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Orginal article

Definitive radiation therapy management for medically non-resectable clinically localised non-small cell lung cancer: results & prognostic factors

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The aim of this paper is to review the experience of radical radiation therapy and the prognostic factors of patient outcome for clinically localised, medically inoperable non-small cell lung cancer (NSCLC) patients.
Clinically staged node-negative NSCLC patients who were not a surgical candidates due to co-morbid diseases but who were eligible for curative treatment, were reviewed in the London Regional Cancer Program (LRCP). This study population was treated between 1st Jan 1985 to 31st Jan 2004. Patients were excluded if they were previously treated with chest radiotherapy. Patients with localised disease, but who refused surgery, were also included in the study. Eligible patients received radiation therapy which was given via localised portals and underwent simulation prior to therapy. The dose prescription range was from 50 Gy in 2.5 Gy per fraction to 60 Gy in 2 Gy per fraction. Hazard ratios and P-values were determined for time to recurrence and patient survival. A total of 74 patients met the study eligibility criteria. The median age of the cohort was 70 years (range 38-92 years). The cohort consisted of 52 males and 22 females. 39/74 (53%) had a pathological diagnosis of squamous cell carcinoma. Clinical stages were 21 (28%) T_1, 40 (54%) T_2, and 13 (18%) T_3, respectively. 59/74 (78%) completed their planned radical radiotherapy but 15/74 declined radiotherapy. The median follow-up time was 17.6 months (range 0.4-123.6 months). For patients who completed radiotherapy, the two-year and five-year disease-free survival (DFS) rates were 38.1% and 11.4%. Overall survival (OS) two-year and five-year rates were 33.2% and 6.9%, respectively. The median DFS and OS for T_1, T_2, and T_3 were 18.7, 14, 15 months; and 23.1, 18.5, 14.5 months, respectively. Patients who received radiotherapy compared to those who did not, had median lung cancer-specific survival (CSS) times of 21 months and 4.9 months ($P<0.001$); OS times of 20 months and 5 months ($P<0.001$), respectively. Tumour size had impact on patient survival in univariate ($P=0.004$) and multivariate ($P=0.002$) analyses. In conclusion, radical radiotherapy significantly improves survival for patients with medically inoperable clinically staged localised NSCLC, and tumour size is a predictor of patient outcome. The OS, CSS, and DFS rates for patients with tumour size greater than 6 cm are significantly worse than those with smaller size tumours.

Keywords: non-small cell lung, cancer, radiation therapy, prognostic factors

Introduction

Surgical resection remains the treatment of choice for patients with early localised non-small cell lung carcinoma (NSCLC) with results showing five-year survival rates of approximately 50% for clinically staged patients [1, 2]. Patients with medically inoperable early stage NSCLC are often challenging in cancer management. Characteristically, these patients have significant co-morbid illnesses, which may impact their tolerance to treatment, and ultimately their survival. Definitive radiation therapy is often the option of treatment for patients who are medically inoperable. Potential confounding issues in this patient population include some patients who are not referred to a cancer centre due to co-morbid disease, and some who are referred, but are not offered radical radiotherapy due to poor outcome expectations. In addition, patients may refuse treatment despite it being offered.

The Canadian health care service is often a balance between health resources and optimum patient care [3-5]. We have reviewed the experience of the London Regional Cancer Program (LRCP) in the last 19 years in order to ascertain the role of definitive radiotherapy

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and the prognostic indicators which are important for medically non-resectable clinically localised NSCLC. This may assist the referring and treating physicians in making an informed decision on the therapy management and potential outcome of their NSCLC patients.

Methods & materials

Data were analysed from patients treated at the LRCP. The selection criteria for our study are given in Table I.

Table I. Selection criteria for our study on NSCLC. 1-5 were inclusion criteria and 6 was an exclusion criterion

1. Cases referred to the LRCP during the period 1985-2004.
2. Cases with a pathological diagnosis of NSCLC.
3. Cases which were staged, at least clinically, (with chest X-ray, CT of the thorax and upper abdomen) if possible, and according to the American Joint Commissioner on Cancer Staging System [6] and without nodal, or distant organ involvement.
4. Patients with significant co-morbid disease and considered to be poor surgical candidates but who were still potentially eligible for curative treatment.
5. Patients with localised disease, but who refused surgery.
6. Patients who has previously received chest radiotherapy, or previous resection surgeries (e.g., lobectomy, pneumonectomy or wedge resection).

