | 31/12/91 | | Diagnosed 2/5/96, but died before dilation |
| PMC118 | R3C | 6/12/93 | 23/5/94 | Second dilation 3/2/95 |

However, we had never retreated a patient who had been previously been given an accelerated course, as in the second case. He rapidly developed odynophagia that was so severe that I decided not to retreat patients on the accelerated arms unless the oesophagus could be excluded from the treated volume. It seemed that the previous treatment had lowered the threshold for the development of oesophagitis; one could speculate – on the basis of this one case - that the accelerated treatment had permanently reduced the total number of stem cells in the basal layer of the oesophageal epithelium, leading to earlier disappearance of the mucosal surface.

As mentioned in the interim toxicity analysis, one patient developed a laryngo-oesophageal fistula. This developed some weeks after the most recent instrumentation, and was not therefore the result of surgical trauma. At autopsy, there was no evidence of cancer at the site of the fistula. Review of the simulation films indicated that the fistula lay at the upper level of the treated volume. The computed dose at the site of the fistula was 62.8 Gy, given in 30 fractions over 3 weeks, slightly higher than the prescribed dose because of the reduced separation in the neck compared with the chest. We therefore classified this as a treatment-related death.

As our experience increased, it became evident that the prolonged symptoms of dysphagia were due not to fibrous strictures of the muscle wall, but to persistence of the mucosal injury, the so-called consequential late reaction. Oesophagoscopy and dilatation [which could not be expected to influence healing of the mucosal reaction] were therefore performed less frequently in the latter part of the trial.

Table XXXXI and Figure 8 provide information on the duration of oesophagitis according to treatment arm and factor. There was a highly significant effect of accelerated treatment on

duration of any oesophageal symptoms, with a median duration of 3.2 months compared with 1.8 months for patients treated with conventional fractionation. Twenty three per cent patients still had symptoms at 6 months, compared with only 3% of patients treated with conventional fractionation [p = < 0.0001]. In some patients the symptoms never resolved.

**Table XXXXI. Duration of acute oesophagitis** (omitting three patients given no radiotherapy and one given 6 Gy)

| | Without carboplatin | | | | With carboplatin | | | |
|---|---|---|---|---|---|---|---|---|
| | R6 (51) | | R3 (46) | | R6C (53) | | R3C (50) | |
| | No. | % | No. | % | No. | % | No. | % |
| Status of oesophagitis by close-out date | | | | | | | | |
| Never had acute oesophagitis | 10 | 20 | 1 | 2 | 8 | 15 | 2 | 3 |
| Resolved | 37 | 73 | 36 | 78 | 39 | 74 | 38 | 76 |
| Not resolved | 4 | 8 | 9 | 20 | 6 | 11 | 10 | 20 |

| | | Estimated median duration of oesophagitis | | Estimated % with oesophagitis lasting | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | >3 months | | >6 months | | |
| | No. of pts | months | 95% CI | % | 95% CI | % | 95% CI | P |
| **All patients** | 200 | 2.4 | 2.1–2.7 | 36 | 29 – 43 | 13 | 8-18 | |
| **By length of field** | | | | | | | | |
| ≤ 120mm | 57 | 2.4 | 1.8-3.0 | 40 | 27-54 | 12 | 3-12 | 0.69 [a] |
| 121-140mm | 67 | 2.3 | 1.6-2.9 | 36 | 24-48 | 13 | 5-21 | |
| 141-160mm | 51 | 2.6 | 1.9-2.8 | 30 | 17-44 | 18 | 6-30 | |
| >160mm | 25 | 2.4 | 2.2-3.0 | 33 | 13-53 | 10 | 0-22 | |
| **By treatment arm** | | | | | | | | |
| R6 | 51 | 1.8 | 1.1-2.2 | 16 | 5-27 | 5 | 0-11 | |
| R3 | 46 | 3.2 | 2.7-5.3 | 59 | 44-73 | 27 | 13-40 | $<10^{-4}$ |
| R6C | 53 | 1.8 | 1.4-2.4 | 23 | 10-35 | 5 | 0-11 | |
| R3C | 50 | 2.8 | 2.3-4.1 | 48 | 33-63 | 19 | 7-31 | |
| **By treatment factor – accelerated** | | | | | | | | |
| Radical RT | 104 | 1.8 | 1.3-2.0 | 19 | 11-27 | 5 | 0-9 | $<10^{-4}$ |
| Accelerated RT | 96 | 3.2 | 2.7-4.1 | 53 | 43-64 | 23 | 14-32 | |
| **By treatment factor – carboplatin** | | | | | | | | |
| No carboplatin | 97 | 2.4 | 2.0-2.9 | 37 | 27-47 | 15 | 8-23 | 0.41 |
| Carboplatin | 103 | 2.3 | 1.9-2.7 | 35 | 25-45 | 11 | 5-18 | |

[a] *log rank test for trend*

There was however no effect of carboplatin on duration of oesophagitis, although there had been a suggestion that it may have influenced the severity. Because the length of oesophagus in the treated volume may have affected the duration of symptoms, we analysed the influence of length of treatment field on symptom duration, but there was no evidence of an association of prolongation of symptoms and longer treatment fields.

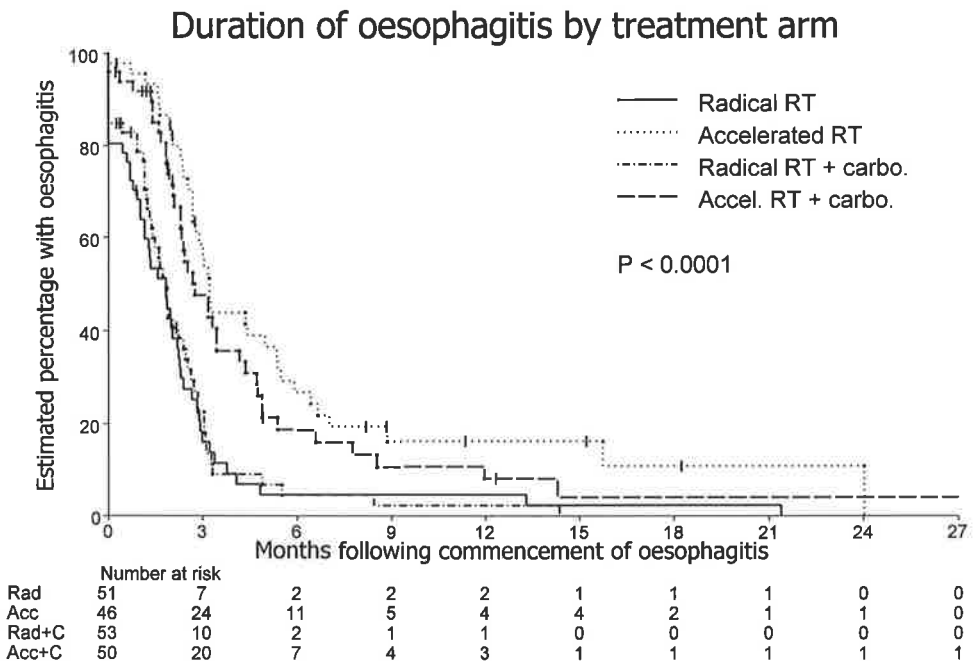


**Figure 8. Duration of oesophagitis according to treatment.**

**Response.**The main endpoint of this study was survival, but response, defined according to the WHO criteria[112], was measured by comparing pre- and post-treatment CT scans. Complete or partial response had to be maintained for at least 4 weeks to be confirmed. The results [best response] are shown in Table XXXXII.

**Table XXXXII. Response rates according to treatment arm.**

| Arm | R6 [%] | R3 [%] | R6C [%] | R3C [%] |
|---|---|---|---|---|
| Complete | 17 | 15 | 19 | 8 |
| Partial | 36 | 46 | 43 | 51 |
| Stable | 28 | 24 | 24 | 29 |
| Progressive | 11 | 11 | 9 | 4 |
| Not evaluable | 8 | 4 | 6 | 8 |

Thirteen patients were inevaluable for response: six patients dying before response could be assessed, four because they did not receive treatment, or treatment according to protocol, two because their disease was only evaluable at bronchoscopy, and one patient had fibrosis obscuring the tumor. The majority of patients had responses, but there were no significant differences between treatment arms. The overall responses [with 95% confidence intervals] for each arm were: R6, 53% [39% - 67%]; R3, 61% [ 45% - 75%]; R6C, 61% [47% - 74%]; and R3C, 59% [44% - 72%]. The differences were not statistically significant [p = 0.81]. Similarly, there were no significant differences when response was measured according to treatment factor.

**Relapse and progression**. A competing risks analysis for sites of first progression is shown in Table XXXXIII and Figure 9.

**Table XXXXIII. Sites of first progression (competing risks analysis)**

| | Estimated cumulative incidence | | | | | |
|---|---|---|---|---|---|---|
| | at 1 year | | at 2 years | | at 5 years | |
| | % | (s.e.) | % | (s.e.) | % | (s.e.) |
| **All patients** | | | | | | |
| Progression in field | 14.7 | (2.5) | 25.0 | (3.0) | 30.1 | (3.2) |
| Progression both in and outside field | 10.3 | (2.1) | 12.3 | (2.3) | 13.2 | (2.4) |
| Progression outside field | 20.6 | (2.8) | 26.5 | (3.1) | 27.5 | (3.1) |
| Progression, sites unknown | 2.9 | (1.2) | 2.9 | (1.2) | 3.5 | (1.3) |
| Death, no progression | 10.3 | (2.1) | 13.7 | (2.4) | 18.8 | (2.9) |
| **R6 (53)** | | | | | | |
| Progression in field | 13.2 | (4.6) | 20.8 | (5.5) | 28.3 | (6.1) |
| Progression both in and outside field | 18.9 | (5.4) | 24.5 | (5.9) | 24.5 | (5.9) |
| Progression outside field | 22.6 | (5.7) | 26.4 | (6.1) | 26.4 | (6.1) |
| Progression, sites unknown | 1.9 | (1.9) | 1.9 | (1.9) | 3.8 | (2.6) |
| Death, no progression | 5.7 | (3.2) | 7.6 | (3.6) | 11.3 | (4.3) |
| **R3 (46)** | | | | | | |
| Progression in field | 21.7 | (6.1) | 30.4 | (6.8) | 37.0 | (7.1) |
| Progression both in and outside field | 8.7 | (4.2) | 8.7 | (4.2) | 8.7 | (4.2) |
| Progression outside field | 17.4 | (5.6) | 21.7 | (6.1) | 23.9 | (6.3) |
| Progression, sites unknown | 0 | (–) | 0 | (–) | 0 | (–) |
| Death, no progression | 10.9 | (4.6) | 19.6 | (5.8) | 23.2 | (6.5) |
| **R6C (54)** | | | | | | |
| Progression in field | 9.3 | (3.9) | 22.2 | (5.6) | 24.1 | (5.8) |
| Progression both in and outside field | 7.4 | (3.6) | 7.4 | (3.6) | 9.3 | (3.9) |
| Progression outside field | 14.8 | (4.8) | 25.9 | (6.0) | 27.8 | (6.1) |
| Progression, sites unknown | 7.4 | (3.6) | 7.4 | (3.6) | 7.4 | (3.6) |
| Death, no progression | 9.3 | (3.9) | 13.0 | (4.6) | 22.6 | (5.9) |
| **R3C (51)** | | | | | | |
| Progression in field | 15.7 | (5.1) | 27.5 | (6.2) | not reached | |
| Progression both in and outside field | 5.9 | (3.3) | 7.8 | (3.8) | | |
| Progression outside field | 27.5 | (6.2) | 31.4 | (6.5) | | |
| Progression, sites unknown | 2.0 | (1.9) | 2.0 | (1.9) | | |
| Death, no progression | 15.7 | (5.1) | 15.7 | (5.1) | | |

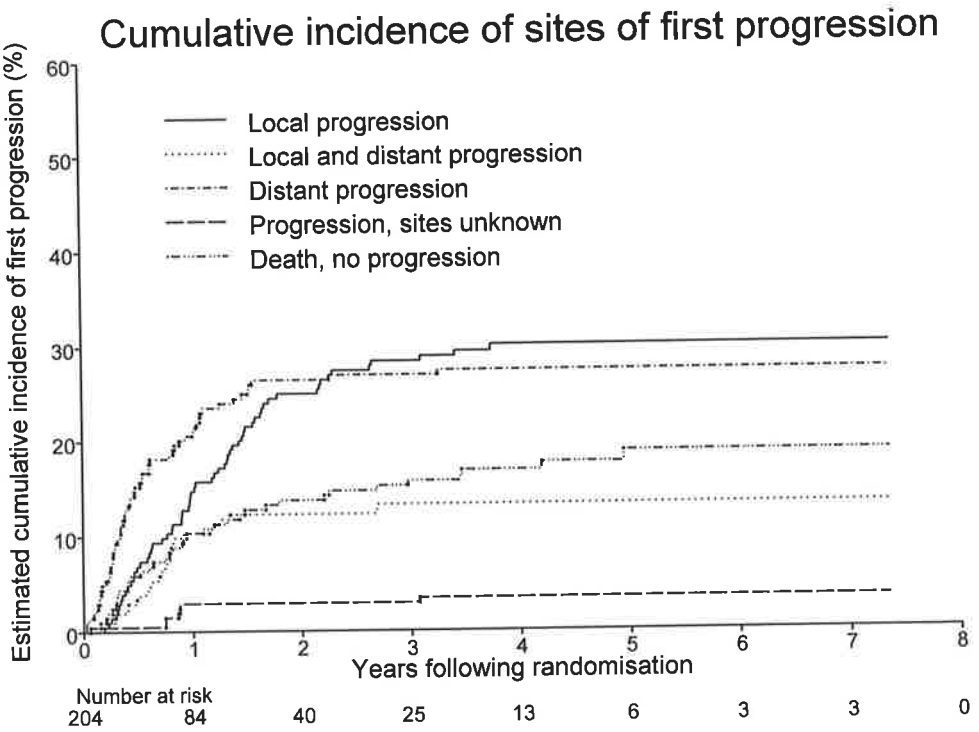


**Figure 9. Cumulative incidence of sites of first progression for all patients.**

At the close-out date, there were 24 patients [11.8%] still alive. Sites of first progression were evenly distributed between in-field failure [30.1% at 5 years], and progression outside the field including distant sites [27.5% at 5 years]. A substantial proportion of patients [18.8%] died of other causes without disease progression. Most of these were cardiorespiratory deaths but two were as a result of second malignancy [one larynx, the other large bowel]. There were no statistically significant differences in progression-free survival when the analysis was performed according to treatment arm or treatment factor.

**Overall survival.** Details of overall survival are shown in Table XXXXIV and Figure 10. The estimated median survival for all 204 patients was 15.7 months, with survival at two years of 31% and at five years, 10%. There were no significant differences in survival according to performance status, histology or institution. Patients with stage I and II disease had longer survival than patients with stage III disease, but this did not achieve statistical significance. Interestingly patients with stage IIIB disease had longer survival than patients with stage IIIA, with median and two year survivals of 17.0 months versus 14.2 months and 34% versus 21% respectively. There was a trend for patients with smaller tumours to have longer survival [p = 0.061]. Weight loss and respiratory function were not predictive of survival. Patients with haemoglobin less than 11.0g/dL had shorter survival than patients with higher values, but this was not statistically signifiicant.

When survival is analysed by treatment arm, the longest survival was observed in patients randomised to R6C, with an estimated median survival of 20.3 months and at two years, 41%. This compares with 14.5 months and 26% respectively in patients randomised to R6, the conventional treatment arm. When survival is analysed according to treatment factor, accelerated versus conventional and carboplatin versus no carboplatin, there were no significant differences.

