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Original Article

Effect of LINAC-based postoperative radiotherapy on local control and survival in patients with non-small cell lung cancer

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Abstract

Aim: To perform a retrospective analysis of survival, local–regional control and the effect of prognostic factors in 61 non-small cell lung cancer patients who were treated with postoperative radiotherapy (PORT) by a linear accelerator (LINAC).

Material and methods: A total of 50–66 Gy PORT with a fractional dose of 1·8–2 Gy was administered to 24 patients (24·5%) for surgical margin positivity, 33 patients (54%) for mediastinal lymph node involvement and 13 patients (21·5%) for both mediastinal lymph node involvement and positive surgical margins.

Results: Median follow-up was 17 months, and the median survival and median distant metastasis-free survival were 25 and 19 months, respectively. Local-regional progression was observed in 10 patients (16·4%). Treatment modality (2D/3D) ($p = 0{\cdot}021$), tumour size >4 cm ($p = 0{\cdot}004$), surgical margin positivity ($p = 0{\cdot}001$), and left lung localisation of the tumour ($p \leq 0{\cdot}05$) were the prognostic factors in terms of survival.

Conclusions: A survey of the literature shows that, without PORT, local recurrence or progression rates increase while overall survival rates decrease. In this study, only patients with PORT are studied and the results show that the local progression and overall survival rates are comparable with literature of LINAC-based PORT. In the case of overall survival, 3D treatment shows better results than 2D treatment modality.

Keywords: linear accelerator (LINAC); non-small cell lung cancer (NSCLC); postoperative radiotherapy (PORT)

INTRODUCTION

Non-small cell lung cancer (NSCLC) accounts for ~85% of all lung cancer cases, and can be classified into three main clinical groups that determine the treatment approach according to the level of the disease: operable disease, locally advanced disease, and distant metastatic disease.[1] The operable disease group accounts for only 20% of all NSCLC patients, and comprises stage I, II and selected stage III patients. A symptomatic disease, >3 cm tumour size, non-squamous cell

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histology, metastasis of numerous lymph nodes, and vascular invasion are among the factors that adversely affect prognosis.

Currently, postoperative radiotherapy (PORT) is indicated for disease with a close or positive surgical margin or for resected N2 (mediastinal lymph node involvement) disease. PORT following adjuvant chemotherapy is recommended for disease with a negative surgical margin that only includes mediastinal lymph node involvement. In these patients, the treatment volume includes the involved lymph node region, as well as the hilum and subcarinal lymph nodes of the same side, depending on the localisation of the primary tumour. In resected N2 disease, the PORT dose is 50 Gy in total. 60–66 Gy PORT is administered only to the surgical margin area in disease with a close or positive surgical margin and no lymph node involvement.

PORT is contraindicated in completely resected stage I disease,[2] and while its role in N2 disease has become gradually more supported based on new data, its role in N1 (pulmonary lymph node involvement) disease is not yet certain.[3–7] Furthermore, randomised prospective studies have found out that PORT increases local control of N2 disease.[8,9] Although its survival effect was not shown in those studies, a Surveillance Epidemiology and End Results analysis reported that radiotherapy decreases survival in N0 (without lymph node involvement) disease, but provides a survival advantage in N1 and N2 disease.[6]

In the current study, we performed a retrospective assessment of the clinical treatment characteristics, local control rates, overall survival, and prognostic factors of 61 patients diagnosed with NSCLC and treated with PORT by a linear accelerator (LINAC).

METHODS

Patient characteristics

A total of 61 patients who were diagnosed with NSCLC and received PORT by a LINAC between the years of 2000 and 2011 were included in the analysis. A summary of patient characteristics can be found in Table 1, and a summary of tumour characteristics and surgery data can be found in Table 2. All patients were treated with a Philips SLI-Plus 25® (Elekta, West Sussex, UK) LINAC between 2000 and 2008.

Table 1. *Patient characteristics*

	Median 60 (range, 36–78)	
	n	**%**
Age		
≥60	31	50·8
<60	30	49·2
Gender		
Male	52	85·2
Female	9	14·8
Cigarette		
Yes	13	21·3
No	4	6·4
Ex smoker	27	44·3
Unknown	17	28
KPS		
<70	10	16·4
70–80	5	8·2
90–100	46	75·4
Weight loss		
None	41	67·2
<5%	10	16·4
Unknown	10	16·4
Comorbidity		
Yes	14	23
No	41	67·2
Unknown	6	9·8

Abbreviation: KPS, Karnofsky performance status.