External beam radiotherapy (EBRT) was given post-simulation for curative intent with dose prescriptions in the range 50 Gy in 2.5 Gy per fraction to 60 Gy in 2 Gy per fraction. The EBRT was delivered either as a small "postage stamp" field, or in localised 2-3 phases with a "shrinking field" to avoid over-irradiation to the spinal cord. In general, T_1 disease was treated with a "postage stamp" field while bulky T_2 and T_3 disease was treated with multi-fields and multi-phased techniques and underwent simulation, planning and before receiving treatment with megavoltage photons within the range 4-18 MV.

At LRCP a combined chemoradiation therapy (CRT) regime was offered to patients who had bulky T_2 disease and/or disease adhered to major vessels. The chemotherapy regimens were Cisplatinum based.

Patients' follow-up assessments were performed every 3-4 months for three years, every six months for two years and yearly thereafter. The follow-up evaluation included chest radiography and screening blood cell count and chemistry. At the time of relapse, investigations were carried out as clinically indicated, including bronchoscopy if possible and chest/abdomen CT scanning.

The patients' disease status was determined from clinic progress notes or by contacting the family physician's office for updated information. Local failure was defined as any recurrence in the ipsilaterally treated lung. Regional failures were those that occurred in the ipsilateral hilum, mediastinum or supraclavicular areas. Biopsy or appropriate imaging confirmed distant metastases. Time intervals for follow-up and the time to first event were calculated from the date of definitive pathological diagnosis.

Kaplan-Meier actuarial calculations and logrank statistics were used to estimate overall and lung cancer-specific survival. Due to existing co-morbidity, the use of cancer-specific survival is more appropriate to adjust for other causes of death. To estimate cancer-specific survival rates, deaths attributed to causes other than lung cancer were treated as censored at the date of death under the assumption that deaths from the underlying cancer were independent of deaths from other causes. Cox regression methods were used to evaluate the impact of radiation therapy, tumour size and chemotherapy.

Results

A total of 74 patients identified from the treatment period 1st Jan 1985 to 31st Jan 2004 at LRCP as medically non-resectable localised NSCLC met the selection criteria, Table I. The patient characteristics of the study population are given in Table II.

Table II. Patient characteristics

Characteristic		Number/percentage of patients
Gender	Male	52 (70%)
	Female	22 (30%)
Age	Median (range)	70 years (38-92 years)
Pathology	Adenocarcinoma	23 (30%)
	Squamous cell carcinoma	39 (53%)
	Large cell carcinoma	12 (17%)
Tumour stage	T_1	21 (28%)
	T_2	40 (54%)
	T_3	13 (18%)
Tumour size	Median (range)	4 cm (0.5-12 cm)
Tumour location	Upper	42 (57%)
	Middle	6 (8%)
	Lower	26 (35%)
Tumour side	Right	45 (60%)
	Left	29 (40%)

Pulmonary related co-morbid diseases were present in 52/74 (70%) cases and there were 5/74 (6.6%) patients who refused surgery. 59/74 (78%) patients completed definitive radiotherapy and in this subgroup the clinical stages were T_1, 17(29%); T_2, 33(56%); and T_3, 9 (15%), respectively. 15/74 (22%) patients declined radiotherapy. They were assessed by observation-only.

No patient had partial or incomplete radiotherapy. 70% of patients received 50 Gy at 2.5 Gy per fraction and 30% received 60 Gy at 2 Gy per fraction. CT (2D) planning for radiotherapy was performed for 66% while for the remaining 34%, planning was using conventional simulation.