**Table XXXXIV. Overall survival**

| | | Estimated median survival | | Estimated percentage surviving at 1 yr | | at 2 yrs | | at 5 yrs | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Months | 95% CI | % | 95% CI | % | 95% CI | % | 95%CI | P |
| **All patients** | 204 | 15.7 | (14.2–17.4) | 63 | (57–70) | 31 | (25–37) | 10 | (5–14) | |
| **By performance status** | | | | | | | | | | |
| ECOG 0 | 67 | 16.8 | (12.9–20.1) | 64 | (53–76) | 25 | (15–36) | 4 | (0–12) | 0.46 |
| ECOG 1 | 137 | 15.4 | (13.6–17.9) | 63 | (55–71) | 34 | (26–42) | 12 | (5–18) | |
| **By histological type** | | | | | | | | | | |
| squamous | 130 | 15.2 | (12.5–17.9) | 60 | (52–68) | 28 | (20–35) | 9 | (3–14) | 0.16 |
| non-squamous | 74 | 16.0 | (13.6–21.1) | 69 | (58–80) | 37 | (26–48) | 11 | (2–20) | |
| **By institution** | | | | | | | | | | |
| PMC | 156 | 15.8 | (14.4–17.9) | 66 | (59–74) | 31 | (24–39) | 11 | (5–16) | 0.65 |
| ADE | 23 | 14.2 | (9.6–26.5) | 52 | (32–73) | 35 | (15–54) | 0 | (–) | |
| QRI | 15 | 12.6 | (5.8–23.7) | 53 | (28–79) | 27 | (4–49) | not reached | | |
| MMN | 8 | 20.8 | (7.9–>43.9) | 63 | (29–96) | 25 | (0–55) | not reached | | |
| GEE | 2 | Patients too few to report survival | | | | | | | | |
| **By stage** | | | | | | | | | | |
| I | 36 | 21.1 | (12.9– 3.9) | 69 | (54–85) | 44 | (28–61) | 17 | (4–30) | 0.09 |
| II | 8 | 42.0 | (20.4–59.3) | 88 | (65–100) | 75 | (45–100) | 17 | (0–46) | |
| IIIA [a] | 101 | 14.2 | (12.0– 5.5) | 58 | (49–68) | 21 | (13–29) | 9 | (3–15) | |
| IIIB | 59 | 17.0 | (12.9-20.7) | 64 | (52-77) | 34 | (22–46) | 7 | (0–14) | |
| **By tumour size** (omitting 57 with unknown size) | | | | | | | | | | |
| ≤ 20 mm | 7 | 17.8 | (5.5–>55.1) | 71 | (38–100) | 43 | (6–80) | not reached | | 0.06 |
| 21 – 40 mm | 53 | 15.7 | (12.5–24.2) | 64 | (51–77) | 38 | (25–51) | 14 | (3–25) | |
| 41 – 60 mm | 58 | 16.0 | (11.9–19.2) | 62 | (50–75) | 28 | (16–39) | not reached | | |
| 61 – 80 mm | 22 | 15.5 | (8.3–30.9) | 64 | (44–84) | 32 | (12–51) | 12 | (0–27) | |
| > 80 mm | 7 | 10.2 | (4.9–24.9) | 43 | (6–80) | 29 | (0–62) | 0 | (–) | |
| **By weight loss** | | | | | | | | | | |
| none | 138 | 16.4 | (14.4–19.2) | 66 | (58–74) | 33 | (25–41) | 8 | (1–14) | 0.38 |
| ≤ 10% | 66 | 14.7 | (11.0–20.1) | 58 | (46–70) | 26 | (15–36) | 11 | (3–18) | |
| **By initial $FEV_1$** (omitting 55 with unknown FEV) | | | | | | | | | | |
| ≥ 2 L | 49 | 15.8 | (12.5–20.4) | 65 | (52–79) | 27 | (14–39) | 14 | (4–24) | 0.36 |
| 1.50 – 1.99 L | 43 | 11.9 | (10.8–14.9) | 47 | (32–61) | 23 | (11–36) | 7 | (0–15) | |
| < 1.50 L | 57 | 20.4 | (13.9–24.2) | 72 | (60–84) | 42 | (29–55) | 13 | (3–23) | |
| **By Hb nadir** (omitting 14 with unknown Hb) | | | | | | | | | | |
| ≥ 14.0 g/dL | 27 | 17.6 | (14.2–24.7) | 81 | (67–96) | 33 | (16–51) | 0 | (–) | 0.92 [a] |
| 11.0–13.9 /dL | 122 | 15.8 | (14.5–20.4) | 67 | (59–76) | 33 | (24–41) | 13 | (7–20) | |
| < 11.0 g/dL | 41 | 12.0 | (7.7–20.4) | 49 | (33–64) | 29 | (15–43) | 9 | (0–21) | |
| **By treatment arm** | | | | | | | | | | |
| R6 | 53 | 14.5 | (11.9–17.6) | 60 | (47–74) | 26 | (15–38) | 9 | (2–17) | 0.43 |
| R3 | 46 | 14.5 | (12.0–17.9) | 63 | (49–77) | 33 | (19–46) | 14 | (3–25) | |
| R6C | 54 | 20.3 | (15.7–24.2) | 69 | (56–81) | 41 | (28–54) | 9 | (0–18) | |
| R3C | 51 | 15.1 | (11.0–20.7) | 61 | (47-74) | 24 | (12–35) | 10 | (1–19) | |
| **By treatment factor - accelerated** | | | | | | | | | | |
| Conventional RT | 107 | 17.0 | (13.9–20.4) | 64 | (55–74) | 34 | (25–43) | 8 | (2–14) | 0.76 |
| Accelerated RT | 97 | 15.0 | (12.9–17.2) | 62 | (52–72) | 28 | (19–37) | 12 | (5–19) | 0.74 [b] |
| **By treatment factor - carboplatin** | | | | | | | | | | |
| No carboplatin | 99 | 14.5 | (12.5–17.2) | 62 | (52–71) | 29 | (20–38) | 11 | (5–18) | 0.38 |
| Carboplatin | 105 | 17.0 | (14.9–20.7) | 65 | (56–74) | 32 | (23–41) | 8 | (2–15) | 0.36 [c] |

When the three experimental arms were compared individually with the standard treatment arm (R6), the P values were as follows. The comparisons were also repeated with adjustment for stage.

| Comparison | P value | P stratified by stage |
|---|---|---|
| R3 *vs* R6 | 0.47 | 0.26 |
| R6C *vs* R6 | 0.10 | 0.22 |
| R3C *vs* R6 | 0.70 | 0.60 |

Notes: a Two patients with T?N2 disease were included in the stage IIIA group.
b When stratified for carboplatin.
c When stratified for accelerated radiotherapy.

In order to compare the results with other published trials on stage III patients, the analysis by treatment arm was repeated for stage III patients only [table XXXXV]. Although the longest median survival was still observed in patients randomised to R6C, the differences were less marked than with the analysis for all patients. Table XXXXVI shows the same analysis restricted to patients with stage I and II disease. Even though the numbers of patients are small, there is a striking difference in median survival between patients randomised to R6C and the other three arms. For the comparison between R6C and R6, the p value is 0.042, but this needs to be interpreted with caution because of the number of comparisons in this subset analysis.

**Table XXXXV. Stage III patients**

| | No. of pts | Estimated median survival months | 95% CI | Estimated percentage surviving at 1 yr % | 95% CI | at 2 yrs % | 95% CI | at 5 yrs % | 95% CI | P |
|---|---|---|---|---|---|---|---|---|---|---|
| **All patients** | 160 | 15 | (12.9-16.8) | 61 | (53-68) | 26 | (19-32) | 8 | (4–13) | |
| **By treatment arm** | | | | | | | | | | |
| R6. | 42 | 13.8 | (10.7–16.9) | 60 | (45–74) | 26 | (13–40) | 10 | (1–18) | 0.84 |
| R3. | 36 | 14.4 | (11.4–17.8) | 61 | (45–77) | 28 | (13–42) | 13 | (1–24) | |
| R6C. | 41 | 17.0 | (10.6–20.4) | 63 | (49–78) | 29 | (15–43) | 8 | (0–18) | |
| R3C. | 41 | 15.0 | (10.9–17.1) | 59 | (43-74) | 20 | (7–32) | 5 | (0–13) | |

When the three experimental arms were compared individually with the standard treatment arm (R6) for stage III patients only, the P values were:

| Comparison | P value |
|---|---|
| R3 vs R6 | 0.56 |
| R6C vs R6 | 0.48 |
| R3C vs R6 | 0.98 |

**Table XXXXVI. Stage I and II patients.**

| | No. of pts | Estimated median survival months | 95% CI | Estimated percentage surviving at 1 yr % | 95% CI | at 2 yrs % | 95% CI | at 5 yrs % | 95% CI | P |
|---|---|---|---|---|---|---|---|---|---|---|
| **All patients** | 44 | 22.8 | (14.4–37.0) | 73 | (60–86) | 50 | (35–65) | 13 | (0–26) | |
| **By treatment arm** | | | | | | | | | | |
| R6 | 11 | 19.5 | (4.7–37.0) | 64 | (35–92) | 27 | (1–54) | not reached | | 0.26 |
| R3 | 10 | 19.3 | (10.2–33.9) | 70 | (42–98) | 50 | (19–81) | 20 | (0–45) | |
| R6C | 13 | 41.6 | (24.1–56.9) | 85 | (65–100) | 77 | (54–100) | 12 | (0–33) | |
| R3C | 10 | 21.1 | (9.6–>56.0) | 70 | (42-98) | 40 | (10–70) | not reached | | |

When the three experimental arms were compared individually with the standard treatment arm (R6) for stage I and II patients only, the P values were:

| Comparison | P value |
|---|---|
| R3 vs R6 | 0.59 |
| R6C vs R6 | 0.042 |
| R3C vs R6 | 0.36 |

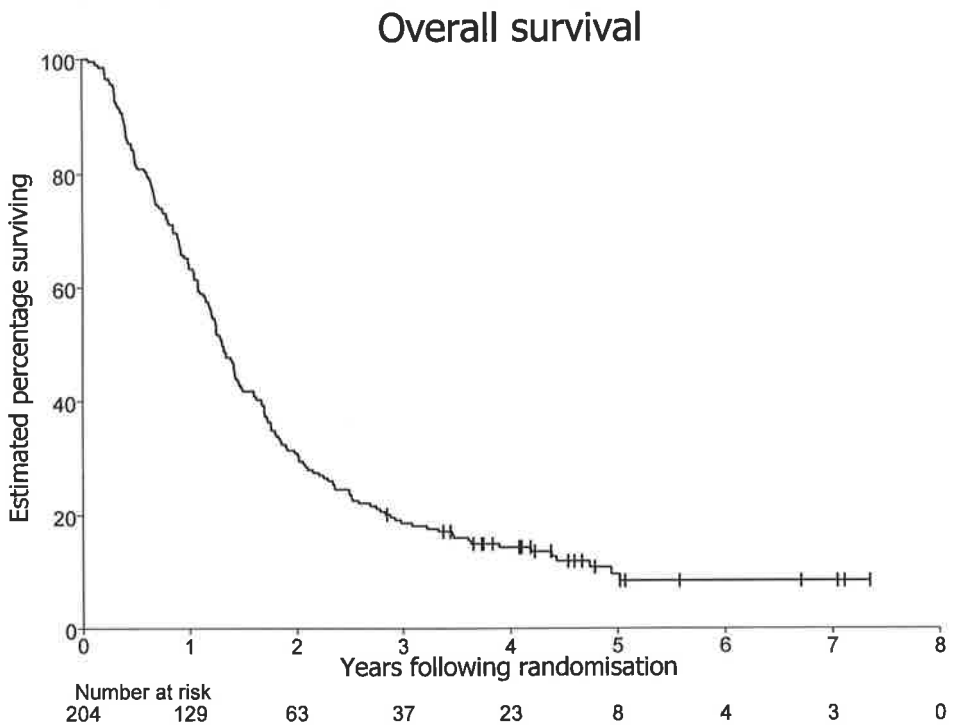


**Figure 10. Survival of all patients.**

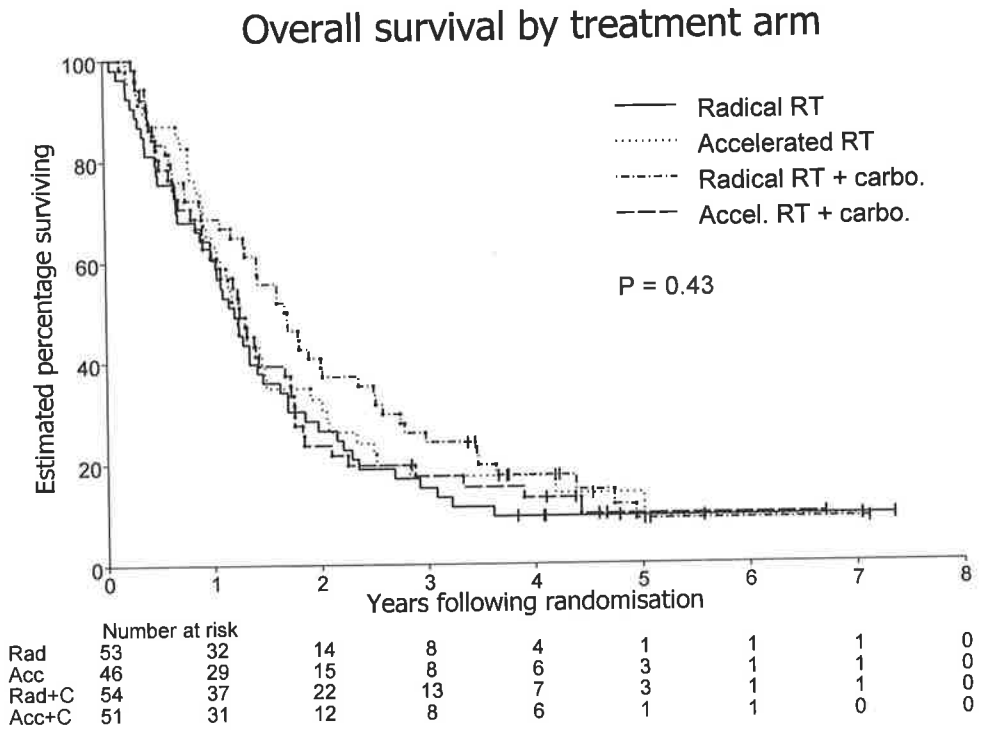


**Figure 11. Survival according to randomisation.**

### 2.3.8 Discussion.

**Survival.** Judged by the primary endpoint, survival, the results of this trial are inconclusive. Although the best survival was observed in patients randomised to R6C, the difference in comparison to R6 was not statistically significant, even though the median survival was almost 40 % longer [20.3 months for R6C versus 14.5 months for R6 ], and survival at two years was 58% better [41% versus 26%]. It is interesting to note that the survival for patients randomised to R6 was almost identical to that of the patients treated with 60 Gy and reported in the first part of this thesis. The median survival for those patients was 14.8 months, with a two year survival of 27%. It is possible that the trial was underpowered to detect a statistically significant benefit in favour of carboplatin, and that if the trial had continued a more statistically robust result may have been obtained. At the time accrual ceased in May 1995, we had reached the protocol-specified target of 200 patients randomised, and the meta-analysis revealing a survival advantage associated with the addition of cisplatin to radical radiotherapy was about to be published[84]. We felt therefore that further accrual to a study in which one of the potential treatments was radiotherapy alone [R6] could not be ethically justified. Furthermore, there was no suggestion of a survival advantage associated with accelerated treatment, but this strategy did result in significant oesophageal toxicity that was both more severe and more prolonged. The longer survival of patients randomised to R6C, if not *statistically* significant, at least appeared to us to be *clinically* significant, especially as the regimen was so well tolerated. Finally, the result was not inconsistent with the meta-analysis which had revealed a benefit for combined therapy.

If the prolongation of survival on R6C was real, and not a chance observation, why was a similar effect not also seen in patients randomised to R3C, and why was carboplatin not beneficial when survival was analysed by factor rather than arm? If there was an effect of

carboplatin, it is reasonable to assume that it would have been less marked on R3C since these patients were given a smaller total dose, and less drug was available at the time of the second daily fraction, over six hours after it had been infused. In contrast, patients randomised to R6C were given twice the total amount of carboplatin, it was given immediately before all ten fractions, and the second cycle was given later in the course of radiotherapy [week 5], which may be more effective than drug given at the beginning of treatment[123].

