1-1-2006

The Role of Radiation Therapy on Medically Inoperable Clinically Localized Non-small Cell Lung Patients: London Regional Cancer Program (LRCP) Clinical Experience

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The Role of Radiation Therapy on Medically Inoperable Clinically Localized Non-small Cell Lung Patients :London Regional Cancer Program (LRCP) Clinical Experience

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INTRODUCTION

- Lung cancer is the most frequent cause of cancer death in both men and women in North America. In 2006, an estimated 22,700 Canadians will be diagnosed with lung cancer and 19,300 will die of it (Canadian Cancer Statistics 2006).
- Approximately 15-20% of NSCLC patients present with early or localized disease.
- Surgical resection of $T_{1\text{-}2}N_0$ NSCLC remains the treatment of choice for this population, and results in a 5-year survival rate of 50-70%.
- Patients deemed medically inoperable have been treated with non-surgical therapies, such as radiation therapy (RT), while some patients have simply been observed without any tumor therapy because of their co-morbid illnesses.
- Potential confounding issues in this patient population include some patients who are not referred to our Centre due to co-morbid disease, and some who are referred, but are not offered radical RT due to poor outcome expectations. In addition, patients may refuse treatment when offered.
- We have reviewed the past 19 years' experience at LRCP in management of this group of patients.

METHODS

- Patients treated at LRCP from 1985-2004 with pathological diagnosis of Non Small Cell Lung Cancer(NSCLC), and clinically staged without nodal or distal organ involvement, were reviewed.
- In general, these patients with medically inoperable disease were referred to us by thoracic surgeons and respirologists. They had significant co-morbid illnesses and were deemed to be poor surgical candidates, but the hope was that they might be eligible for potential curative treatment at our Centre.
- Patients with localized diseases, but who refused surgery, were also included.
- Patients who previously received chest RT, had clinically positive nodes, or with distal diseases, were excluded.
- RT was given in localized portal with patients who had undergone simulation prior to therapy. RT doses ranged from 50-64 Gy at 2 to 2.5 Gy fraction.
- Localized RT was given either as a small " postage stamp" field for patients with small peripheral disease , or localized 2-3 phases to come off the spinal cord for patients with large relatively central localized disease. In general T_1 disease was treated with postage stamp field while T_2 (central />6cm) and T_3 disease was treated with 2-3 phases underwent simulation and planning. RT was delivered by mega voltage photons of greater than 4 MV .
- Chemotherapy was Cisplatinum based regimens for those who received combined modalities of chemoradiation (CRT).
- Patient disease status was determined from clinic progress notes or from updated information provided by family physicians.
- 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. Distant metastasis was confirmed by biopsy or appropriate imaging. Time intervals for follow up and time to first event were calculated from date of definitive pathological diagnosis .
- Overall survival and time to recurrence was assessed using hazard ratios. Predictors of survival were estimated using multivariate logistic regression .

TABLE 1: Patient characteristics

Gender	Male Female	53(70%) 23(30%)
Age	Median Range	70 y.o. 38-92 y.o.
Pathology	Adeno Squamous Large	23(30%) 40(53%) 13(17%)
Tumor stage	T_1 T_2 T_3	21(28%) 41(54%) 14(18%)
Tumor size	Median(range)	4 cm(0.5-12cm)
Tumor location	Upper Middle Lower	43(57%) 6(8%) 27(35%)
Tumor location	Right Left	46(60%) 30(40%)

