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**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
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by

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Contents

	Page
Declaration	5
Preface	6
Acknowledgments	11
List of abbreviations	12
List of figures	13
List of tables	14
Abstract	17
Part 1. Radiotherapy dose studies in non-small cell lung cancer	20
1.1 History and background: definitive radiotherapy for non-small cell lung cancer	21
1.2 Treatment policies of the Peter MacCallum Lung Unit 1981- 1995	29
1.3 The Peter MacCallum Lung Cancer Database	39
1.3.1 Introduction	39
1.3.2 Patient characteristics	43
1.3.3 Survival analysis	48
1.3.4 Discussion	71
Part 2. Treatment intensification for non-small cell lung cancer	84
2.1 Introduction and background	85
2.1.1 Hyperfractionation	85
2.1.2 Dose escalation	87
2.1.3 Radiosensitisation with concurrent chemotherapy	89
2.1.4 Induction chemotherapy	95
2.1.5 Reduction in overall treatment time	103

2.2	A pilot study of concurrent carboplatin chemotherapy and conventional and accelerated radiotherapy for non-small cell lung cancer	107
2.2.1	Study design	108
2.2.2	Results	110
2.2.3	Discussion	115
2.3	A randomized trial of accelerated and conventional fractionation radiotherapy with and without carboplatin for inoperable non-small cell lung cancer	116
2.3.1	Study design and rationale	116
2.3.2	The protocol	118
2.3.3	Statistical methods	123
2.3.4	Accrual	125
2.3.5	Results	126
2.3.6	Interim analysis	126
2.3.7	Final analysis	128
	– Toxicity	137
	– Response	147
	– Relapse and progression	147
	– Survival	150
2.3.8	Discussion	156
	– Survival	156
	– Patterns of failure	166
	– Toxicity	167
	– Prognostic factors	174

Conclusions and future studies	178
References	180
Appendix A. The Peter MacCallum lung cancer database: case report forms	205
Appendix B. Protocol for the randomised trial of accelerated and conventional radiotherapy with and without carboplatin	211
Appendix C. Case report forms for the randomised trial	229

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.