Subgroup analysis of survival by stage suggested that the effect of carboplatin was more marked in patients with stage I and II disease. The estimated median survival of 13 stage I and II patients randomised to R6C was 41.6 months with 77% estimated survival at two years; for 11 patients randomised to R6 the coresponding figures were 19.5 months and 27% [p = 0.042]. Since one would expect fewer patients with early stage tumours to have subclinical metastatic disease, a treatment whose primary objective is improved local control might perform best in this subgroup.

Although the addition of carboplatin to radical radiotherapy was well tolerated, with no statistically significant increases in nausea and vomiting, oesophagitis or pulmonary toxicity, the largest number of variations in protocol treatment occurred in patients randomised to R6C, with 10 patients [19%] not receiving protocol dose, including 4 patients who could not have the second cycle because of haematologic toxicity. The inability to give the second course – which we had already experienced with 2 patients in the pilot study – leads to the tantalizing question: if all patients randomised to R6C had been able to receive protocol dose, would their survival have improved to the extent that it was statistically significant? Could the carboplatin have been given more reliably using pharmacologically-guided dosing which is now our current practice[124]?

There are at least four other randomised trials in which carboplatin has been used as a radiosensitiser in patients with NSCLC. Two have shown a survival advantage in favour of combining carboplatin with radiotherapy, and two have shown no benefit. None demonstrated a detrimental effect of combined therapy.

The first of these studies was reported by Jeremic and colleagues in the *Journal of Clinical Oncology* in 1995[125]. In a 2 year period, 169 patients with stage III NSCLC and Karnofsky performance status $\geq$ 50% were randomised to one of three arms: Group I, hyperfractionated radiotherapy alone, 64.8 Gy in 54 fractions using twice daily 1.2 Gy fractions; Group II, the same radiotherapy schedule plus chemotherapy consisting of carboplatin 100 mg on days 1 and 2 and 100 mg of VP-16 on days 1 to 3 of each week during the radiotherapy course; and Group III, same radiotherapy regimen with carboplatin 200 mg on days 1 and 2 and VP-16 on days 1 to 5 of the first, third and fourth weeks of the radiotherapy course. The method of randomisation was not stated. There were uneven numbers of patients in each arm: 61 in Arm I, 52 in Arm II and 56 in Arm III. Most patients had Karnofsky performance status of 80-100 and there were no significant differences between groups. Patients in Group I had a median survival of 8 months; in Group II, 18 months and in Group III, 13 months. Five year survivals were 5%, 21% and 16% respectively. The survival difference between Groups I and II was statistically significant [p = 0.0027], but the others were not. The authors concluded that weekly administration of carboplatin and VP-16 was associated with a survival advantage, and this appeared to be mediated through improved local control. Less frequent administration of carboplatin appeared to be less effective, even though the total dose was the same. There are a number of concerns in relation to this manuscript which appear to have escaped the reviewers' notice. The first concern is that although the study was reported as a randomised trial, there is evidence to suggest that it was not. The treatment groups were uneven in size, and no information regarding the method of randomisation is provided to explain how this

may have come about. Most importantly, the toxicity data were published earlier in a separate manuscript in *Cancer*, in which there is no mention of a randomised trial[126]. The second concern relates to the results published in the *Journal of Clinical Oncology* report, in which the authors state that "All deaths were due to local recurrence or distant metatasis, and no patient died of intercurrent disease." [125] This is surprising, given the multiple comorbidities in patients with lung cancer, and the fact that in our own study 26 of 180 [14.4%] deaths were due to other causes. A third concern stems from a further report, based on the same group of patients published in 1996[127]. In this analysis, Jeremic and Shibamoto examined the effect of the length of interfraction interval on survival in the patients, all of whom had been treated with hyperfractionated radiotherapy. According to the authors, various interfraction intervals between 4.5 and 6 hours were used, but the interval was kept constant for each patient. The patients were divided into two groups: those in whom the interfraction interval was 4.5 – 5 hours, and those in whom it was 5.5 – 6 hours. There was a highly significant difference in survival in favour of patients treated with the shorter interval [median 22 months for the shorter interval versus 7 months for the longer interval, and at 5 years 27% and 0% respectively; $p<10^{-5}$], and this difference was still highly significant after adjusting for the influence of other prognostic factors. On multivariate analysis, which included interfraction interval in the model, treatment with or without carboplatin was no longer significant. Now it is extremely difficult to demonstrate the effect of any therapeutic intervention in stage III NSCLC, and when differences have been observed they are usually less than a 50% increase in median survival[67, 105]. It is therefore surprising that a small difference in interfraction interval of 1.0-1.5 hours can increase median survival by over 200%! All of these discrepancies cast doubt on the credibility of Jeremic's data and conclusions, even though they are consistent with the results of our own trial.

The second randomised trial of carboplatin in conjunction with radiotherapy was reported a year later in 1996, again by Jeremic and colleagues[128]. This study followed on immediately from the previous trial, and as a result the control arm was not the best arm of the first study, but consisted of hyperfractionated radiotherapy to a slightly higher dose of 69.6 Gy. The investigational arm was the same radiotherapy together with chemotherapy carboplatin 50 mg and etoposide 50 mg given each day of radiotherapy. Similar eligibilty criteria to the first trial were used, and 135 patients were randomised, of whom 131 were eligible for analysis. As with the first study, it accrued between January and December the following year, and it was conducted in a single hospital. Remarkably, "all deaths were due to local recurrence or distant metastasis, and no patients died of other causes" – as in the first study. The patients randomised to the combination had a superior survival, median 22 months, compared with 14 months for patients randomised to radiotherapy alone. Four year survivals were 23% and 9% respectively, and the difference was statistically significant [$p = 0.021$]. It is interesting to observe that the increase in radiotherapy dose in the control arms from 64.8 Gy in the first study to 69.6 Gy in the second was associated with an improvement in median survival from 8 to 14 months. A longer survival associated with a shorter interfraction interval was again observed, although in this trial it was not significant on multivariate analysis. In this study, Jeremic et al observed a remarkably large difference in survival between patients with stage IIIA and stage IIIB disease, with median survivals of 25 and 13 months respectively [$p < 0.0001$]. Although it might be expected that the more advanced stage would be associated with a worse prognosis, and that may be true for patients treated surgically, we observed no significant difference in survival when comparing stages IIIA and IIIB in our own trial [median 14.5 months versus 17.1 months respectively]. Our experience is by no means unusual; there are other reports that the distinction between IIIA and IIIB is not of prognostic significance in patients treated either with radiotherapy alone[129], with induction chemotherapy followed by radiotherapy[82], or with concurrent radiotherapy and chemotherapy[130]. Presumably

the absence of a survival difference is related to the fact that the two stage groupings bear no relationship to the volume of tumour[131], which one might expect would influence radiocurability. Why the survival of the patients in the Jeremic study fitted nicely with the predictions of what is essentially a surgical staging system, rather than with the published observations of others, is not clear. If nothing else, it draws attention to deficiencies in the existing staging system, exposing its inability to consistently predict the outcomes for two supposedly homogeneous prognostic groups.

It is difficult to know what to make of the Jeremic studies. There is something about them that is too glib, the results seem to spill out too easily, and they always confirm the starting hypothesis. More information is required regarding the method of randomisation before the two studies are fully credible, despite their having been published in one of the more respected oncology journals.

The third study was conducted by the CALGB, and was a randomisation to either induction chemotherapy followed by radiotherapy or the same induction chemotherapy followed by radiotherapy combined with concomitant weekly carboplatin, designed to test its radiosensitising properties[130]. The eligibility criteria were restricted to patients with stage IIIA and IIIB disease. The induction chemotherapy was the same as in the original CALGB study, consisting of two cycles of cisplatin and vinblastine[67]. Radiotherapy was given as 60 Gy to the primary and mediastinum, with a reduction to the tumor only after 40 Gy. Patients assigned to carboplatin were given 100 $mg/m^2$ on the first day of each week of radiotherapy. The total number of eligible patients available for analysis was 250. There was no difference in the survival in the two arms, median survival being 13.5 and 13.4 months for the control and investigational arms respectively. Interestingly, while stage had no influence on survival, there was a highly significant effect of tumour size, with tumours greater than 70 $cm^2$ having a

worse survival [median 7.2 months] compared with tumours less than 70 $cm^2$ [median 14 months, p = 0.01]. What are the differences from our own study which may explain why there is not even a suggestion of an effect of the addition of carboplatin? First, all patients in the CALGB study were given induction chemotherapy, which may have resulted in an increased proportion of platinum-resistant clones, no longer susceptible to the radiosensitising properties of carboplatin. This hypothesis is however not supported by the preclinical studies of Groen and colleagues in human small cell cancer lines, in which similar radiation dose enhancement ratios were achieved by carboplatin in both cisplatin-sensitive and cisplatin-resistant lines[75]. Second, the chemotherapy was scheduled differently. Although there were no substantial differences in the total doses of carboplatin between the trials, in our study it was given daily for two weeks, rather than weekly. Since it appears that the effects of the platinum drugs are achieved through their ability to inhibit the repair of sublethal damage in the interfraction interval, repeated rather than intermittent administration might be expected to result in more cell killing, an hypothesis supported by the results of the original EORTC study in which daily cisplatin was associated with longer survival than weekly cisplatin[66]. Finally, the two treatment populations were different. In the CALGB study, only patients with stage III disease were eligible; the Australian study randomised patients with inoperable stage I and II disease as well. If we compare the survival of the patients in the carboplatin plus 60 Gy arms of the two studies, restricting the analysis to patients with stage III disease, it appears longer in the Australian trial [median 17.0 months] compared with the CALGB study [13.4 months], although the 95% confidence intervals overlap. The poor survival observed in the CALGB trial in the small group of patients with large tumours highlights the fact that large variations in tumor burden are permissible within the one stage grouping[131]; this alone may be sufficient explanation for the different outcomes observed in various trials purportedly studying patients in the same stage grouping. It is worth noting that although no survival benefit was observed in the CALGB study, there was a reduction in the number of local

failures in patients randomised to carboplatin. Theoretically, an effect of improved local control on survival is more likely to be observed in patients who have a lower competing risk of distant relapse, i.e. patients with early stage disease without nodal invovement, for whom, in our own study, the greatest benefit of the addition of carboplatin was observed.

The fourth randomised study comparing radiotherapy and carboplatin with radiotherapy alone has at the time of writing only appeared in abstract form[132]. Based on a phase I study which established the maximum tolerable dose of continuous infusion carboplatin with 60 Gy radiotherapy[133], Groen and colleagues randomised 143 patients with stage III NSCLC to either radiotherapy alone, 60 Gy in 30 fractions, or the same radiotherapy together with continuous infusion carboplatin 840 mg/m$^2$ given over six weeks. There was no difference in survival between the arms, the medians being 11.5 and 10.9 months for the combined treatment and radiotherapy alone arms respectively. The striking feature of this study is the poor survival, especially in the combined modality arm, which appears inferior to what has been achieved with concomitant platinum-based chemotherapy and radiotherapy by ourselves and others[75, 125, 128], although similar to the survival reported for the CALGB's experimental arm[130]. The apparently poor survival may be related to patient selection, but until the study is published in full, it will remain unexplained.

While the evidence for a survival advantage resulting from the use of concomitant carboplatin and radiotherapy is not as strong as it is for cisplatin, it has not deterred various groups from continuing to test it in various combinations, with concomitant radiotherapy, seemingly as a replacement for cisplatin[134]. The attraction of the more acceptable toxicity profile of carboplatin is undeniable, and some physicians and patients clearly feel that it may counterbalance any small reduction in its cytotoxicity or radiosensitising effect. It now seems unlikely that the effects of cisplatin and carboplatin will ever be compared directly in a

randomised study, which would have to be very large to be powered to detect equivalence. The simple fact is there are much more interesting research opportunities with new agents and combinations than comparing the activities of the two platinum drugs.

The second hypothesis tested in this trial was that shortening overall treatment time would improve survival. The design of the study enabled us to directly compare the two innovative strategies of concomitant platinum-based chemotherapy versus radiotherapy with treatment acceleration. Unlike the CHART study[104], any benefit associated with a reduction in overall treatment time in this trial was small, and not statistically significant. The size of our study was much smaller than the CHART trial, and a benefit is more likely to have been missed[121]. The hazard ratios for risk of death have been calculated for R6C and R3 relative to R6, and they are shown, together with 95% confidence intervals in Table XXXXVI along with the hazard ratios for CHART [105] and the cisplatin/radiotherapy meta-analysis[84]. Carboplatin combined with radiotherapy was associated with a 28% reduction in risk of death, compared with 22% for CHART. The CHART authors have responded by saying that the small and statistically non-significant reduction in risk of death associated with accelerated radiotherapy [14%] is consistent with the result of CHART[135].

**Table XXXXVII. Hazard ratios for survival: chemotherapy vs treatment acceleration**

| Comparison | Hazard ratio | 95% confidence interval |
|---|---|---|
| Cisplatin/RT v RT[84] | 0.87 | 0.79 - 0.96 |
| CHART v RT[105] | 0.78 | 0.65 - 0.94 |
| Carboplatin/RT v RT[122] | 0.72 | 0.48 - 1.07 |
| Accelerated RT v RT[122] | 0.86 | 0.56 - 1.30 |

That may be so, but at what cost? The oesophageal toxicity associated with treatment acceleration was unacceptably severe in our patients, more so than in the CHART study. The

oesophageal toxicity proved acceptable in the CHART patients because they were treated with a lower total dose and smaller doses per fraction than in the Australian study. But the dose per fraction was only 1.5 Gy and so acceleration could only be achieved by treating three times a day, seven days a week, from 8 am to 8 pm. If two treatment strategies are equally effective, then the strategy that is less demanding on staff and departmental resources is clearly preferable. Whilst a cost benefit analysis has demonstrated a modest cost of 2400 pounds per year of life saved by CHART compared with conventional radiotherapy, a similar comparison has not been made with the cost benefit of adding chemotherapy to radiotherapy. The CHART triallists largely sidestepped any discussion of the relative efficacies of combined modality therapy and accelerated treatment by saying 'We do feel, however, in view of the results of the CHART trial, that addition of concurrent chemotherapy should not be at the expense of intense radiotherapy.'[135] This is in spite of the fact that level I evidence is available for combined modality therapy, whereas that for CHART is level II. Theirs is a difficult argument to sustain, more so - as Dr Tobias and I argued in an editorial in the British Medical Journal - because CHART 'has proved logistically difficult for most departments to implement .... Chemoradiation ... will probably prove a more feasible and practical means of achieving similar benefit.'[136]

Recognising the difficulties associated with its implementation, the group at Mt Vernon have modified CHART so that treatment is only administered during the working week – so-called CHARTWEL ['CHART weekend less'].[137] They were able to demonstrate the feasibility of escalating the total dose from 54 Gy to 60 Gy. The higher dose was achieved by increasing the total number of fractions from 36 to 40, so keeping the individual fraction size the same. This small increase in total dose was associated with a statistically significant increase in the severity of acute oesophagitis, but no increase in its duration. In the discussion, the authors signalled their intention to evaluate the CHARTWEL 60 Gy regimen with concurrent

chemotherapy. Referring to our publication[119], they stated that the 'extra amount of cell kill' [due to chemotherapy] 'may precipitate more early severe early or late toxicity'[137] even though there was a non-significant increase in grade 3 and 4 toxicity from 35% to 39% when carboplatin was given concomitantly with accelerated radiotherapy, and there was no difference in the duration of symptoms. So the story of CHART is by no means complete, but in busy departments with strained resources it seems destined to remain a curiosity. It is, after all, only one schedule that reduces overall treatment time, and similar results may be achievable using accelerated regimens which do not impose such demands on the patients and their treaters.