RESULTS

- From January 1985 to January 2004 there were 76 patients meeting the selection criteria , including 70% male and 30% female. The median age of the study group was 70 years old (range from 38 to 92 years old). There were 30% Adenocarcinoma, 53% Squamous cell carcinoma and 17% Large cell carcinoma (Table 1).
- Clinical stages were T_1 (28%), T_2 (54%) and T_3 (18%). Median follow up was 17.6 months (range from 0.4 to 123 months). At the time of analysis 72 (94 %) of the patients were dead and 4(6 %) were alive.
- Seventy eight percent of the patients completed radical RT while 22% declined RT.There were 6(8%) patients treated with combined CRT (bulky >6cm and/or adhered to major vessels). For patients who completed RT 2-and 5-year disease free survival (DFS) rates were 38.1% , and 11.4% ; overall survival (OS) rates were 33.3% and 6.9%, respectively. The median DFS and OS rates 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 RT compared to no RT had median cancer specific survival (CCS) rates of 21 months and 4.9 months (P<0.001) (Figure 1); OS rates of 20 months and 5 months (P<0.001) (Figure 2), respectively. Patients treated with RT increasing tumor sizes worsened cancer control and survival (Figure 3). Tumor size of < 6cm had an 18.7 month median DFS rate with RT, compared to those who had >6 cm and had 11 months (P=0.017).
- For patients receiving CRT the median CSS rate of 15.2 months compared to those of 20 months with RT only(P=0.738) (Figure 4).
- Univariate and multivariate analyses showed radiation treatment and tumor size have influence on patients survival (Table 2).

TABLE 2: Factors influence on patient survival

	UNIVARIATE		MULTIVARIATE	
Factors	Hazard ratio (95% CI)	P-Value	Hazard ratio (95% CI)	P-Value
Gender	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 T1 vs. T2 T1 vs. T3	 1.19(0.69,2.105) 1.31(0.64, 2.69)	 0.737		 NS
Tumor Size	1.17(1.05, 1.30)	0.004*	1.19(1.07,1.33)	0.002*
Tumor Location Upper vs lower Right vs. left	 1.04(0.65, 1.74) 1.08(0.67, 1.74)	 0.871 0.765		 NS NS
Radiation treatment	3.27(1.85, 5.78)	<0.001*	2.51(1.31,4.84)	<0.001*

*P<0.05
NS = not significant

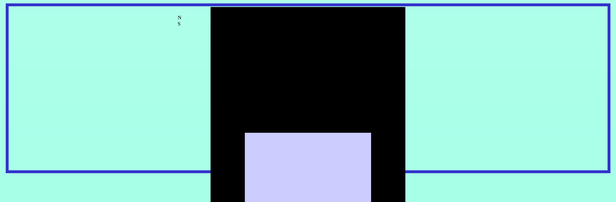
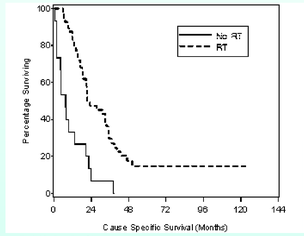
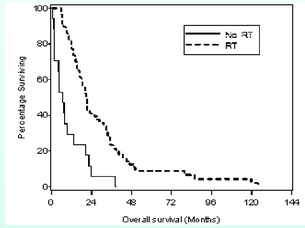


FIGURE 1



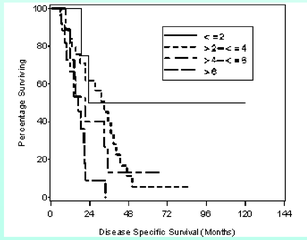
(P<0.001,Log Rank)

FIGURE 2



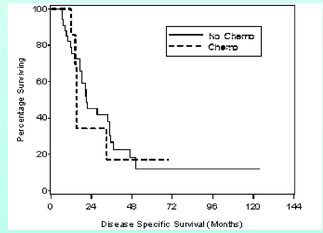
(P<0.001,Log Rank)

FIGURE 3



(P<0.008,Log Rank)

FIGURE 4



(P<0.738, ,Log Rank)

CONCLUSION

- Radical RT improves survival in patients with localized medically inoperable NSCLC. 'Observation – only' has inferior outcome for this group of patients and may not be an optimal treatment option.
- There is interaction between RT and tumor size with poor cancer control and patient outcome for tumors with larger sizes.
- Further clinical trials with conformal treatment and respiratory gating technologies to minimize potential treatment morbidities are on going, including in-house conformal (IMRT/Tomotherapy with and without gating) RT, national and international clinical trials(NCIC Br-25, RTOG 0236).
- The role of combined CRT in bulky localized medically inoperable NSCLC patients management needs further investigations.