The treatment target volume included the gross tumour volume with a 2 cm margin. 8/74 (13.6%) patients among the 59 treated with definitive radiotherapy received combined CRT. The regimens used were four cycles of Vinblastine and Cisplatinum with radiotherapy given concurrently at the third cycle of chemotherapy [7] from 1998 to 2004 (n=2), and two cycles of Vinblastine and Cisplatinum chemotherapy regimens follow by radiotherapy [8] from 1985 to 1998 (n=6).

The median follow-up time was 17.6 months (range 0.4-123.6 months). With radiotherapy 13/74 (22%) patients achieved complete response (CR), 24 (41%)

Table III. Results of univariate and multivariate analyses undertaken to determine which factors have an influence (P<0.05) on survival. * indicates those factors with P<0.05. NS indicates not significant at the P=0.05 level. CI indicates confidence interval

Factors	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Gender Male versus female	1.59 (0.95, 2.69)	0.08		NS
Age	1.19 (0.94, 1.51)	0.159		NS
Histology	1.24 (0.73, 2.12)	0.727		NS
T stage T_2 versus T_1 T_3 versus T_1	 1.19 (0.69, 2.05) 1.31 (0.64, 2.69)	 0.737		 NS
Tumour size	1.17 (1.05, 1.30)	0.004*	1.19 (1.07, 1.33)	0.002*
Tumour location Upper versus Lower	 1.04 (0.65, 1.74)	 0.871		 NS
Right versus Left	1.08 (0.67, 1.74)	0.765		NS
Radiation treatment Without versus with	3.27 (1.85, 5.78)	<0.001*	2.51 (1.31, 4.84)	<0.001*

partial response (PR), 16 (27%) had stable disease while six (10%) had progression of disease as defined by chest X-ray or chest CT. Disease progression with a local component as failure was found in 75%, and with a distant component as failure in 58%.

For patients who completed radiotherapy the two-year and five-year disease-free survival (DFS) rates were 38.1% and 11.4%; and the overall survival (OS) rates were 33.2% and 6.9%, respectively. The median DFS times and OS times for T_1, T_2, and T_3 were 18.7, 14, 15 months; and 23.1, 18.5, 14.5 months, respectively. The one-year, three-year, and five-year CSS rates for T_1, T_2 and T_3 were 93%, 41%, 16.4%; and 80%, 26%, 8%; and 67%, 22%, 5%, respectively.

Factors influencing patient survival are summarised in Table III. Age, gender, histology, tumour T-stage, tumour size, tumour location and radiation treatment were considered as potential predictors for patient outcome. Patients not receiving radiation therapy fared poorly with respect to overall survival in univariate analysis, and in multivariate analysis (P<0.001): see the bottom row of results in Table III.

For those patients treated with radiotherapy, analyses showed neither the dose (P=0.642, hazard ratio of 1.18, 95% confidence interval 0.59-2.37), nor the fraction size (P=0.569, hazard ratio of 1.21, 95% confidence interval 0.63-2.35) had a significant impact on survival.

Patients treated with RT (n=59) had a median OS time of 20 months compared with 5 months for those (n=15) who did not receive radiotherapy (P<0.001), Figure 1a, and median CSS time of 21 months compared to 4.9 months (P<0.001, Figure 1b. Among the radiotherapy treated patients, 12 (20%) died of non-cancer related disease compared to one (7%) of those patients who declined radiotherapy treatment.

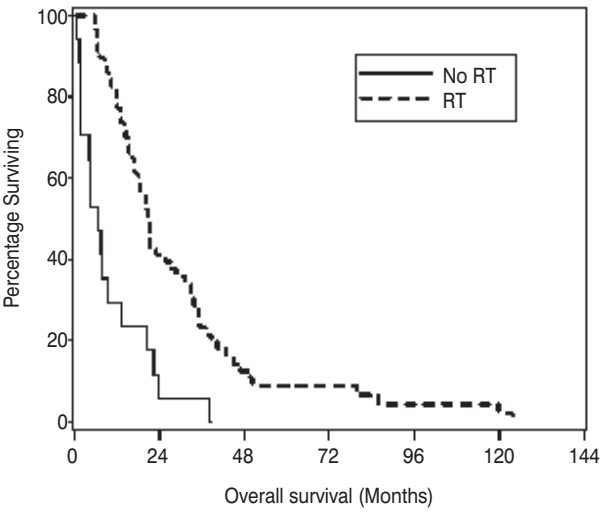

Figure 1a. The effect of radical radiation therapy on patient outcome, overall survival: logrank test P<0.001