**Patterns of Failure.** A recurring theme in this thesis has been the importance of achieving local control as a means of lengthening survival in patients with locoregional NSCLC. It is therefore of interest to analyse the patterns of failure based on site of first progression, which was documented as accurately as possible, although histo/cytologic confirmation was not required. In most instances the diagnosis of progression was based on imaging. Examination of the cumulative incidence of failure [Table XXXXIII and Figure 9] reveals that for all patients, progression outside the field predominates early, but with the passage of time there is a steady increase in local failure. By 5 years local progression had occurred in 30.1% of patients, and was the predominant site. This is consistent with radiotherapy having some local effect which diminishes with time; the treatment [as might be expected] has less effect on systemic disease, and therefore progression outside the field occurs at a faster rate. Comparing sites of failure by treatment arm, there is no suggestion that there is a lower incidence of distant progression in patients randomised to the carboplatin arms. Indeed, the arm with the highest incidence of distant progression was R3C. It was not expected that carboplatin would affect systemic disease because it was employed as a radiosensitiser.

While few conclusions can be drawn from this analysis regarding the influence of the different treatments on the patterns of failure, the results do emphasize the fact that progression at the primary site is a major problem in patients whose NSCLC is treated by radiotherapy [as observed in the CHART study], and that improvements in local control may lead to longer survival in approximately a third of patients. The high incidence of distant progression within the first 12 months of randomisation suggests that more sensitive means of detecting clinically silent metastatic disease are required to avoid treating patients for whom local therapy will be of limited or no use. In our experience pre-treatment scanning using 18-F fluorodeoxyglucose positron emission tomography is helpful in this regard[138].

Finally, it is noteworthy that 18.8% of patients had died at 5 years without evidence of progression. To a small degree this was related to the toxicity of treatment, but appeared in most cases to be a result of the serious comorbidities that patients with lung cancer commonly suffer. Analysis of the patterns of failure in RTOG 8808 [see section 2.1.4] revealed that approximately 20% of patients in all treatment arms died without progression[79], very similar to our own experience, but distinctly at odds with the reports of Jeremic et al[125, 128]. It cautions readers to be wary of disease-specific survival in reports of lung cancer outcomes, since censoring individuals dying of other causes will have a significant and apparently beneficial effect on the survival curve.

**Secondary analyses: Toxicity**

**Haematologic toxicity.** As expected patients who were treated on the carboplatin arms had significantly more haematologic toxicity than those treated with radiotherapy alone. Haematologic toxicities in R6 and R3 were negligible, although a small proportion of patients developed anaemia. Although this did not influence treatment delivery, it may have adversely affected outcome, by increasing tumor hypoxia. This will be discussed later.

In patients treated on the carboplatin arms, we did not observe any serious haematologic toxicity, but in those patients randomised to have two cycles of carboplatin [R6C], 19% either had to have a dose reduction, or the second dose was withheld because of ongoing myelosuppression. We can only speculate on whether this adversely affected the survival for some patients randomised to R6C. Further, there may have been patients with normal renal function who were given the protocol dose according to body surface area but in whom efficient clearance reduced the area under the curve [AUC] to less than 6, so that they may have been effectively underdosed[124]. To examine this possibility, a retrospective analysis was performed on the 75 trial patients treated with carboplatin at Peter MacCallum. The carboplatin dose administered was recalculated and converted to the AUC, using the Chatelut formula[139]. The resulting AUC's were correlated with the falls in platelet and neutrophil counts. The median AUC was 5.15, with a range of 2.98 to 7.95. There was however no significant correlation between the recalculated AUC's and the degree of haematologic toxicity. This is not surprising, since the majority [72%] of the patients had an AUC of less than 6, which is less than full dosage when administered without concomitant chest irradiation[124]. It does suggest that there was scope for safely increasing the dose in almost three quarters of the patients randomised to R6C or R3C.

**Oesophageal toxicity** This study has provided important information on the oesophageal toxicity of both accelerated radiotherapy and the combination of carboplatin and radiotherapy. Oesophagitis has become the most consistent acute dose-limiting toxicity in patients receiving intensive radiotherapy regimens for lung cancer, and this was confirmed by our own experience.

The addition of carboplatin to conventional radiotherapy resulted in an increase in grade 3 and 4 toxicity from 12% to 21% . The addition of carboplatin to accelerated radiotherapy produced an increase in grade 3 and 4 toxicity from 32% to 48%. When analysed by factor, carboplatin was associated with an increase in acute toxicity, but this was not statistically significant [p = 0.13]. The duration of oesophagitis was not influenced at all by the concomitant administration of carboplatin to either conventionally fractionated or accelerated radiotherapy [figure 8]. We can therefore conclude that if standard doses of carboplatin increase radiation-induced oesophageal toxicity, then the effect is mild and not of clinical significance.

This was not however the conclusion of Kelly and colleagues based on a phase I study designed to determine the MTD of daily low dose carboplatin with concurrent accelerated hyperfractionated radiotherapy[140]. All patients were given radiotherapy, 60 Gy in 26 days, using 1.2 Gy b.d. The first dose level of carboplatin was 25mg/m$^2$, given daily before the first fraction, i.e. a total of 500 mg/m$^2$ concomitantly with radiotherapy, in contrast to the 700 mg/m$^2$ in patients randomised to R6C in our study. Five patients [21%] developed grade 3 oesophageal toxicity at this dose level and 3 [13%] developed grade 4. When the carboplatin dose was increased to 30 mg/m$^2$ [total = 600 mg/m$^2$], 1 of 6 [17%] patients developed grade 3 oesophagitis and 2 [33%] developed grade 4. Dose level 1 was therefore taken to be the MTD. Unlike our own study, this was not a randomised trial and so we do not know what the incidence of severe oesophageal toxicity might have been in patients treated with radiotherapy alone. The numbers treated at dose level 3 were small and the observed incidence of grade 4 toxicity could therefore have been a chance observation. Hence the authors' claim that carboplatin was responsible for the dose-limiting oesophagitis must remain open to question.

A Japanese single arm study investigated the feasibility of giving daily carboplatin [25 $mg/m^2$] concomitantly with accelerated hyperfractionated radiotherapy [60 Gy in 40 1.5 Gy fractions, administered b.d.][141]. Twenty three per cent of patients developed grade 3 or 4 oesophagitis, but because of the study design, it is not possible to determine how much was due to the fractionation schedule, and how much due to the addition of carboplatin.

If there is doubt about the degree to which carboplatin enhances radiation-induced oesophagitis, if at all, then there is none about the effect of accelerating the radiotherapy. The increase in acute oesophageal symptoms was highly significant, whether the comparison is by treatment arm [R3 versus R6, $p < 0.0002$ and R3C versus R6, $p < 0.0001$] , or by factor [accelerated versus conventional fractionation, $p < 0.0001$]. Only 3 patients [3 %] treated with accelerated radiotherapy had no oesophageal symptoms, compared with 18 [17 %] who were treated with conventional fractionation. Although the severity of acute symptoms was worse overall for the accelerated radiotherapy group, the number of patients who developed particularly severe symptoms [grade 4 – alimentation not possible] was surprisingly small; 2 patients [4 %] on R3 and 1 [2%] on R3C, no different to the number of patients developing severe toxicity with conventional fractionation.

Acceleration of radiotherapy is expected to be associated with more severe acute reactions, since there is less time for repopulation of the mucosal surface by the remaining stem cells in the basal layer. Dysphagia was noted to be more severe, as in our study, and it occurred sooner in patients randomised to CHART compared with conventional fractionation[104]. In patients with small cell lung cancer, who were treated to exactly the same total dose [45 Gy], but who were randomised to have their treatment in either three weeks [b.d. fractionation] or five weeks [daily fractionation], oesophageal toxicity was significantly worse in patients treated twice a day[142]. Because the dose was the same in both arms, as in our study, we can

conclude that it is an effect of overall treatment time, and not a result of some adjustment to the number of fractions or the size of dose per fraction.

In our patients the acute oesophageal toxicity which developed during treatment was manageable with diet, local anaesthetics and opiates, but the time taken for symptoms to settle after completion of treatment in patients treated with the accelerated schedule was particularly troublesome. The median duration of oesophageal symptoms was 3.2 months for the 96 patients having accelerated treatment, compared with 1.8 months for the 104 patients receiving conventional fractionation [Table XXXXI]. At six months 23% of patients on the accelerated regimen still had oesophageal symptoms, compared with only 3% of patients treated with conventional fractionation. These differences were highly statistically significant [$p = < 0.0001$]. In contrast the median duration of oesophageal symptoms in the 103 patients treated with carboplatin was 2.3 months, compared with 2.4 months for 97 patients treated with radiotherapy alone [$p = 0.47$].

There are two potential explanations for the longer duration of symptoms in patients treated with accelerated radiotherapy. The first is that the patients developed fibrous strictures, as a consequence of damage to the submucosa and muscular layers in the oesophageal wall. This is the classical concept of late oesophageal injury, which does not resolve spontaneously[143]. However, there was a gradual decline in patients reporting symptoms throughout the period of observation [Figure 8], indicating that unless the patients were having dilatations, the pathologic process underlying their dysphagia was self limiting. In fact, only 11 patients were dilated, and 7 of these had been treated with the accelerated schedule.

The more likely explanation for the prolongation of symptoms is that there was a delay in the healing of the acute mucosal injury, rather than permanent damage to the late-reacting

mesenchymal tissues. Such chronic mucosal reactions are termed 'consequential late reactions', and their occurrence in patients having accelerated treatment for head and neck cancer [in whom it is possible to visualise and score the reaction] is well documented[144]. The slow healing can be attributed to more severe cellular depletion in patients having the more intensive treatment, leading to longer time to repopulate the mucosal surface. In these circumstances, instrumentation of the oesophagus might aggravate the injury by traumatising the healing epithelium.

It is interesting to note that there was no prolongation of dysphagia in patients treated with CHART, compared with those treated with conventional fractionation[104]. Dysphagia was more severe, and developed earlier in the CHART arm, but at 3 months it was still present in 9% of the CHART patients, and 7% of the conventional patients. There are several reasons why late oesophageal morbidity may have been different in the Australian and CHART studies. First, the total dose in the CHART study was 10% lower than in our study. Second, the target volume remained the same throughout treatment in our study, whereas the volume was reduced for the latter part of treatment in the CHART trial. The protocol specified that the fields should cover the primary lesion and the adjacent mediastinum. It is likely therefore that all patients received full dose to at least a portion of their oesophagus. In the CHART study, the primary tumor and mediastinum were irradiated to 37.5 Gy in 25 fractions, and in the second phase [16.5 Gy in 11 fractions], only the primary tumor and known sites of nodal involvement were included. Thus there may have been a number of patients who received only 37.5 Gy to the oesophagus.

Because the length of oesophagus irradiated might influence the total area of epithelial loss [and therefore the time to re-epithelialisation], we analysed the effect of length of field on the duration of symptoms. It can be seen from Table XXXXI that there were no significant

differences in the duration of dysphagia whether the length of field was shorter than 12 cm, longer than 16 cm, or somewhere in between.

Finally, there were a number of patients who did develop strictures requiring mechanical dilatation. These included one patient on R6, six patients on R3, three patients on R6C, and one patient on R3C. All but three patients had their dilatations six months or more post treatment; three patients, all on R3, had dilatations at 1.5, 3 and 5 months. The symptoms in these patients may have been due to consequential reactions rather than fibrotic strictures. Thus there is no evidence that accelerated radiotherapy was associated with an increased risk of oesophageal stricture.

If there were a significant survival advantage associated with accelerated radiotherapy, the more severe and prolonged symptoms of dysphagia may have been an acceptable price to pay. In the absence of any benefit, it is hard to justify the more intensive schedule, particularly as one patient died as a result of a treatment-induced fistula. It is conceivable that some of the oesophageal toxicity observed could have been avoided by using a 'shrinking field' technique, so that the oesophagus was excluded from the treated volume during the latter part of the course. If this is not possible, the applicability of accelerated regimens will be to some extent limited by the associated mucosal toxicity, unless an effective systemic or surface protectant becomes available. The use of such an agent [amifostine] for this purpose is currently under investigation by the RTOG in their study 98-01[145].

In contrast, any enhancement of oesophageal toxicity by carboplatin in this study was negligible, suggesting that as a single agent, it can be safely administered with both conventional and accelerated radiotherapy.

**Other toxicities.** A major deterrent to patients consenting to have chemotherapy is the risk of nausea and vomiting. This has been a major problem with cisplatin, particularly in the era prior to the introduction of the 5HT3 antagonists, and was dose-limiting in a Phase I study of the EORTC[64]. In our study, there was no increase in nausea and vomiting associated with the use of carboplatin compared with radiotherapy alone [Table XXXIX].

There were no differences in pulmonary toxicity comparing treatment arms and treatment factors. Two patients developed fatal radiation pneumonitis, one on R3 and the other on R3C. One patient on R3C developed severe pulmonary fibrosis. An abscess developed in the region of fibrosis and he subsequently succumbed to the effects of chronic sepsis. It is not clear to what extent this event could be attributed to treatment, since in-field fibrosis which develops in most patients who have high dose radiotherapy usually remains uncomplicated.

No patient developed alopecia. There was no enhancement of acute skin reaction either by accelerated radiotherapy or by the addition of carboplatin.

Hence it is not surprising that when patients were asked about their overall quality of life, the average values from randomisation to time to progression or the close-out date showed no differences according to treatment arm or treatment factor [data not shown].

**Secondary analyses: Prognostic Factors.** To be eligible for this study, patients had to have good prognostic features: performance status ECOG 0 or 1, weight loss less than 10%, and no evidence of distant metastases. We did not exclude patients with early stage disease if they were inoperable on medical grounds or refused surgery. Thus we had some limited opportunities to examine the effects of some established and suspected prognostic factors on survival [Table XXXXIV]. In interpreting these results it needs to be borne in mind that the

study population was relatively small, and all the analyses were unifactor, so the effects of each factor have not been adjusted for the influence of other prognostic factors or the effect of treatment.

**Performance status.** The majority of patients had an ECOG performance status of 1; their median survival was slightly inferior to that of patients with a performance status of ECOG 0 [15.4 months versus 16.8 months]; however the overall survival difference was not statistically significant [p = 0.46].

**Histology.** Patients with squamous histology had a slightly inferior survival, but this was not significant [p = 0.16].

**Institution.** There were no statistically differences in survival between the 5 participating institutions.

**Stage.** As might be expected, the survival of patients with stage I disease appeared to be better than for stage III disease. The survival of patients with stage I disease was 17% [95% C.I.: 4–30] at 5 years. The majority of patients with stage I disease were staged clinically; had they been surgically staged, a number may have been found to have stage III disease. The poor sensitivity of the imaging techniques used in this study for the detection of nodal disease results in blurring of the survival characteristics of patients with stage I and stage III disease. The number of patients with stage II disease [8] is too small to enable comment. The patients with the shortest survival were those with stage IIIA disease, ie predominantly patients with mediastinal nodal involvement. Their median survival was 14.2 months [95% C.I.: 12.0-15.5], compared with a median survival of 17.0 months [95% C.I.: 12.9-20.7] for patients with stage IIIB disease. The failure of the subgroupings IIIA and IIIB to provide prognostic information

in patients treated by non-surgical means has been referred to above. It has been observed by others[82, 129, 130], and is presumably a reflection of the classification separating patients on the basis of technical resectability rather than tumor burden or size. Indeed, tumours that are T3 or T4 can be *any size*; the distinguishing features are related instead to extension into surrounding structures, or proximity to the carina. When the influence of tumor size on survival is analysed, there is a trend for smaller tumours to have a longer survival [$p = 0.061$]. However the size was only known for 147 patients, and was based on a single maximum diameter measurement.

**Weight loss.** Patients with some weight loss had shorter survival than those who reported no weight loss; the difference was not however significant [$p = 0.38$].