Table 2. *Tumour characteristics and surgery data*

	n	**%**
Tumour location		
Upper right	17	27·9
Mid right	3	4·9
Lower right	11	18
Upper left	21	34·4
Lower left	9	14·8
Type of surgery		
Wedge	5	8·3
Lobectomy	43	70·4
Pneumonectomy	13	21·3
Histology		
Squamous cell	30	49·2
Non-squamous cell	31	50·8
Dissected lymph node		
0	7	11·5
≤6	21	34·4
>6	33	54·1
Surgery margin		
Negative	33	55
Positive	28	45

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After 2008, patients were treated with a Philips SLI-Plus 25® or an Elekta Synergy Platform® (Elekta) LINAC. PORT was administered to 15 patients (24·5%) for a positive surgical margin, 33 patients (54%) for mediastinal lymph node involvement, and 13 patients (21·5%) for both mediastinal lymph node involvement and a positive surgical margin.

A total of 33 patients received 2D treatment, while 3D treatment was planned for 28 of the patients; 50–66 Gy conformal radiotherapy with a fractional dose of 1·8–2 Gy was administered to the bronchial stump + ipsilateral hilum + mediastinal region for 58 patients and to the bronchial stump + ipsilateral hilum for three patients.

During the first 2 years following radiotherapy, the patients were evaluated using complete blood counts, routine biochemical examinations, physical examination and thoracic computerised tomography (CT) on a quarterly basis. Evaluations between the 2nd and the 5th years were performed semi-annually.

There were no selection criteria for the patients of this study. All the patients who received PORT during years 2000–2011 were included.

Statistical analysis

Statistical analysis was performed with SPSS™ 16 software (SPSS Inc., Chicago, IL, USA). Disease-free survival, overall survival, and local–regional control were calculated by the Kaplan–Meier method using the period from the date of surgery to the date of death or last evaluation. The variables which were significant ($p \leq 0{\cdot}05$) in univariate analyses were included in multivariate analyses, which utilised Cox's regression model to assess the prognostic factors.

RESULTS

In the median 17-month follow-up period, 23 patients were disease-free, six had local relapse, three had distant metastasis, two had both local relapse and distant metastasis, and 27 died due to disease-related reasons. In their first evaluation in the 3rd month after PORT, all of the patients were examined by thoracic CT or positron emission tomography. Upon examination, we observed a complete response in 93·4% of the patients, local–regional and systemic progression in 4·9%, and a partial response in 1·6%.

Median survival was 25 months, while distant metastasis-free survival was 19 months. The 2- and 5-year overall survival rates were 49 and 32%, respectively, while the 2-year distant metastasis-free survival rate was 61%.

Treatment modality was a factor for overall survival. Out of 33 2D patients 10 survived (six disease-free survival), while out of 28 3D patients 24 survived (17 disease-free survival) which corresponded to a p-value of 0·021. Tumour size >4 cm ($p = 0{\cdot}004$), a positive surgical margin ($p = 0{\cdot}01$), and left lung localisation ($p < 0{\cdot}05$) of the tumour were also significant prognostic factors in terms of overall survival. Factors such as lower Karnofsky performance status (KPS), advanced age, history of smoking, weight loss, comorbidity, type of surgery, total radiotherapy (RT) dose, stage and chemotherapy did not have a statistically significant effect on overall survival.

The median for local–regional control was 20 months. Local–regional progression was determined in 10 of the 61 patients. None of the prognostic factors had any statistically significant effect on local–regional control.

Distant metastasis developed in 19 patients. The 2-year distant metastasis-free survival rate was 61%. Treatment modality (2D/3D) ($p = 0{\cdot}005$) and lymph node positivity ($p = 0{\cdot}013$) were significant prognostic factors on the distant metastasis-free survival. The distant metastasis-free survival rate in patients with negative lymph node status was 8·4 times higher (95% CI 1·57–45·45).

DISCUSSION

In the present study, we found the 5-year overall survival rate and the local recurrence rate to be 32 and 16%, respectively, which are comparable with the retrospective studies listed in Table 3.