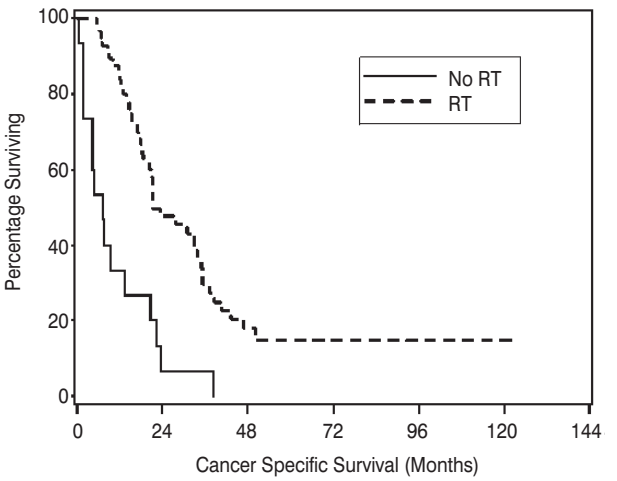

Figure 1b. The effect of radical radiation therapy on patient outcome, cancer-specific survival: logrank test P<0.001

Tumour size had a significant impact on patient outcome in both univariate, Table III. Figure 2a shows an interaction of radiation treatment with tumour size. Tumour size (<2 cm, 2-4 cm, 4-6 cm and >6 cm) had influence on OS rate (P=0.021), and on CSS rate (P=0.008), Figure 2b.

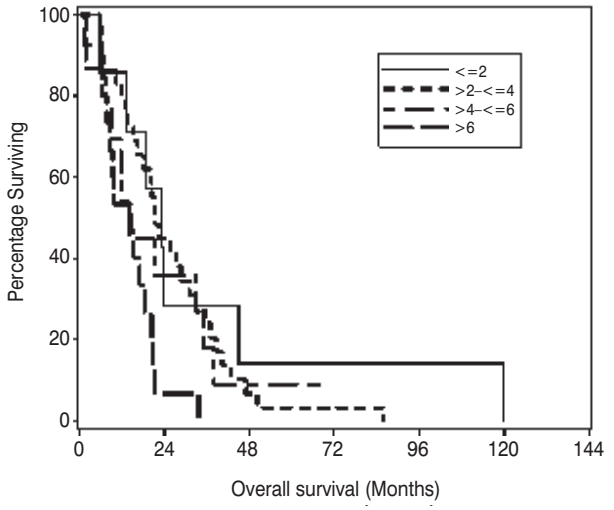

Figure 2a. The effect of various tumour size on patient outcome post-radical radiation therapy, overall survival logrank test P=0.021

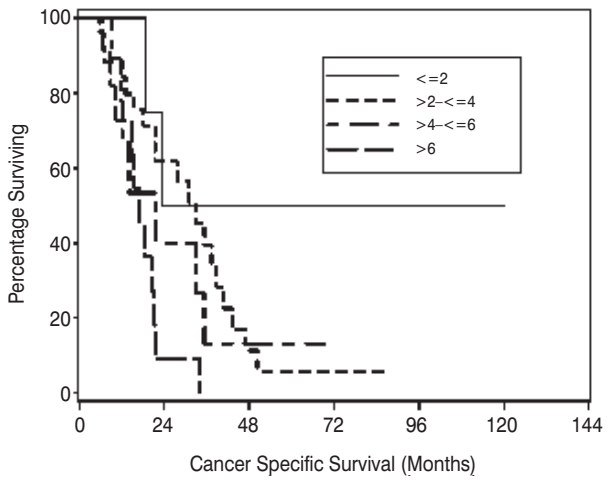

Figure 2b. The effect of various tumour size on patient outcome post-radical radiation therapy, cancer- specific survival: logrank test P=0.008

The prognosis for patients with a tumour size greater than 6 cm (n=15) when compared to a tumour size of less than 6 cm (n=44) is significantly worse for the OS rate (P= .003, Figure 3a, the CSS rate, P=0.002, Figure 3b, and the DFS rate, P=0.017, Figure 3c. For patients receiving CRT (n=8) the median, one-year, three- year, and five-year CSS rates were 15.2 months, 85%, 28%, 17.1%; compared to those with RT alone (T2/T3, n=34), 20 months, 76%, 26.6%, and 12.2% respectively (P=0.738).