**Haemoglobin.** Survival was correlated with the lowest measured level of haemoglobin. The shortest survival was seen in patients who were anaemic [$< 11$ g/dL]; their median survival was only 12.0 months, compared with a median survival of 17.6 months for patients whose lowest haemoglobin was $\geq 14.0$ g/dL. However the differences had disappeared at 2 years, and overall the effect of haemoglobin nadir was not significant. The poorer survival of patients who became anaemic suggests that the significance of anaemia warrants further investigation. In a retrospective study of patients receiving radiotherapy for carcinoma of the cervix, the average weekly haemoglobin nadir was a significant predictor of survival, and the negative prognostic effect of a low haemoglobin appeared reversible by blood transfusion[146]. Since anaemia was significantly worse in patients having carboplatin, and the protocol did not require its correction, it is conceivable that a similar effect to that observed in the patients with cervical cancer may have masked some beneficial effect of the carboplatin in our patients. The effect was more marked in patients receiving two cycles of carboplatin, yet this group had the longest survival. It is tempting to speculate that the survival of this group may

have been even longer if there had been a policy of correcting anaemia with transfusion. The potential significance of anaemia occurring both before and during treatment, which may render tumours more hypoxic and therefore more radioresistant[147], should not in future be overlooked.

**Conclusions and future studies.**

At the end of the twentieth century, it is recognised that the survival of patients with NSCLC is among the worst of all malignancies. This has led to a perception that very little has been achieved in the management of NSCLC, such that even in 1995, there were still advocates for minimal intervention for all patients with inoperable NSCLC, regardless of prognostic factors. In reporting the survival of 38 patients, most of whom had good performance status, and who were treated with a hypofractionated regimen, Stevens and Begbie claimed that the median survival observed [35 weeks] 'was consistent with best international end results.'[148]

It is hard to share Stevens and Begbie's view when comparing the survival of patients with inoperable NSCLC thirty years ago with those treated in the last decade. For example the survival of patients with squamous cell carcinoma randomised to receive an inert compound in the Veterans Administration Study [published 1966] was 13.4% at 12 months, and the median survival less than 5 months[8]. In contrast the 12 month survival of patients randomised to the best arm of our study [R6C] – published 1999 - was 69%, with a median of 20.3 months. On the basis of these figures – a five fold increase in 12 month survival and a four fold increase in median survival - it would be hard to deny that improvements have been achieved in the management of NSCLC. It seems reasonable to conclude, and the data presented in this thesis are consistent with these conclusions, that these improvements are a result of:

(a) improved patient selection based on a better understanding of prognostic factors;

(b) longer survival resulting from the use of radical doses of radiotherapy; and

(c) the concurrent administration of platinum based chemotherapy with radical radiotherapy.

The results presented also suggest that the combination of platinum-based chemotherapy and radical radiotherapy may produce a survival advantage similar to that observed with the CHART regimen, but with fewer practical delivery problems

Although we have adopted a modification of R6C as our standard treatment for selected patients with inoperable NSCLC[124], we recognise that there are numerous opportunities for improving outcomes even further. In regard to patient selection, the use of PET scanning to exclude patients with otherwise undetectable metastases may reduce the number of patients for whom a local therapy can never be curative by up to a third[138]. For these carefully selected patients new therapeutic opportunities abound: dose escalation; altered fractionation to take advantage of the benefit observed in the CHART study; new drugs specifically cytotoxic to hypoxic cells such as tirapazamine[149]; and biological agents which block the epidermal growth factor receptor [EGFR][150, 151].

In this thesis I have described some of our work which has provided such a secure foundation for these exciting future studies. This body of work included the first major randomised trial involving radiotherapy for lung cancer designed and conducted in Australia [described in section 2.3], and as such it has provided us with valuable lessons in trial methodology for future application. I hope to have shown that the nihilism attached to the treatment of lung cancer that was so prevalent during the 1970's and 1980's is no longer defensible. Certainly, the thousands of Australians for whom prevention is no longer an option, and who are destined to develop lung cancer which will contribute to more years of life lost than any other cancer, deserve better[152].

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# APPENDIX A

## The Peter MacCallum lung cancer database: case report forms

S1

Peter MacCallum Cancer Institute

CARCINOMA OF LUNG

HISTORY & EXAMINATION FORM A

Surname
Given name
U.R. No.
Date of Birth

**Please answer all questions, use '9' to indicate unknown, '-' not done or not relevant.**

S2

1. [ ] SEX.
1 = Male
2 = Female

2. [ ][ ][ ][ ] ONSET OF SYMPTOMS (mm,yy)

3. [ ][ ][ ][ ] DATE OF DIAGNOSIS (mm,yy)

4. [ ][ ][ ][ ] FIRST SEEN AT PMH FOR THIS CONDITION (mm,yy)

5. [ ] TUMOUR TYPE
1 = Squamous cell
2 = Adenocarcinoma
3 = Alveolar cell
4 = Small cell anaplastic
5 = Large cell undifferentiated
6 = Carcinoma Unspecified
7 = Mixed Histology
8 = Other
9 = Unknown

6. [ ] BASIS OF DIAGNOSIS
1 = Biopsy, locoregional
2 = Biopsy/Aspiration of metastasis
3 = Sputum Cytology
4 = Needle aspiration
5 = Clinical

7. [ ] SMOKING HISTORY
1 = Never smoked
2 = Smoked

**PREVIOUS TREATMENT:**
Use 1=No, 2=Yes for Q8-11

8. [ ] Surgery (definitive, primary site)

9. [ ] Chemotherapy

10. [ ] Radiotherapy

11. [ ] Other treatment (excluding observation)

**CLINICAL PRESENTATION AT PMCI:**
Use 1=No, 2=Yes, 3=Equivocal for Q12-18

12. [ ] Symptoms/signs due to locoregional disease (of primary site only)

13. [ ] Symptoms/signs due to metastases

14. [ ] Malaise

15. [ ] Paraneoplastic syndrome

16. [ ] Pleural effusion

17. [ ] Pericardial effusion

18. [ ] S.V.C. obstruction

19. [ ] Weight loss
1 = None
2 = Less 10% in 3/12
3 = Greater 10% in 3/12
4 = Unspecified amount

20. [ ] PERFORMANCE STATUS
0 = Fully active, asymptoma
1 = Ambulatory, capable of light work, symptomati
2 = In bed <50% of time, a to care for self but n working
3 = In bed >50% of time, a in part to care for se
4 = Completely bedridden

Please answer all questions, use '9' to indicate unknown, '_' not done or not relevant.

S3

EXTENT OF LOCOREGIONAL DISEASE AFTER CLINICAL OR STAGING INVESTIGATIONS AT PMCI:

1. ☐ PRIMARY SITE
   1 = Not involved (previous treatment, excluding surgery)
   2 = Involved (initial or recurrent disease)
   3 = Completely excised
   4 = Incompletely excised (residual intrathoracic disease)

2. ☐ RECURRENT LOCOREGIONAL DISEASE
   1 = No
   2 = Yes
   3 = Equivocal

3. ☐ HEMITHORAX INVOLVEMENT
   1 = No
   2 = Right
   3 = Left
   4 = Both

4. ☐ SITES WITHIN LUNG
   1 = Apical
   2 = Other
   3 = Both

5. ☐ CERVICAL NODE METASTASES (Including supraclavicular)
   1 = No
   2 = Yes
   3 = Equivocal

SITES OF DISTANT METASTASES AFTER CLINICAL OR STAGING INVESTIGATIONS AT PMCI:

Use 1=No, 2=Yes, 3=Equivocal, 4=Recurrence for Q6-15

6. ☐ Bone
7. ☐ Liver
8. ☐ Brain
9. ☐ Kidney
10. ☐ Lung
11. ☐ Adrenal
12. ☐ Skin
13. ☐ Distant nodes
14. ☐ Spinal cord compression
15. ☐ Other sites

**PLANNED TREATMENT:**

Use 1=No, 2=Yes for Q16-18

16. ☐ Surgery
17. ☐ Chemotherapy
18. ☐ Radiotherapy
19. ☐ OTHER
    1 = No
    2 = Yes
    3 = Observation

Peter MacCallum Cancer Institute

CARCINOMA OF LUNG

TREATMENT FORM B

Surname
Given name
U.R. No.

This form must be completed after the patient receives radiotherapy. Please answer all questions, use '9' to indicate unknown, '-' not done or not relevant.

S5

1. [ ][ ][ ][ ][ ][ ] COMMENCED (dd,mm,yy)

2. [ ][ ][ ][ ][ ][ ] CEASED (dd,mm,yy)

3. [ ] TREATMENT INTENT
1 = Radical
2 = Palliative
3 = Prophylaxis

4. [ ] MODALITY
1 = MVT
2 = DXRT
3 = Both
8 = Other

5. [ ] SITE TREATED
1 = Locoregional
2 = Metastases
3 = Both
8 = Other

6. [ ] PLANNING
1 = CT assisted
2 = From radiograph
8 = Other

7. [ ] RADIOTHERAPY COMPLETED
1 = No
2 = Yes
3 = Completed but interrupted

8. [ ][ ].[ ] TOTAL TUMOUR DOSE
For multiple sites state maximum dose given to any 1 site

9. [ ][ ] NUMBER OF FRACTS

10. [ ][ ] FRACTS PER WEEK

11. [ ] OBJECTIVE RESPONSE TO RADICA
Code (-) for Q11 & 12 if pat has no measurable disease
1 = No
2 = Yes
3 = Not assessable

12. [ ][ ][ ][ ][ ][ ] ASSE
(dd,

13. [ ] PALLIATION SUCCESS
1 = Not successful
2 = Successful
3 = Partially successful
4 = Not assessable

COMMENTS:

S4

Cancer Institute

CARCINOMA OF LUNG

Surname
Given name
U.R. No.
Date of Birth

DEATH FORM D

To be completed when the patient dies. Please answer all questions, use '9' to indicate unknown, '-' not done or not relevant.

1. ☐☐☐☐☐☐ DATE OF DEATH (dd,mm,yy)

**KNOWN SITES OF DISEASE AT TIME OF DEATH:**
Use 1=No, 2=Yes, 3=Equivocal for Q2-11

2. ☐ Locoregional (excluding supraclav. nodes)
3. ☐ Bone
4. ☐ Liver
5. ☐ Brain
6. ☐ Kidney
7. ☐ Lung
8. ☐ Adrenal
9. ☐ Skin
10. ☐ Extrathoracic nodes
11. ☐ Other sites
12. ☐ **CAUSE OF DEATH**
    1 = Tumour related
    2 = Treatment related
    3 = Other causes
    9 = Unknown

**COMMENTS:**

S7

Cancer Institute

CARCINOMA OF LUNG

Surname
Given name
U.R. No.
Date of Birth

Follow Up Form E

Please answer all questions, use '9' to indicate unknown, '–' not done or not relevant.

1. [ ][ ][ ][ ][ ][ ] DATE OF LAST CONTACT (dd,mm,yy)

2. [ ] STATUS AT THAT TIME
1 = Alive
2 = Lost to follow-up
3 = Dead (complete Form D)

3. [ ] DELAYED COMPLICATIONS OF XRT (since last follow-up)
Only use codes 1-4, 8 or 9 if XRT has been given to the primary site
1 = None
2 = Pneumonitis
3 = Oesophageal stricture
4 = Both
8 = Other
9 = Unknown

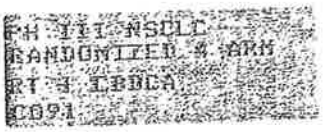
4. [ ][ ][ ][ ][ ][ ] DATE (dd,mm,yy)

COMMENTS:

# APPENDIX B

# Protocol for the randomised trial of accelerated and conventional radiotherapy with and without carboplatin

# A RANDOMISED PHASE III STUDY OF ACCELERATED FRACTIONATED AND STANDARD RADICAL RADIOTHERAPY WITH CONCURRENT CARBOPLATIN IN NON-SMALL CELL LUNG CANCER



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APPENDICES:

I ECOG PERFORMANCE STATUS

II TOXICITY CRITERIA

III PATIENT INFORMATION CONSENT FORM

IV DOSE ADJUSTMENT FOR RENAL IMPAIRMENT

V TNM CLINICAL CLASSIFICATION

1. SCHEMA

Stratify for Institution, ECOG Performance Status and Histology

RANDOMIZE

1. Radical Radiotherapy
60Gy in 30 fractions at 5 fractions/week for 6 weeks

2. Accelerated Fractionated Radiotherapy
60Gy in 30 fractions at 10 fractions/week for 3 weeks

3. Radical Radiotherapy (as in 1) plus carboplatin 70mg/$m^2$/day IV days 1 to 5, weeks 1 and 5

4. Accelerated Fractionated Radiotherapy (as in 2) plus carboplatin 70mg/$m^2$/day IV days 1 to 5, week 1

RADIOTHERAPY: Radiotherapy when given with carboplatin, radiation is to be given 1/2 to 1 hour after the completion of the carboplatin infusion.

CARBOPLATIN: 70 mg/$m^2$/day IV infusion over 1 hour on days 1, 2, 3, 4, 5 and again on days 29, 30, 31, 32, 33 of radiotherapy.

## 2. BACKGROUND

In 1982 the Victorian Cancer Registry recorded 1173 men and 321 women with lung cancer.[1] This would estimate an incidence similar to the world standardized figure of 52 and 12 per 100,000 for males and females respectively. In the decade 1982 to 1992 the Victorian Cancer Registry has predicted a 61% increase in the incidence of lung cancer in males and 214% increase in females.[2] Victorian End-results Registry from 1960 to 1975 suggest the median survival for patients of either sex with lung cancer is 4 months. The one year survival for all patients is approximately 22% with only 6% alive at 5 years. There has been no improvement in survival over the last 16 years.

The outlook for patients with unresectable lung cancer is dismal. Radiotherapy offers palliation of symptoms in advanced disease. However, radical radiotherapy results in 5-year survival rates of only 5 to 7% with median survival of less than 1 year.[3,4] It is therefore important to devise new methods to improve therapy in non-small cell lung cancer.

Potentiation of radiation-induced killing by cisplatinum in hypoxic bacterial spores and subsequently in cultured cells and animal tumours have provided a rationale for combining platinum complexes with radiation.[6,7]

Carboplatin (cis-diammine 1, 1-cyclobutane dicarboxylate Pt (II), JM-8, NSC 241240 or CBDCA) is a cisplatin analogue developed for its high degree of activity in pre-clinical screens, its reduced gastrointestinal toxicity and lack of nephrotoxicity.[7]. Carboplatin dosing allows higher platinum administration, higher peak platinum levels in plasma and the potential for higher platinum levels with solid tumours. Significant radiation potentiation by 200 m carboplatin has been reported in hypoxic S. typhimurium cells.[8] Carboplatin has been observed to be an hypoxic cell radiosensitizer in V79 and CHO cells.[9] Carboplatin results in an enhancement of approximately 1.8 when a 500 m concentration of carboplatin is administered to V79 cells for 1 hour at 37° prior to and during radiation. These concentrations of carboplatin are approximately 50 x the levels of cisplatin that are practiceable. Studies with mouse mammary adenocarcinoma (MTG-B) have produced tumour growth delay with carboplatin and a single radiation dose superior to that for either modality alone.[9]

In experiments with cisplatin there was no significant enhancement of skin damage in the irradiated field inspite of the high measured levels of platinum in skin. Similar experiments have not yet been done with carboplatin.

In studies measuring the platinum level in experimental tumours, equivalent toxic does of cisplatin and carboplatin resulted in 6 times more intra-tumour platinum in treated mice.[9] These higher levels correlate with the higher peak plasma levels in carboplatin treated animals. Thus a higher therapeutic ratio as a radiation sensitizer may be present with carboplatin in in vivo tumours.

We have performed a phase I study of carboplatin 70mg/m$^2$ IV days 1 to 5 (350mg/m$^2$/course) during weeks 1 and 5 of radiotherapy on 6 patients with NSCLC. All patients completed radiotherapy but 2 pts could not have a second cycle of carboplatin because of leukopenia. Treatment was well tolerated, with WHO grade[10] 3 nausea and vomiting in 1 pt and oesophagitis which required palliative medication in 2 pts. Haematologic toxicity consisted of WHO grade 3 leukopenia in 2 pts and 1 pt had grade 2 thrombocytopenia. One pt developed

L'Hermittes sign. No patient developed renal or pulmonary toxicity. These results indicate that carboplatin can be given concurrently with radical radiotherapy without enhancement of acute normal tissue injury.