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Table 3. Retrospective studies of PORT

Study	PORT	Stage	Number of patients	Dose (Gy)	Local recurrence (%)	Overall survival (%)	Follow-up
Kirsh et al.[4]	No	IIIA	20	–	NR	0	5 years
	Yes		110	50–60	NR	26	
Dai et al.[10]	No	IIIA-N2	125	–	53·3	30·6	35 months
	Yes		96	60	36·1	36·6	
Corso et al.[12]	No	II-IIIA	27122	–	NR	27·8 (N2)	5 years
	Yes		3430	45–>60	NR	34·1 (N2)	
Sawyer et al.[14]	No	IIIA	136	–	60	22	4 years
	Yes		88	45–66	17	43	
Moretti et al.[17]	No	IIIA-pN2	44	–	NR	21 (2 years)	64 months
	Yes		39	50–60	23	43 (2 years)	
Zou et al.[19]	No	III-N2	79	–	66·2	22·2	72 months
	Yes		104	48–54	26·8	30·5	
Karakoyun et al.[20]	Yes		98	54	22	50	52 months
Astudillo and Conill[22]	No	IIIA	60	–	20	28	3 years
	Yes		86	45–50	13	20	
Gren et al.[23]	No	I-IIIA	94	–	NR	16	5 years
	Yes		125	50–60	NR	31	
Choi et al.[24]	No	IIIA	55	–	31	8	5 years
	Yes		93	40–56	14	43	
Chung et al.[3]	No	I-IIIA	68	–	32	28	3 years
	Yes		50	46	10	40	
Paterson et al.[25]	No	T3N0-2	22	–	27	30	5 years
	Yes		13	20–50	0	56	
Robinson et al.[26]	No	pN2	2633	–	NR	40·7	22 months
	Yes		1850	≥45	NR	45·2	
Chen et al.[27]	No	IIIA	75	–	NR	24 (3 years)	25·6 months
	Yes		81	60	NR	44·4 (3 years)	
Kim et al.[28]	No	P N2	111	–	23·7	53·3	48 months
	Yes		38	50–56	43·2	51·0	
Current study	Yes	I-IV	61	50–66	16	49 (2 years) 32 (5 years)	17 months

Abbreviations: PORT, postoperative radiotherapy; NR, not reported.

In their study on stage IIIA-N2 patients, Dai et al. found that, with PORT, local recurrence-free, distant metastasis-free, disease-free, and overall survival rates were significantly higher in the 1st, 3rd and 5th years.[10] There are also studies that report a significant increase in 5-year overall survival for N1 and N2 patients who received PORT.[11,12] Furthermore, Shen et al. observed higher overall survival rates among stage IIIA pN2 patients with two or more positive mediastinal lymph nodes that were treated with PORT and chemotherapy.[13] In our study, the effect of the N stage on survival was not statistically significant. We determined that lymph node positivity was a prognostic factor for distant metastasis-free survival. Distant metastasis-free survival rates in N1 or N2 patients were eight times higher than in N0 patients ($p = 0{\cdot}013$).

Many prognostic factors that affect survival in lung cancer are reported in the literature.[14–16] A significant increase in the rates of local recurrence-free survival ($p < 0{\cdot}001$), recurrence-free survival ($p = 0{\cdot}013$), and overall survival ($p = 0{\cdot}002$) following PORT was reported in a study by Moretti et al. on 83 patients with pathological N2 disease. The number of involved lymph nodes or stations, presence of extracapsular invasion, and a positive surgical margin were considered to be significant prognostic factors in overall survival.[17] Mantovani et al. found out that that the number of positive mediastinal lymph nodes is a prognostic factor for local control in pN2 patients.[18] In our study, the presence of a positive surgical margin did not have a significant effect on local–regional control or distant metastasis-free survival, but it was a significant prognostic factor for overall survival.

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50 Gy RT and two to six cures of CT (median four cures) were given to the patients in a study by Zou et al. on stage III-N2 patients.[19] Five-year overall survival rate was 30·5% in the patients who received postoperative chemo-radiotherapy and 14·4% in those who did not ($p = 0{\cdot}007$). Higher disease-free survival rates were found with postoperative chemo-radiotherapy ($p = 0{\cdot}003$). PORT and having received at least three cures of CT were found to be prognostic factors in terms of overall survival and disease-free survival. In our study, CT did not have a significant contribution to survival. However, CT information of many of the patients could not be obtained from their files.