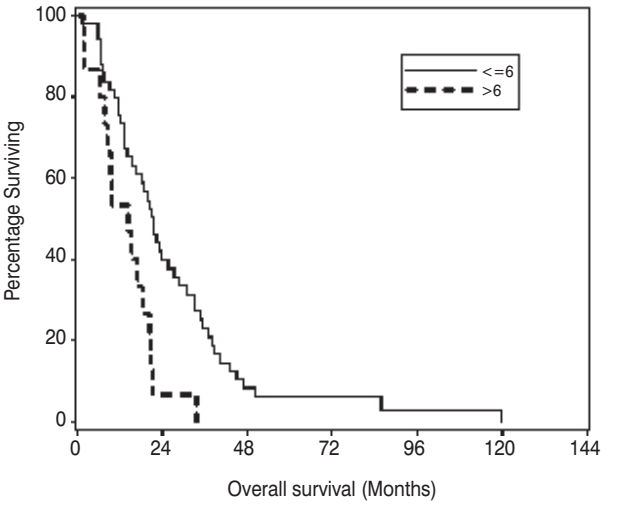

Figure 3a. The effect of large tumour size (> 6cm) on patient outcome post-radical radiation therapy, overall survival: logrank P=0.003

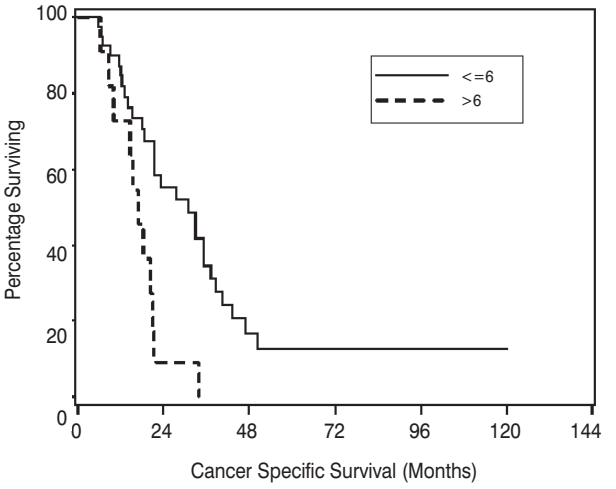

Figure 3b. The effect of large tumour size (>6cm) on patient outcome post-radical radiation therapy, cancer-specific survival, logrank P = 0.002

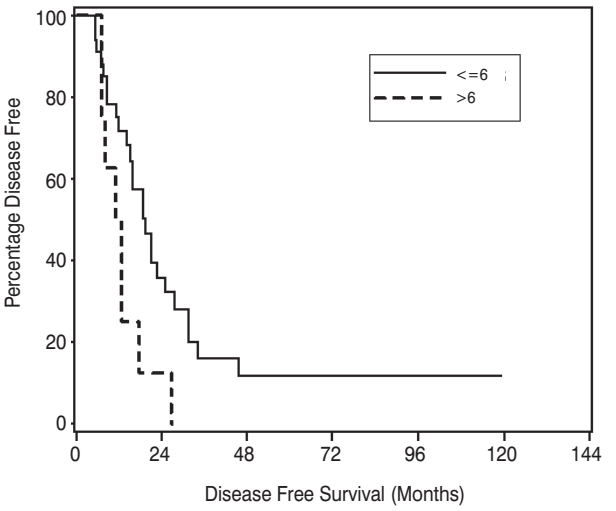

Figure 3c. The effect of large tumour size (>6cm) on patient outcome post-radical radiation therapy, disease-free survival, logrank P=0.017.