Since doses of carboplatin cannot be escalated further and toxicity is acceptable, 70mg/$m^2$/day, days 1-5, was recommended for the phase IIII trial (see below).

Accelerated fractionation is another approach to overcome radioresistance of NSCLC. For example, the potential doubling time of squamous cell tumours is approximately 4 days. Thus, repopulation of surviving clonogenic tumour cells during fractionated radiotherapy may result in treatment failure if the time between fractions is too long. Shortening the time between fractions could also, potentially, improve drug radiation interactions. This four arm randomized study will study the influence of concurrent carboplatin on standard radical radiotherapy and accelerated fractionated radiotherapy. The study endpoints will be objective response rate, local recurrence within the radiation field, relapse free survival, survival, toxicity, quality of life and control of symptoms.

## 3.0 AIMS

3.1 To compare the efficacy of concurrent radical radiotherapy and carboplatin with radiotherapy alone. The endpoints for efficacy will be response, time to disease progression and survival. Of these the last two parameters are the most important.

3.2 To compare the efficacy of accelerated fractionated radiotherapy with standard radical radiotherapy.

3.3 To compare the toxicities of these four regimens.

3.4 To compare the quality of life of patients on this program.

3.5 To evaluate prognostic factors in this patient population.

## 4.0 ELIGIBILITY CRITERIA

4.1 Patients with histologically or cytologically proven non-small cell lung cancer.

4.2 Patients with ECOG performance status 0 to 1.

4.3 Patients with disease confined to the primary site (normal bone and CT scans of liver, no cervical nodes, M0). Stage T1-3 and N0-N2 disease[10] are eligible (see appendix 5). In addition patients with T4 disease are eligible but not with pleural effusions.

4.4 All patients must have clinically evident disease present. Patients with measurable or evaluable disease are preferred. Patients with inevaluable disease are still eligible since time to disease progression and survival are the major study endpoints.

4.5 Peripheral blood counts with granulocytes >1,500 x $10^6$/L and platelets >100,000 x $10^6$/L. Patients with renal impairment are eligible but with dose modification as in Appendix 4.

4.7 Patients must give written informed consent.

4.8 Patients with greater than 10% weightloss are excluded.

## 5.0 RANDOMIZATION PROCEDURE

Patients considered eligible will be seen jointly by Dr Bishop and Dr Ball at Peter MacCallum Cancer Institute or Dr O'Brien in Adelaide prior to randomization on this program. If patients are eligible they will be registered and will be randomized by the responsible Data Manager and the appropriate trial forms will be generated (call extension 5605). Toxicity data will be recorded weekly while on radiotherapy and thereafter monthly. Follow-up will include assessment of time to progression, survival and documentation of long term side effects. Quality of life will be done prior to therapy and at each assessment.

## 6.0 STUDY PARAMETERS

6.1 Since the major aim of this study is to compare the efficacy of therapy, frequent clinical monitoring is required. Patients will be seen weekly by the joint chairmen while on MVT then monthly. Haematological investigations should be performed weekly while on therapy and to continue weekly until they return to normal.

6.2 **Summary of Study Parameters**

| | Pre-Therapy | Weekly on MVT + 4 weeks post-MVT | Weeks 10, 14,18,22, |
|---|---|---|---|
| History | + | + | + |
| Physical Examination | + | + | + |
| Toxicity Notation[a] | + | + | + |
| ECOG Performance Status[b] | + | + | + |
| FBE and Differential | + | + | + |
| Electrolytes | + | + | + |
| Liver Function Tests | + | + | + |
| Urinary Creatinine Clearance | + | | |
| Chest X-Ray | + | | + |
| Bone Scan | + | | |
| CT Scan [c] | + | | |
| TNM Staging (d) | + | | |
| CT Scan Planning | + | | |
| Spirometry[e] | + | | + |

a = Toxicity Notation - WHO (Miller) Criteria
(See Appendix 2 and Reference 11)
b = ECOG performance status (See Appendix 1)
c = CT scan will be repeated to assess maximal response at 10-12 weeks
d = TNM Staging
(See Appendix 5 and Reference 10)
e = Spirometry without bronchodilator

## 7.0 TREATMENT PLAN

### 7.1 Schema

Stratify for Institution, ECOG Performance Status and Histology

RANDOMIZE

1. Radical Radiotherapy 60Gy in 30 fractions at 5 fractions/week for 6 weeks
2. Accelerated Fractionated Radiotherapy 60Gy in 30 fractions at 10 fractions/week for 3 weeks
3. Radical Radiotherapy (as in 1) plus carboplatin 70mg/$m^2$/day IV days 1 to 5, weeks 1 and 5
4. Accelerated Fractionated Radiotherapy (as in 2) plus carboplatin 70mg/$m^2$/day IV days 1 to 5, week 1

### 7.2 Radiotherapy

Radiotherapy will be given to all study patients. Patients will be treated in the recumbent position on a megavoltage machine. Planning of treatment will be isocentric and will utilise conventional simulation and CT techniques. This will allow formulation of optimal plans/fields individualised for each patient. Initially the fields will cover the primary lesion and adjacent mediastinum with a 20mm margin. Fields will be designed to cover the lesion whilst allowing maximal sparing of normal lung tissues (ant/post and oblique fields are required). The dose to the spinal cord will be kept at less than 45 Gy. Check films will be taken weekly and patients will be reviewed each week. It is desirable that the spinal cord not be included in the treatment volume when concurrent radiotherapy and carboplatin are given. Hence, on the days of carboplatin infusion, the technique used after chemotherapy administration will be obliques or laterals to exclude the spinal cord. On the days that carboplatin is not administered, radiotherapy will be given via ap/pa fields.

#### 7.2.1 Radical Radiotherapy

Patients will be given 60 Gy in 30 fractions at 5 fractions/week over 6 weeks. Spinal cord dose is not to exceed 45 Gy. The dose will be corrected for tissue inhomogeneities using CT data for all field arrangements. Radiotherapy will be given approximately 1/2 to 1 hour after the completion of the carboplatin infusion.

#### 7.2.2 Accelerated Fractionated Radiotherapy

Patients will be given as above but as 60Gy in 30 fractions as two daily factions at 10 fractions/week over 3 weeks with a minimum time of 6 hours between fractions given on the same day. In patients receiving two treatments per day, it is preferable that the spinal cord be treated only once a day on as many days as possible. Hence for the first two weeks of treatment the fields used are obliques (to avoid spinal cord) in the morning (which also ensures that carboplatin is not given simultaneously with spinal irradiation in patients randomized to both accelerated radiotherapy and chemotherapy) and ap/pa in the afternoon i.e. spinal cord receives only 2.00Gy per day. For the final week of treatment, ap/pa fields are used in the morning and afternoon.

7.3 Carboplatin Therapy

Patients randomized to receive carboplatin in addition to radiotherapy will be given carboplatin on day 1 of treatment approximately 90 minutes to 2 hours before each daily radiation dose (i.e. radiation to be given 1/2 to 1 hour after completion of the carboplatin infusion).

| | |
|---|---|
| FIRST COURSE | (For both standard radical radiotherapy and accelerated radiotherapy) |
| Carboplatin | 70mg/$m^2$ IV in 500mls N saline over 1 hour days 1, 2, 3, 4, 5 to be given before the daily radiation fraction. |
| SECOND COURSE | (For standard radical radiotherapy arm only) |
| Carboplatin | 70mg/$m^2$ IV over 1 hour days 29, 30, 31, 32, 33 to be given before the daily radiation fraction. |

If, on day 29, myelosuppression persists from course 1 with neutrophils <1,500 x $10^6$/L and/or platelets <100,000 x $10^6$/L, the second carboplatin course can be deferred for one week.

7.4 Dose Modifications

7.4.1 If grade 4 toxicity is encountered following the first course of carboplatin in any patients, the subsequent course of carboplatin will be reduced by 50%. The withdrawal of a patient from the study because of toxicity or any other reason can only occur after consultation between the study chairmen (Drs Bishop and Ball) for PMCI patients and after consultation between treating oncologists in Newcastle

7.4.2 Renal Impairment

Patients with renal impairment (serum creatinine >0.15 mmol/L or creatinine clearance <0.8ml/sec) will require dose modification using the schema of Egorin (see Appendix IV).[13]

7.4.3 The intent of this protocol is to deliver the radiotherapy as planned without modification if at all possible.

8.0 RESPONSE CRITERIA

Criteria of response will be those of the WHO guidelines.[11]

8.1 Measurable disease

8.1.1 Complete response (CR): The disappearance of all known disease for at least 4 weeks.

8.1.2 Partial response (PR): A decrease of 50% or more in the sum of the diameters of all measured lesions for at least 4 weeks.

8.1.3 Stable disease (SD): A decrease of <50% in the sum of the diameters of measured lesions or an increase of <25%.

8.1.4 Progressive disease (PD): An increase of >25% or more in the sum of the diameters of any measured lesions or the appearance of any new lesions.

8.2 Evaluable (Non-Measurable) Disease

8.2.1 CR: Complete disappearance of all known disease for at least 4 weeks.

8.2.2 PR: A decrease of 50% or more of known disease for at least 4 weeks.

8.2.3 SD: No significant change in evaluable disease or a decrease <50% or increase <25% in evaluable lesions.

8.2.4 PD: An increase of >25% in the size of any lesions or the development of any new lesion.

8.3 Time to disease progression (TTP) and survival will be measured from randomization and are considered the major study endpoints.

## 9.0 STATISTICAL CONSIDERATIONS

This study employs a 2x2 factorial design. Initially it is intended to randomize 200 patients, 50 in each arm. With an anticipated accrual rate of 60-70 patients per annum, a total of 3 years accrual will be required. The response and survival rates in each of the 4 individual arms will then be estimated with a maximum standard error of 7%. In addition, responses will be analysed using logistic regression analysis incorporating indicator variables for each of the two factors (accelerated fractionation and carboplatin) together with a possible interaction term. Likewise survival and relapse free survival will be analysed using Cox's regression analysis incorporating equivalent terms. The power of the study to detect a significant treatment effect (for either of the 2 factors) will be dependent on the nature of the interaction. If there is no interaction then the study has a probability (power) of detecting a change in response rates from 60% to 80% say, associated with a given factor, when tested at significance level 0.05 using a 2-tailed test. Similarly a 60% increase in the median survival from 7.5 to 12 months say, could be detected if the data are analysed when 72% of the patients have died. The data will be monitored throughout the trial and consideration will be given to closing accrual in one or more arms if unacceptable toxicity is experienced, or the arm (or factor) is associated with significantly inferior results when tested as the 0.01 level of significance. At the completion of accrual of 200 patients the data will be carefully analysed and consideration may be given to extending the trial if necessary.

## 10.0 DOCUMENTATION REQUIRED

10.1 Registration Form A to be completed by the Trial Centre Data Manager at the time of registration and randomization

10.2 On Study Form B1: To be completed by the investigator at the time of randomization and sent to the trial centre.

10.3 Pre treatment B2: To be completed by the investigator at the time of randomization.

10.4 Life Orientation Scale B3: To be completed by the investigator at the time of randomization and at the 1st post treatment assessment.

10.5 Treatment Summary Form C1 and C2: To be completed weekly during treatment.

10.6 Treatment Summary Form C3: To be completed on completion of protocol therapy.

10.7 Assessment Form D1 and D2: To be completed when an assessment of response and sympton control is made.

10.8 Toxicity Flow Sheet E1 and E2: To be completed weekly while on treatment and as necessary if toxicity persists.

10.9 Quality of Life Assessment Form F: To be completed prior to treatment and at each assessment.

10.10 Relapse Progression Form G: To be completed when patient relapses or progesses.

10.11 Death Form H.

10.12 Follow-up Form I: To be completed on request from Trial Centre.

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## APPENDIX I

### ECOG PERFORMANCE STATUS CRITERIA

| GRADE | SCALE |
|---|---|
| 0 | Fully, active, able to carry on all pre-disease performance without restriction (Karnofsky 90-100). |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work (Karnofsky 70-80). |
| 2 | Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky 50-60). |
| 3 | Capable of only limited self-care, confined to bed or chair more than 50% of waking hours (Karnofsky 30-40). |
| 4 | Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair. (Karnofsky 10-20). |
| 5 | Dead. |

## APPENDIX II

## TOXICITY CRITERIA[10]

GRADES

| HAEMATOLOGICAL | 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|
| Hb | >11.0 | 9.50-10.9 | 8.0-9.4 | 6.5-7.9 | <6.5 |
| Granulocytes | >2.0 | 1.50-1.99 | 1.0-1.49 | 0.5-0.99 | <0.5 |
| Platelets | >100 | 75-99 | 50-74 | 25-49 | <25 |
| Haemorrhage | None | Petechiae | Mild blood loss | Gross blood loss | Debilitating blood loss |
| STOMATITIS | None | Soreness/ erythema | Erythma ulcers,can eat solids | Ulcers, requires liquid diet only | Alimentation not possible |
| NAUSEA & VOMITING | None | Nausea | Transient vomiting | Vomiting requiring therapy | Untractable vomiting |
| PULMONARY | None | Mild Symptoms | Exertional dyspnoea | Dyspnoea at rest | Complete bed rest required |
| PERIPHERAL NEUROPATHY | None | Paraesthesias &/or decreased tendon reflexes | Severe paraesthesias &/or mild weakness | Intolerable paraesthesias &/or marked motor loss | Paralysis |
| DIARRHOEA | None | Transient <2 days | Tolerable but >2 days | Intolerable requiring therapy | Haemorrhagic dehydration |
| CARDIAC | None | Sinus tachycardia | Unifocal VES atrial dysrhythmia | Multifocal VES | Ventricular tachycardia |
| ALOPECIA | None | Minimal hair loss | Moderate, patchy | Complete | - |
| OESOPHAGEAL | None | Mild Discomfort | Moderate Discomfort Can eat solids | Liquid diet only | Not able to eat or drink |
| SKIN | None | Erythema | Dry desquamation | Moist desquamation | Exfoliative dermatitis |
| OTHER | None | Mild | Tolerable | Intolerable | Life-threateni |

Peter MacCallum Cancer Institute

*Patron: His Excellency The Honourable Richard E. McGarvie, Governor of Victoria.*

In reply please quote .....

481 Little Lonsdale Street,
Melbourne, Victoria, 3000, Australia
Telephone: 641 5555
Facsimile: 670 3357

## PATIENT INFORMATION CONSENT FORM

## PHASE III STUDY OF RADIOTHERAPY PLUS CARBOPLATIN AS INITIAL TREATMENT FOR NON-SMALL CELL LUNG CANCER (NSCLC)

A COPY OF THIS FORM MUST BE PROVIDED TO THE PATIENT PRIOR TO STUDY ENTRY

1. This is a clinical trial for patients with non-small cell lung cancer.

2. This study will compare the results using two different schedules of radiotherapy alone or radiotherapy with a drug called carboplatin. This study includes radiotherapy which has been used for many years in this disease but also includes a new drug, carboplatin.

3. One schedule of radiotherapy will be given more quickly by giving it twice daily for 3 weeks.

4. Carboplatin is a new anti-cancer drug derived from a drug which is successful in the treatment of many tumours. Preliminary results have suggested that this new analogue is more effective in some tumours than the older drug and has fewer side effects. Carboplatin has been widely used in humans with a variety of cancers including lung cancer. The side effects are known.

5. You will be randomly allocated to receive one of the two radiotherapy schedules either with, or without the addition of carboplatin.

6. The aim of this treatment is to:

   i) control your cancer

   ii) to assess the effect of combined radiotherapy and carboplatin in a number of similar patients with lung cancer

   iii) to carefully assess any side-effects which may occur.