In a study by Karakoyun et al., RT dose, KPS, age, left lateralisation of tumour and pneumonectomy were prognostic factors for overall survival.[20] There was a higher mortality rate in patients who received >54 Gy RT to left-sided tumours which was reported to be potentially due to cardiac toxicity. In our study, the overall survival rates were also low in the case of left-lung tumours irrespective of the total RT dose applied ($p = 0{\cdot}03$).

Billiet et al. studied PORT patients in three groups: patients who received RT via Co-60, patients receiving RT via LINAC, and patients receiving RT with both Co-60 and LINAC simultaneously. The overall survival rates of the LINAC group were 13% higher and local recurrence was 10% lower than the mean.[21] It is important to note that all of the patients included in our study were treated with a LINAC.

The modality of the treatment of PORT in the clinic has been upgraded to field-in-field and intensity-modulated radiation therapy (IMRT) starting from 2012. Until then, all the patients received 2D or 3D conformal radiotherapy. These patients received doses ranging from 50 to 66 Gy and even the fraction dose was not constant (1·8 or 2 Gy). These differences in the dose scheme may have had negative impact on the study. Another limitation was the lack of chemotherapy information. Only 32 out of 61 patients' info was reachable. Also higher total number of patients would have yielded more decisive results.

CONCLUSIONS

Wider treatment regions were exposed with Co-60 in many of the previously published PORT studies on patients diagnosed with and operated on for NSCLC. In our study, the results on overall survival and local control are compatible with other LINAC-based studies. The study shows better overall survival results with 3D-conformal modality with respect to 2D treatment. Today 3D-conformal PORT is accepted as the standard treatment by many clinicians for operable stage II-III disease. In the light of all the related studies, prospective randomised studies assessing adjuvant RT are needed based on modern radiotherapy standards such as field-in-field and IMRT.

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Conflicts of Interest

None.

References

1. Halperin E C, Perez C A, Brady L W. Principles and Practice of Radiation Oncology, Wolters Kluwer, Lippincott Williams & Wilkins, Philadelphia, USA, 6th edition. 2013: 939–973.
2. Port Meta-Analysis Trialist Group. Postoperative radiotherapy in non small cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomised clinical trials. Lancet 1998; 352: 257–263.
3. Chung C K, Stryker J A, O'Neill M Jr, DeMuth W E Jr. Evaluation of adjuvant postoperative radiotherapy for lung cancer. Int J Radiat Oncol Biol Phys 1982; 8: 1877–1880.
4. Kirsh M, Sloan H. Mediastinal metastases in bronchogenic carcinoma: influence of postoperative irradiation, cell type and location. Ann Thorac Surg 1982; 33: 459–463.
5. Douillard J Y, Rosell R, De Lena M. Impact of post-operative radiation therapy on survival in patients with complete resection and stage I, II or IIIA non-small cell lung cancer treated with adjuvant chemotherapy: The Adjuvant Navelbine International Trialist Association (ANITA)

randomized trial. Int J Radiat Oncol Biol Phys 2008; 72: 695–701.