Discussion

The one-year, three-year, and five-year cancer-specific survival rates for patients who were treated with radiation therapy in our study are well within the range of those reported in the literature [9-16], Table IV, and from the SEER database [17] for NSCLC patients treated using curative radiation doses. Patients with unresected tumours were not pathologically staged, and some patients who were classified as having clinically stage I or II cancer may actually have had more extensive disease. One would expect the outcomes for these patients to be worse compared to the results for those patients with stage I or stage II cancers who have undergone resection.

We found that radiotherapy alone when compared to observation-only is associated with statistical significance in lung cancer survival benefit for patients with localised T_1, T_2 and T_3 disease. This is consistent with data obtained from the SEER database by Wisnivesky et al [17]. The increase in survival with radiotherapy is unlikely to be due to co-morbid illness among untreated patients because patient outcome was analysed using lung cancer-specific survival.

Although the medically inoperable early stage patients had a high rate of intercurrent causes of death, in most radiotherapy series [9, 12, 18] this amounts to 10-30% of all causes of death. In our series there was 20% intercurrent deaths in the group treated with radiotherapy. The primary cause of death in these patients remains uncontrolled lung cancer. Our data also showed that among patients who did not receive radiotherapy, 93% died from cancer and only 7% from an intercurrent disease. This is consistent with the report of McGarry et al [19] that cancer deaths in untreated patients were greater than 50% of the total deaths.

Unlike Wisnivesky et al [17] our data also demonstrated that there is a radiotherapy interaction with tumour size. Tumour size greater than 6 cm had a significantly poor progression-free survival and overall survival when compared to those patients with tumour size of less than 6 cm when treated with radiotherapy.

Some studies were not able to show a relationship between tumour size and survival [16, 17] and among those studies which demonstrated a relationship [14, 20, 21] the exact threshold tumour size and the overall prognosis were controversial.

Mery et al [20] suggested that patients with a tumour size of less than 2 cm had significantly better prognosis and that this would reflect the T-stage of <2 cm for T_1 rather than <3 cm for our current staging. Our data were not able to show the precise threshold: only tumours of size greater than 6 cm demonstrated a significantly worse local control and survival than those with size less than 6 cm.

Our results are consistent with Lopez-Encuentra et al [22] in a multi-institutional study of patients completely resected by thoracotomy and with pathological early stage NSCLC ($pT_{1-2}\ N_0\ M_0$), where the five-year survival rate of those with > 7 cm primary tumours, was 38%, when compared to a five-year survival rate of 62% if the primary tumour size was < 2 cm.

Non-surgically treated early stage NSCLC patients with a distant failure rate of 16-50% have been reported [23, 24]. It was logical to incorporate adjuvant systemic treatment for these patients, particularly those with bulky advanced but clinically node negative disease. Jeremic et al [25] reported a trial of 56 patients with stages I or II NSCLC who were treated with hyperfractionated radiotherapy (67.6 Gy in twice-daily 1.3 Gy fractions) with concurrent low dose carboplatin and paclitaxel. Five-year OS and DFS rates were 36% and 43%, respectively, with acute grade 4 toxicity of 7% in lung, 7% in oesophageal and 22% in haematological related complications.

With the rising interest in different modern agents in adjuvant systemic treatment for surgically treated patients, future trials will need to incorporate chemotherapy with regimens effective for subgroup of medically inoperable patients, including elderly age [26], who have reasonable performance status, and are

Table IV. Lung cancer-specific survival rates from the literature for patients with stage I and stage II NSCLC treated with radiation therapy alone. * Denotes a point estimate with 95% confidence interval from data from the Surveillance, Epidemiology, and End Results (SEER) Registry [17]

	Survival rates (%) & (95% Confidence intervals)		
Data Source	One-year	Three-year	Five-year
Stage I NSCLC			
Literature survey median range [9-16]	72% (55%-90%) *66% (67%-71%)	33% (22%-56%) *29% (27%-32%)	17% (13%-39%) *15% (13%-17%)
This current LRCP study by Yu, Tai, Ash et al.	87%	34%	13%
Stage II NSCLC			
Literature survey median range [9-16]	70% *55% (50%-60%)	20% *25% (19%-30%)	12% *11% (6%-16%)
This current LRCP study by Yu, Tai, Ash et al.	67%	22%	5%

Table V. Ongoing clinical studies

The Cancer and Leukemia Group B (CALGB) is evaluating acceleration and hypofractionation in stage I (tumour size < 4 cm) NSCLC (CALGB 39904).