7. **Treatment Program**

   i) All patients will receive radiotherapy to the chest which is a standard method of treatment of your disease. Radiotherapy will be given either in a standard 5 times a week schedule for 6 weeks or 10 times a week (twice a day) for 3 weeks.

   ii) Some patients will receive the drug carboplatin in addition. This drug will be given once a day for 5 days on the first and may be repeated in the 5th week of your radiotherapy.

   iii) After completion of this treatment, no further treatment will be given except follow up in outpatients.

   iv) Weekly blood tests will be required while on treatment. In addition the usual scans and X-rays will be required to assess your response to therapy.

CONSENT FORM (continued)

8. Possible Side Effects

i) Nausea and vomiting may occur on the night of therapy. This may not occur or be very mild in most cases. Anti-sickness medication usually controls this side effect.

ii) The blood counts may be temporarily lowered by this therapy. If this occurs, the counts are lowest about 2 to 3 weeks after starting therapy and recover by themselves within a few days. You will not usually feel any different with low counts. However, for this short period you may be more likely to pick up an infection. If you feel feverish, take your temperature. If you have a temperature of 38° C or more ring the Hospital and ask to talk to your doctor. You may require antibiotics in hospital if this occurs. Bruising or bleeding are rare complications which should be reported if they occur.

iii) You may experience pain or difficulty swallowing. If this occurs please notify your doctor so that appropriate medication can be given.

9. Your Rights

i) You may ask questions regarding this clinical trial and can expect clear understandable answers in return.

ii) You may withdraw from this study at any time you wish without jeopardizing further treatment at this hospital.

iii) If any complications of the disease or of this treatment occur the Hospital will provide appropriate treatment for these problems.

10. Whom To Call

i) The doctors you should contact should any problems arise are Dr .....
Telephone Number ..... After hours ask for the chemotherapist on call.

ii) During working hours you can also call Day Ward .....

Dr ..... has discussed this trial with me.

I ..... have read the above consent form.

I have had the opportunity to ask questions about this trial and I have received answers that are satisfactory to me. I agree to participate in this study.

PATIENT'S SIGNATURE: ..... Date: .....

PHYSICIAN'S SIGNATURE: .....
.....
PRINT BLOCK LETTERS

WITNESS' SIGNATURE: .....
.....
PRINT BLOCK LETTERS

## APPENDIX IV

## DOSE ADJUSTMENT FOR RENAL IMPAIRMENT[14]

| CREATININE CLEARANCE (ml/sec) | % INITIAL CBDCA DOSE % |
|---|---|
| > 0.8 | 100% |
| 0.6–0.8 | 75% |
| 0.4 - 0.59 | 50% |
| < 0.4 | Ineligible |

# APPENDIX V

## TNM Clinical Classification

### T-Primary Tumour

TX Primary tumour cannot be assess, or tumour proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy.

T0 No evidence of primary tumour.

T1 Tumour 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e. not in the main bronchus)[1].

T2 Tumour with any of the following features of size or extent:
More than 3 cm in greatest dimension.
Involves main bronchus, 2 cm or more distal to the carina.
Invades visceral pleura.
Associated with atelectasis or obstructive pneumonitis which extends to the hilar region but does not involve the entire lung.

T3 Tumour of any size which directly invades any of the following: chest wall (including superior sulcus tumours), diaphragm, mediastinal pleura, parietal pericardium; or tumour in the main bronchus less than 2 cm distal to the carina[1]) but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung.

T4 Tumour of any size which invades any of the following: mediastinum, heart, great vessels, trachea, oesophagus, vertebral body, carina; or tumour with malignant pleural effusion.

Notes: 1. The uncommon superficial spreading tumour of any size with its invasive component limited to the bronchial wall which amy extend proximal to the main bronchus is also classified T1.

2. Most pleural effusions associated with lung cancer are due to tumour. However, there are a few patients in whom mulltiple cytopathological examinations of pleural fluid are negative for tumour, the fluid is non-bloody and is not an exudate. Where these elements and clinical judgement dictate that the effusion is not related to the tumour, the effusion should be excluded as a staging element and the patient should be classified T1, T2 or T3.

### N - Regional Lymph Nodes

NX Regional lymph nodes cannot be assessed.
N0 No regional lymph node metastasis.
N1 Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, including direct extension.
N2 Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s).
N3 Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene or supraclavicular lymph node(s).

# APPENDIX C

# Case report forms for the randomised trial

**PHASE III NSCLC**
**FOUR ARM RT & CARBOPLATIN TRIAL**

**REGISTRATION FORM A**

REGISTRATION NO. | | | | | | |

(eg. PMC001, ADE001)

SURNAME _____

GIVEN NAMES _____

U.R. NUMBER _____

DATE OF BIRTH (ddmmyyyy) _____

*Affix label here*

*S1*

6. | | | | | | | DATE OF RANDOMISATION (ddmmyy)

7. | | RANDOMISATION ARM
*1 = radical MVT*
*2 = accelerated MVT*
*3 = radical MVT + carboplatin*
*4 = accelerated MVT + carboplatin*

*TO BE COMPLETED AT REGISTRATION. Please answer all questions, ticking the appropriate boxes.*

**ELIGIBILITY CHECK**

| | YES | NO |
|---|---|---|
| 1. Patient has histologically or cytologically proven non-small cell lung cancer. *Specify histology* ..... | ☐ | ☐ |
| 2. Patient is ECOG Performance Status 0-1. *Specify* ..... | ☐ | ☐ |
| 3. Patient has disease confined to primary site (no bone, liver, cervical node or brain metastases or pleural effusions). | ☐ | ☐ |
| 4. Patient has measurable or evaluable disease. Patients with inevaluable disease may be eligible provided there is clinical evidence of disease. | ☐ | ☐ |
| 5. Pre-treatment neutrophil count $\geq 1.5 \times 10^9$/L ..... and platelet count $\geq 100 \times 10^9$/L. ..... | ☐ | ☐ |
| 6. Patient has **not** received prior chemotherapy or radiotherapy. | ☐ | ☐ |
| 7. Weight loss 10% or less. | ☐ | ☐ |
| 8. Patient has given written informed consent. | ☐ | ☐ |

If the answers to all 8 questions above are YES, then the patient is eligible.

SIGNATURE OF CLINICIAN: ..... DATE: .....

**Please arrange with Diagnostic Radiation Department for copies to be made of any outside chest X-rays or scans.**



Please return to: Trial Centre, Peter MacCallum Cancer Institute, 481 Little Lonsdale Street, Melbourne Vic 3000.

**PHASE III NSCLC**
**FOUR ARM RT & CARBOPLATIN TRIAL**

**ON STUDY FORM B1**

REGISTRATION NO. ☐☐☐☐☐☐

(eg. PMC001, ADE001)

SURNAME _____

GIVEN NAMES _____ *Affix label here* _____

U.R. NUMBER _____

DATE OF BIRTH (ddmmyyyy) _____

S2

*TO BE COMPLETED AT REGISTRATION. Please answer all questions, use '9' to indicate unknown, '–' to indicate not done or not relevant. Please return to the Trial Centre on completion.*

1. ☐ SEX
   1 = male
   2 = female

7. ☐ HISTOLOGY
   1 = squamous
   2 = non-squamous

8. ☐ T STAGE

9. ☐ N STAGE
   (see Appendix V of protocol)

2. ☐.☐ B.S.A. ($m^2$)

3. ☐☐☐☐☐☐ DATE OF DIAGNOSIS (ddmmyy) *(Use '99' if day unknown.)*

4. ☐ DIAGNOSIS ESTABLISHED BY
   1 = sputum cytology
   2 = bronchoscopic cytology
   3 = bronchoscopic biopsy
   4 = node biopsy
   5 = needle biopsy of lung
   6 = open lung biopsy
   7 = any combination of 1-6*
   8 = other*
   **Specify* .....

5. ☐☐☐ SIZE OF PRIMARY TUMOUR ON CHEST X-RAY OR CT SCAN
   (largest diameter in mms) *(Use '999' if unknown.)*

6. ☐ WEIGHT LOSS IN LAST THREE MONTHS
   1 = none
   2 = weight loss ≤ 10%

**PRE-TREATMENT INVESTIGATIONS (as close to commencing treatment as possible)**
*(Give actual values. Use '999' if unknown.)*

| | | |
|---|---|---|
| White cell count | ($10^9$/L) | |
| Hæmoglobin | (g/dL) | |
| Platelets | ($10^9$/L) | |
| Neutrophils | ($10^9$/L) | |
| Serum creatinine | (mmol/L) | |
| Serum sodium | (mmol/L) | |
| Serum bilirubin | (µmol/L) | |
| Serum alkaline phosphatase | (U/L) | |
| Serum AST | (U/L) | |
| FEV | (L) | |
| Creatinine clearance *(arms 3 & 4 only)* | (ml/sec) | |

9/7/92 JD

Please return to: Trial Centre, Peter MacCallum Cancer Institute, 481 Little Lonsdale Street, Melbourne Vic 3000.

**PHASE III NSCLC**
**FOUR ARM RT & CARBOPLATIN TRIAL**

**PRE-TREATMENT ASSESSMENT FORM B2**

REGISTRATION NO. ☐☐☐☐☐☐

(eg. PMC001, ADE001)

SURNAME _____

GIVEN NAMES _____ *Affix label here* _____

U.R. NUMBER _____

DATE OF BIRTH (ddmmyyyy) _____

S3

*TO BE COMPLETED PRIOR TO COMMENCEMENT OF THERAPY. Please answer all questions, use '9' to indicate unknown, '–' to indicate not done or not relevant. Please return to the Trial Centre on completion.*

1. ☐☐☐☐☐☐ DATE OF PRE-TREATMENT ASSESSMENT (ddmmyy)

| SITES OF DISEASE | INVOLVEMENT | EVALUABILITY | MAIN METHOD |
|---|---|---|---|
| HILUM | 2. ☐ | 6. ☐ | 10. ☐ |
| LUNG PARENCHYMA | 3. ☐ | 7. ☐ | 11. ☐ |
| MEDIASTINAL NODES | 4. ☐ | 8. ☐ | 12. ☐ |
| OTHER, *specify* ..... | 5. ☐ | 9. ☐ | 13. ☐ |
| ..... | | | |
| | *1 = not involved*<br>*2 = involved* | *1 = measurable*<br>*2 = evaluable, but not measurable*<br>*3 = not evaluable* | *1 = clinical only*<br>*2 = X-ray*<br>*3 = CT scan*<br>*8 = other, specify* |

.....

.....

**PRE-TREATMENT SYMPTOMS** (0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe)

14. ☐ CHEST PAIN
15. ☐ COUGH
16. ☐ HÆMOPTYSIS
17. ☐ DYSPNOEA
18. ☐ OTHER, *specify* .....
19. ☐ OTHER, *specify* .....
20. ☐ OTHER, *specify* .....
21. ☐ ECOG PERFORMANCE STATUS AT RANDOMISATION *(see coding sheet)*



Please return to: Trial Centre, Peter MacCallum Cancer Institute, 481 Little Lonsdale Street, Melbourne Vic 3000.

**PHASE III NSCLC**
**FOUR ARM RT & CARBOPLATIN TRIAL**

**TREATMENT SUMMARY FORM C1**

REGISTRATION NO. | | | | | | |

(eg. PMC001, ADE001)

SURNAME _____

GIVEN NAMES _____ *Affix label here* _____

U.R. NUMBER _____

DATE OF BIRTH (ddmmyyyy) _____

S6-7

*Tests to be done **prior** to the commencement of therapy, **weekly** while on treatment and weekly thereafter until blood counts return to normal. Use '999' for unknown, '–' for not done or not relevant.*

| **TREATMENT** | | **WEEK 1** | **WEEK 2** | **WEEK 3** | **WEEK 4** | **WEEK 5** | **WEEK 6** |
|---|---|---|---|---|---|---|---|
| Date commenced | (dd/mm/yy) | / / | / / | / / | / / | / / | / / |
| Total Carboplatin Dose | (mg/wk) | | | | | | |
| MVT Dose | (Gy/wk) | | | | | | |
| ECOG STATUS *(see coding sheet)* | | | | | | | |

**INVESTIGATIONS PERFORMED** *(Give actual values. Use '–' if not done.)*

| DATE OF TESTS | (dd/mm/yy) | / / | / / | / / | / / | / / | / / |
|---|---|---|---|---|---|---|---|
| White cell count | ($10^9$/L) | | | | | | |
| Hæmoglobin | (g/dL) | | | | | | |
| Platelets | ($10^9$/L) | | | | | | |
| Neutrophils | ($10^9$/L) | | | | | | |
| Serum creatinine | (mmol/L) | | | | | | |
| Serum sodium | (mmol/L) | | | | | | |
| Serum bilirubin | (µmol/L) | | | | | | |
| Serum alkaline phosphatase | (U/L) | | | | | | |
| Serum AST | (U/L) | | | | | | |
| FEV | (L) | | | | | | |
| Creatinine clearance *(arms 3 & 4 only)* | (ml/sec) | | | | | | |

**COMMENTS**



Please return to: Trial Centre, Peter MacCallum Cancer Institute, 481 Little Lonsdale Street, Melbourne Vic 3000.

**PHASE III NSCLC**
**FOUR ARM RT & CARBOPLATIN TRIAL**

# TREATMENT SUMMARY FORM C2

REGISTRATION NO. | | | | | | |

(eg. PMC001, ADE001)

SURNAME

GIVEN NAMES

U.R. NUMBER

DATE OF BIRTH (ddmmyyyy)

*Affix label here*

S7-9

*Tests to be done **weekly** while on treatment and weekly thereafter until blood counts return to normal. Use '999' for unknown, '–' for not done or not relevant.*

| **TREATMENT** | | **WEEK 7*** | | | | | |
|---|---|---|---|---|---|---|---|
| Date commenced | (dd/mm/yy) | / / | / / | / / | / / | / / | / / |
| Total Carboplatin Dose | (mg/wk) | | | | | | |
| MVT Dose | (Gy/wk) | | | | | | |
| ECOG STATUS *(see coding sheet)* | | | | | | | |

**INVESTIGATIONS PERFORMED** *(Give actual values. Use '–' if not done.)*

| DATE OF TESTS | (dd/mm/yy) | / / | / / | / / | / / | / / | / / |
|---|---|---|---|---|---|---|---|
| White cell count | ($10^9$/L) | | | | | | |
| Hæmoglobin | (g/dL) | | | | | | |
| Platelets | ($10^9$/L) | | | | | | |
| Neutrophils | ($10^9$/L) | | | | | | |
| Serum creatinine | (mmol/L) | | | | | | |
| Serum sodium | (mmol/L) | | | | | | |
| Serum bilirubin | (µmol/L) | | | | | | |
| Serum alkaline phosphatase | (U/L) | | | | | | |
| Serum AST | (U/L) | | | | | | |
| FEV | (L) | | | | | | |
| Creatinine clearance *(arms 3 & 4 only)* | (ml/sec) | | | | | | |

**COMMENTS**

* *If treatment is given in **WEEK 7** because of delays, record protocol violation on Form C3.*



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**PHASE III NSCLC**
**FOUR ARM RT & CARBOPLATIN TRIAL**

**TREATMENT SUMMARY FORM C3**

REGISTRATION NO. ☐☐☐☐☐☐ (eg. PMC001, ADE001)

SURNAME _____

GIVEN NAMES _____ *Affix label here* _____

U.R. NUMBER _____

DATE OF BIRTH (ddmmyyyy) _____

S10 *TO BE COMPLETED ONE MONTH AFTER COMPLETION OF TREATMENT. Use '9' for unknown, '–' for not done or not relevant.*

**RADIOTHERAPY**

1. ☐☐☐☐☐☐ DATE RADIOTHERAPY COMMENCED (ddmmyy)
2. ☐☐☐☐☐☐ DATE RADIOTHERAPY COMPLETED (ddmmyy)
3. ☐☐.☐ TOTAL DOSE (Gy)
4. ☐☐ NUMBER OF FRACTIONS
5. ☐☐☐ FIELD SIZE ($cm^2$)

12. ☐☐☐ LENGTH OF FIELD (mm)

**CHEMOTHERAPY (CARBOPLATIN)**

6. ☐☐☐☐☐☐ DATE COMMENCED CARBOPLATIN (ddmmyy)
7. ☐☐☐☐☐☐ DATE COMPLETED CARBOPLATIN (ddmmyy)
8. ☐ NUMBER OF COURSES GIVEN
9. ☐☐☐ C1 ☐☐☐ C2 TOTAL DOSE CARBOPLATIN (mg/course)

**TOTAL PROTOCOL TREATMENT**

10. ☐ WAS THERE A DEVIATION FROM THE PROTOCOL?
    1 = no
    2 = yes, *specify* .....
    *give reason* .....