6. Lally B E, Zelterman D, Colasanto J M, Haffty B G, Detterbeck F C, Wilson L D. Postoperative radiation therapy for stage II or III non-small cell lung cancer using the surveillance, epidemiology, and end results database. J Clin Oncol 2006; 24: 2998–3006.
7. Le Péchoux C, Dunant A, Pignon J P et al. Need for a new trial to evaluate adjuvant postoperative radiotherapy in non-small cell lung cancer patients with N2 mediastinal involvement. J Clin Oncol 2007; 25: e10–e11.
8. Lung Cancer Study Group. Effects of postoperative mediastinal radiation on completely resected Stage II and Stage III epidermoid cancer of the lung. N Engl J Med 1986; 15: 1377–1381.
9. Medical Research Council Lung Cancer Working Party. The role of postoperative radiotherapy in non-small cell lung cancer: a multicentre randomised trial in patients with pathologically staged T1-2, N1-2, M0 disease. Br J Cancer 1996; 74: 632–639.
10. Dai H, Hui Z, Ji W et al. Postoperative radiotherapy for resected pathological stage IIIA-N2 non-small cell lung cancer: a retrospective study of 221 cases from a single institution. Oncologist 2011; 16: 641–650.
11. Liu W S, Zhao L J, Wang S et al. Benefits of postoperative radiotherapy in multimodality treatment of resected small-cell lung cancer with lymph node metastasis. Eur J Surg Oncol 2014; 40 (9): 1156–1162.
12. Corso C D, Rutter C E, Wilson L D, Kim A W, Decker R H, Husain Z A. Re-evaluation of the role of postoperative radiotherapy and the impact of radiation dose for non-small-cell lung cancer using the National Cancer Database. J Thorac Oncol 2015; 10 (1): 148–155.
13. Shen W Y, Ji J, Zuo Y S et al. Comparison of efficacy for postoperative chemotherapy and concurrent radio-chemotherapy in patients with IIIA-pN2 non-small cell lung cancer: an early closed randomized controlled trial. Radiother Oncol 2014; 110 (1): 120–125.
14. Sawyer T E, Bonner J A, Gould P M et al. Effectiveness of postoperative irradiation in stage IIIA non small cell lung cancer according to regression tree analysis of recurrence risks. Ann Thorac Surg 1997; 64: 1402–1407 discussion 1407–1408.
15. Jazieh A R, Hussain M, Howington J A et al. Prognostic factors in patients with surgically resected stages I and II non-small cell lung cancer. Ann Thorac Surg 2000; 70: 1168–1171.
16. Caro J J, Salas M, Ward A, Goss G. Anemia as an independent prognostic factor for survival in patients with cancer: a systemic, quantitative review. Cancer 2001; 91: 2214–2221.
17. Moretti L, Yu D S, Chen H et al. Prognostic factors for resected non-small cell lung cancer with pN2 status: implications for use of postoperative radiotherapy. Oncologist 2009; 14: 1106–1115.
18. Mantovani C, Levra N G, Filippi A R et al. Postoperative radiotherapy for patients with completely resected pathologic N2 non-small-cell lung cancer: a retrospective analysis. Clin Lung Cancer 2013; 14 (2): 194–199.
19. Zou B, Xu Y, Li T et al. A multicenter retrospective analysis of survival outcome following postoperative chemo-radiotherapy in non-small-cell lung cancer patients with N2 nodal disease. Int J Radiation Oncology Biol Phys 2010; 77: 321–328.
20. Karakoyun-Çelik O, Yalman D, Bolukbasi Y, Cakan A, Cok G, Ozkok S. Postoperative radiotherapy in the management of resected non-small-cell lung carcinoma: 10 years experience in a single institute. Int J Radiation Oncology Biol Phys 2010; 76: 433–439.
21. Billiet C, Decaluwé H, Peeters S et al. Modern post-operative radiotherapy for stage III non-small cell lung cancer may improve local control and survival: a meta-analysis. Radiother Oncol 2014; 110 (1): 3–8.
22. Astudillo J, Conill C. Role of postoperative radiation therapy in stage IIIA non-small cell lung cancer. Ann Thorac Surg 1990; 50: 618–623.
23. Green N, Kurohara S S, George F W III, Crews Q E Jr III. Postresection irradiation for primary lung cancer. Radiology 1975; 116: 405–407.
24. Choi N C, Grillo H C, Gardiello M, Scannell J G, Wilkins E W Jr. Basis for new strategies in postoperative radiotherapy of bronchogenic carcinoma. Int J Radiat Oncol Biol Phys 1980; 6: 31–35.
25. Paterson R, Russell M H. Clinical trials in malignant disease. IV-Lung cancer. Value of postoperative radiotherapy. Clin Radiol 1962; 13: 141–144.
26. Robinson C G, Patel A P, Bradley J D et al. Postoperative radiotherapy for pathologic N2 non-small-cell lung cancer treated with adjuvant chemotherapy: a review of the National Cancer Database. J Clin Oncol 2015; 33 (8): 870–876.
27. Chen S, Cheng YL, Li S T, Ni Y J, Gu B. Effect analysis of chemoradiotherapy after operation in patients with stage III A non-small cell lung cancer. Asian Pac J Trop Med 2012; 5 (10): 823–827.
28. Kim B H, Kim H J, Wu H G et al. Role of postoperative radiotherapy after curative resection and adjuvant chemotherapy for patients with pathological stage N2 non-small-cell lung cancer: a propensity score matching analysis. Clin Lung Cancer 2014; 15 (5): 356–364.

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