The European Organization for Research and Treatment of Cancer (EORTC) is conducting a phase I dose-escalation study in patients who have medically inoperable stage I and II disease (EORTC 22994).

The Radiation Therapy Oncology Group (RTOG) is performing a phase II trial (RTOG 0236) of stereotactic radiotherapy (SRT) for medically inoperable stage I/II NSCLC (tumour size <5 cm, peripherally located tumour and N_0).

The National Cancer Institute of Canada (NCIC) has developed a phase II study (BR. 25) of accelerated hypofractionated 3-D conformal radiotherapy for inoperable stage I/II NSCLC (tumolur size <5 cm, peripherally located tumour and N_0).

The Radiation Therapy Oncology Group (RTOG) is also examining the role of combined chemoradiation therapy in another trial (RTOG 0117) with chemotherapy of weekly paclitaxel and carboplatin to concurrent 3D conformal radiotherapy with dose intensification in patients with inoperable stages I-III.

treated with small field or involved field radiotherapy [27]. Small field or involved field radiotherapy has the potential advantage of minimising radiotherapy treatment complications such as radiation oesophagitis and pneumonitis.

Local control of cancer is still a major problem in the treatment of early localised NSCLC. Our data showed that disease progression with a local component failure of 75% and a distant failure component of 58% is consistent with the data of Cheung et al [27] who reported 68.9% at initial relapse with a local component in early stage NSCLC treated with radiotherapy alone.

In addition our data did not show the radiotherapy dose and fraction size of schedule of 50-60Gy in 2.5-2.0 Gy fractions had any impact on patient outcome. A high dose radiotherapy schedule with doses greater than 60-65 Gy has been reported to have a significantly lower intra-thoracic recurrence rate [11, 16, 28]. It is logical that improving local tumour control may translate into a better overall survival.

Sibley et al [15] reported a five-year cause-specific survival of 46% among patients with primary tumour control, which is significantly better when compared to 12% survival for patients who failed locally.

Qiao et al [29] have reviewed and analysed 18 studies reported during the period 1988-2000. They were able to show an inverse relationship between local component failure and biological equivalent dose (BED) with improving local failure associated with increasing BED. More conformal and sophisticated radiotherapy delivery systems are being developed to assist the safe delivery of high dose radiotherapy schedules [30-32].

It is unlikely that a randomised trial will be designed to confirm the benefit of radical radiotherapy over observation-only in early stage NSCLC. However, further development of new approaches to improve the delivery of radical radiotherapy and local tumour control for this subgroup of patients are ongoing. Several large cooperative group studies are in progress to confirm the efficacy of the new approaches to non-surgical management of early stage medically inoperable NSCLC, Table V. The results of these trials may offer further insight and new approaches to non-surgical management of early stage NSCLC.

Conclusions

This study presents our Canadian experience on management of patients with localised medically inoperable disease. Our results demonstrate inferior outcome among the subset of patients with localised medically inoperable disease who did not receive radical RT, and observation-only for this group of patients may be an inferior option. This is also clinically relevant to patients with localised disease, who will not undergo surgery. On the other hand many patients who received radical RT developed local failures. The larger the tumour size, the worse the outcome and prognosis was significantly poor with tumour size greater than 6 cm. The management of each clinical case should be individualized and clinicians are encouraged to offer full discussion with their patients of treatment options, goals of the therapy, potential adverse effect, and available ongoing clinical trials. Further investigations involving more conformal technique, high tumour dose, and suitable dose fractionation are ongoing.

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