11. ☐ BEST RESPONSE OF TREATED TUMOUR *(Please see section 8 of protocol)*
    1 = complete response
    2 = partial response
    3 = stable disease
    4 = progressive disease
    5 = not evaluable, *give reason* .....

**COMMENTS**

9/7/92 JD

Please return to: Trial Centre, Peter MacCallum Cancer Institute, 481 Little Lonsdale Street, Melbourne Vic 3000.

**PHASE III NSCLC**
**FOUR ARM RT & CARBOPLATIN TRIAL**

**ASSESSMENT FORM D**

REGISTRATION NO. | | | | | | |

(eg. PMC001, ADE001)

SURNAME _____

GIVEN NAMES _____ *Affix label here* _____

U.R. NUMBER _____

DATE OF BIRTH (ddmmyyyy) _____

S11-14

*To be completed 10-12 weeks after commencing therapy then every 4 weeks for the next 12 weeks, then every 8 weeks thereafter until local progression occurs. Use '9' for unknown, '–' for not done or not relevant. See section 8 of protocol for response criteria. Use additonal Forms D as required.*

| | | | | | | |
|---|---|---|---|---|---|---|
| DATE ASSESSED (dd/mm/yy) | / / | / / | / / | / / | / / | / / |
| ECOG STATUS *(see coding sheet)* | | | | | | |

**LOCAL DISEASE RESPONSE** (1 = CR, 2 = PR, 3 = SD, 4 = PD or new disease, 5 = NE, '–' = disease never present)

| | | | | | | |
|---|---|---|---|---|---|---|
| HILUM | | | | | | |
| LUNG PARENCHYMA | | | | | | |
| MEDIASTINAL NODES | | | | | | |
| OTHER, *specify* ..... | | | | | | |
| OVERALL RESPONSE | | | | | | |

**SYMPTOMS OF DISEASE** (0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe)

| | | | | | | |
|---|---|---|---|---|---|---|
| CHEST PAIN | | | | | | |
| COUGH | | | | | | |
| HÆMOPTYSIS | | | | | | |
| DYSPNOEA | | | | | | |
| OTHER, *specify* ..... | | | | | | |
| OTHER, *specify* ..... | | | | | | |
| OTHER, *specify* ..... | | | | | | |

**COMMENTS**



Please return to: Trial Centre, Peter MacCallum Cancer Institute, 481 Little Lonsdale Street, Melbourne Vic 3000.

**PHASE III NSCLC**
**FOUR ARM RT & CARBOPLATIN TRIAL**

# TOXICITY FLOW SHEET E1

REGISTRATION NO. | | | | | | |

(eg. PMC001, ADE001)

SURNAME _____

GIVEN NAMES _____ *Affix label here* _____

U.R. NUMBER _____

DATE OF BIRTH (ddmmyyyy) _____

S15-18

*To be completed **weekly** while on treatment and weekly thereafter until hæmatological toxicities resolve, then at each **assessment**. See coding sheet for toxicity grades. Use '9' for unknown, '–' for not done or not relevant. Record both **acute** and **late effects**. Use extra flow sheets E as required.*

| DATE ASSESSED (dd/mm/yy) | / / | / / | / / | / / | / / | / / |
|---|---|---|---|---|---|---|

**HÆMATOLOGICAL TOXICITIES** *(Record **worst** toxicity encountered since previous assessment.)*

| | | | | | | |
|---|---|---|---|---|---|---|
| White cells | | | | | | |
| Hæmoglobin | | | | | | |
| Platelets | | | | | | |
| Neutrophils | | | | | | |

**OTHER TOXICITIES** *(Record **worst** toxicity encountered since previous assessment.)*

| | | | | | | |
|---|---|---|---|---|---|---|
| Alopecia | | | | | | |
| Nausea & vomiting | | | | | | |
| Oesophagitis | | | | | | |
| Stomatitis | | | | | | |
| Pulmonary | | | | | | |
| Renal (creatinine) | | | | | | |
| Hepatic (AST) | | | | | | |
| Cardiac | | | | | | |
| Infection | | | | | | |
| Skin reaction | | | | | | |
| Other (1) *specify* ..... | | | | | | |
| Other (2) *specify* ..... | | | | | | |
| Other (3) *specify* ..... | | | | | | |



Please return to: Trial Centre, Peter MacCallum Cancer Institute, 481 Little Lonsdale Street, Melbourne Vic 3000

**PHASE III NSCLC**
**FOUR ARM RT & CARBOPLATIN TRIAL**

**RELAPSE/PROGRESSION FORM G**

REGISTRATION NO. | | | | | | |

(eg. PMC001, ADE001)

SURNAME _____

GIVEN NAMES _____ *Affix label here* _____

U.R. NUMBER _____

DATE OF BIRTH (ddmmyyyy) _____

S23

*TO BE COMPLETED WHEN PATIENT RELAPSES OR PROGRESSES. Please answer all questions.*
*Use '9' to indicate unknown, '–' to indicate not done or not relevant.*

1. | | | | | | | Date of relapse/progression (ddmmyy)

2. | | ECOG performance status *(see coding sheet)*

**SITES OF DISEASE AT TIME OF RELAPSE/PROGRESSION** *(Please see section 8 of protocol)*

1 = CR 4 = PD
2 = PR 5 = NE
3 = SD '–' = disease never present

3. | | **Hilum** and hilar nodes in radiation field
4. | | **Hilum** and hilar nodes outside radiation field
5. | | **Lung parenchyma** in radiation field
6. | | **Lung parenchyma** outside radiation field
7. | | **Mediastinal nodes** in radiation field
8. | | **Mediastinal nodes** outside radiation field
9. | | Ipsilateral **pleural effusion**.
10. | | Contralateral **pleural effusion**
11. | | Extrathoracic nodes (including cervical)
12. | | Liver
13. | | Bone
14. | | CNS
15. | | Other, *specify* .....
16. | | TREATMENT AT TIME OF RELAPSE/PROGRESSION
    1 = none
    2 = protocol treatment
    8 = other, *specify* .....
17. | | PLANNED FUTURE TREATMENT
    1 = none
    2 = MVT
    8 = other, *specify* .....

9/7/92 JD

Please return to: Trial Centre, Peter MacCallum Cancer Institute, 481 Little Lonsdale Street, Melbourne Vic 3000.

**PHASE III NSCLC**
**FOUR ARM RT & CARBOPLATIN TRIAL**

**DEATH FORM H**

REGISTRATION NO. ☐☐☐☐☐☐

(eg. PMC001, ADE001)

SURNAME _____

GIVEN NAMES _____ *Affix label here* _____

U.R. NUMBER _____

DATE OF BIRTH (ddmmyyyy) _____

S24

*TO BE COMPLETED WHEN PATIENT DIES.*
*Please answer all questions, use '9' to indicate unknown, '–' to indicate not done or not relevant.*

1. ☐☐☐☐☐☐ DATE OF DEATH (ddmmyy)

2. ☐ DISEASE STATUS AT TIME OF DEATH *(Please see section 8 of protocol)*
   1 = CR 4 = PD
   2 = PR 5 = NE
   3 = SD

3. ☐ CAUSE OF DEATH
   1 = progression of disease
   2 = protocol treatment related*
   3 = other cause*
   **Specify* .....

## SITES OF DISEASE AT TIME OF DEATH

1 = absent
2 = present

| Clinical | Autopsy | |
|---|---|---|
| 4. ☐ | 14. ☐ | Hilum and hilar nodes |
| 5. ☐ | 15. ☐ | Lung parenchyma |
| 6. ☐ | 16. ☐ | Mediastinal nodes |
| 7. ☐ | 17. ☐ | Ipsilateral pleural effusion |
| 8. ☐ | 18. ☐ | Contralateral pleural effusion |
| 9. ☐ | 19. ☐ | Extrathoracic nodes (including cervical) |
| 10. ☐ | 20. ☐ | Liver |
| 11. ☐ | 21. ☐ | Bone |
| 12. ☐ | 22. ☐ | CNS |
| 13. ☐ | 23. ☐ | Other, *specify* ..... |



Please return to: Trial Centre, Peter MacCallum Cancer Institute, 481 Little Lonsdale Street, Melbourne Vic 3000

**PHASE III NSCLC**
**FOUR ARM RT & CARBOPLATIN TRIAL**

**FOLLOW-UP FORM I**

REGISTRATION NO. | | | | | | |

(eg. PMC001, ADE001)

SURNAME _____

GIVEN NAMES _____ *Affix label here* _____

U.R. NUMBER _____

DATE OF BIRTH (ddmmyyyy) _____

S25

*TO BE COMPLETED ON REQUEST FROM TRIAL CENTRE.*
*Please answer all questions, use '9' to indicate unknown, '–' to indicate not done or not relevant.*

1. | | | | | | | DATE OF LAST CONTACT (ddmmyy)

2. | | STATUS AT LAST CONTACT
1 = alive
2 = lost
3 = dead

3. | | DISEASE STATUS AT LAST CONTACT *(Please see section 8 of protocol)*
1 = CR
2 = PR
3 = SD
4 = PD
5 = NE

4. | | TREATMENT AT LAST CONTACT
1 = no
2 = yes, *specify* .....



Please return to: Trial Centre, Peter MacCallum Cancer Institute, 481 Little Lonsdale Street, Melbourne Vic 3000

# PMCI
# FOUR ARM RT & CARBOPLATIN TRIAL

## CODING SHEET

### ECOG PERFORMANCE STATUS

0 = Fully active, able to carry on all pre-disease performance without restriction.
1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature.
2 = Ambulatory and capable of all self-care but unable to carry out any work; up and about > 50% of waking hours.
3 = Capable of only limited self-care, confined to bed or chair > 50% of waking hours.
4 = Completely disabled; cannot carry out any self-care; totally confined to bed or chair.

### TOXICITY CRITERIA

(Note: N = upper limit of normal range)

| GRADES | 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|
| **HÆMATOLOGICAL** | | | | | |
| White cells (10⁹/L) | ≥ 4.00 | 3.00-3.99 | 2.00-2.99 | 1.00-1.99 | < 1.00 |
| Hæmoglobin (g/dL) | ≥ 11.0 | 9.5-10.9 | 8.0-9.4 | 6.5-7.9 | < 6.5 |
| Platelets (10⁹/L) | ≥ 100 | 75-99 | 50-74 | 25-49 | < 25 |
| Neutrophils (10⁹/L) | ≥ 2.00 | 1.50-1.99 | 1.00-1.49 | 0.50-0.99 | < 0.50 |
| **OTHER TOXICITIES** | | | | | |
| Alopecia | none | minimal hair loss | moderate, patchy | complete hair loss | |
| Nausea & vomiting | none | nausea | transient vomiting | vomiting requiring therapy | intractable vomiting |
| Oesophagitis | none | soreness, no medication | soreness, requests medication | soreness, liquid diet only | alimentation not possible |
| Stomatitis | none | soreness/ erythema | erythema, ulcers, can eat solids | ulcers, requires liquid diet only | alimentation not possible |
| Pulmonary | none | mild symptoms | exertional dyspnoea | dyspnoea at rest | complete bed rest required |
| Renal (Creatinine) (N = 0.12 mmol/L) | ≤ 1.25 x N | 1.26 - 2.5 x N | 2.6 - 5 x N | 5.1 - 10 x N | > 10 x N |
| Hepatic (SGOT/AST) (N = 40 U/L) | ≤ 1.25 x N | 1.26 - 2.5 x N | 2.6 - 5 x N | 5.1 - 10 x N | > 10 x N |
| Cardiac | none | sinus tachycardia > 110 at rest | unifocal VES, atrial dysrhythmia | multifocal VES | ventricular tachycardia |
| Infection | none | minor infection | moderate infection | major infection | major infection with hypotension |
| Skin reaction | none | erythema | dry desquamation | moist desquamation | exfoliative dermatit |
| Other toxicities | none | mild | tolerable | intolerable | life-threatening |

**PHASE III NSCLC**
**FOUR ARM RT & CARBOPLATIN TRIAL**

**QUALITY OF LIFE ASSESSMENT FORM F**

REGISTRATION NO. | | | | | | |

(eg. PMC001, ADE001)

SURNAME _____

GIVEN NAMES _____ *Affix label here* _____

U.R. NUMBER _____

DATE OF BIRTH (ddmmyyyy) _____

S19-22

*To be completed **pre-treatment** and at each **assessment**.*

*Example: How hungry do you feel?*

Not hungry at all — Extremely hungry

This would be interpreted as "slightly hungry".

1. | | | | | | | DATE (ddmmyy)

Please answer each question below by making a mark ( | ) on the line to indicate your feelings.

2. In general, how **well** do you feel physically ?
   very poorly — very well

3. How is your **mood**?
   very miserable — very happy

4. How **anxious** do you feel?
   very anxious — not anxious at all

5. How good is your **appetite**?
   very poor — very high

6. How **limited** are you in your daily activities?
   very limited — not limited at all

7. How is your overall **quality** of life?
   very poor — very high

8. How has your **quality** of life changed since your last assessment?
   *(not applicable at pre-treatment assessment)*
   much worse — much better



Please return to: Trial Centre, Peter MacCallum Cancer Institute, 481 Little Lonsdale Street, Melbourne Vic 3000.

**PHASE III NSCLC**
**FOUR ARM RT & CARBOPLATIN TRIAL**

**LIFE ORIENTATION FORM B3**

REGISTRATION NO. | | | | | | |

(eg. PMC001, ADE001)

SURNAME _____

GIVEN NAMES _____ *Affix label here* _____

U.R. NUMBER _____

DATE OF BIRTH (ddmmyyyy) _____

S4-5

*TO BE COMPLETED AT REGISTRATION AND AT THE FIRST POST-TREATMENT ASSESSMENT.*

**LIFE ORIENTATION SCALE** 13. | | | | | | | DATE (ddmmyy)

The following statements are general statements about aspects of life. Indicate the extent to which the statement describes you, by showing how much you agree or disagree with it.

| | Agree strongly | Agree | In between | Disagree | Disagree strongly |
|---|---|---|---|---|---|
| 1. In uncertain times, I usually expect the best. | 1 | 2 | 3 | 4 | 5 |
| 2. It's easy for me to relax. | 1 | 2 | 3 | 4 | 5 |
| 3. If something can go wrong for me it will. | 1 | 2 | 3 | 4 | 5 |
| 4. I always look on the bright side of things. | 1 | 2 | 3 | 4 | 5 |
| 5. I'm always optimistic about my future. | 1 | 2 | 3 | 4 | 5 |
| 6. I enjoy my friends a lot. | 1 | 2 | 3 | 4 | 5 |
| 7. It's important for me to keep busy. | 1 | 2 | 3 | 4 | 5 |
| 8. I hardly ever expect things to go my way. | 1 | 2 | 3 | 4 | 5 |
| 9. Things never work out the way I want them to. | 1 | 2 | 3 | 4 | 5 |
| 10. I don't get upset too easily. | 1 | 2 | 3 | 4 | 5 |
| 11. I'm a believer in the idea that "every cloud has a silver lining". | 1 | 2 | 3 | 4 | 5 |
| 12. I rarely count on good things happening to me. | 1 | 2 | 3 | 4 | 5 |

**COMMENTS**



Please return to: Trial Centre, Peter MacCallum Cancer Institute, 481 Little Lonsdale Street, Melbourne Vic 3000.