RESEARCH ARTICLE

Underutilization of Curative Treatment among Patients with Non Small Cell Lung Cancer: Experience from a Tertiary Care Centre in India

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Abstract

Background: Lung cancer is one of the commonest and most lethal cancers throughout the world. The majority of the patients present at advance stage and are not suitable for curative intent treatment. Even among patients with localized disease, there has been underutilization of curative treatment modalities. The aim of this study was to analyze the radical treatment utilization rates in patients with non small cell lung cancer (NSCLC) treated at our centre. Materials and Methods: We analyzed case records of 104 patients with a pathologically confirmed diagnosis of NSCLC having stage 1-3B disease who were treated at our centre over last 3 years, to assess the utilization of curative treatment modalities i.e. surgery or radical radiotherapy. Results: The median age of this cohort was 58 years. Out of 104 patients only 33 (31.7%) received curative intent treatment, 14 undergoing curative resection and 19 receiving radical doses of radiotherapy. The baseline characteristics of both the groups (with or without radical treatment) were not different. Major factors associated with underutilization with curative treatment were progressive disease or loss of follow up after chemotherapy and inappropriate use of TKI and/or palliative radiotherapy in patients with stage 1-3B disease. Patients who did not receive radical treatment had inferior PFS and OS than those who received radical treatment. Conclusions: In our practice we observed gross underutilization of curative intent treatment modalities in patients with NSCLCs which is associated with inferior survival.

Keywords: Non small cell lung cancer - treatment utilization - curative intent treatment - India

Asian Pac J Cancer Prev, **15 (6)**, 2875-2878

Introduction

Lung cancer is one of the commonest cancers and cause of cancer related mortality worldwide. It accounts for 12.7% of all new cancer cases and 18.2% of all cancer related deaths, throughout the world (Parkin DM). In India, it is the commonest and most lethal cancer among males accounting for 10.9% of all cancer cases and 13% of cancer related mortality (Parkin DM). Despite recent advances in biological understanding and newer treatment modalities, the overall outcome of lung cancer remains poor. Survival is better in patients who receive optimum anticancer treatment compared with those who do not (Fry et al., 1999). In a disease with increasing incidence and poor survival, outcome can only be improved with the delivery of adequate anticancer treatment and early diagnosis.

There are variations in delivery and utilization of treatment in lung cancer worldwide. In actual practice, a large number of patients of lung cancer do not receive any anticancer treatment. These figures vary from 19% in USA, 33% in Australia, 37% in Scotland, and 50% in Ireland and New Zealand (Mahmud et al., 2003; Stevens et al., 2007; Erridge et al., 2008; Vinod et al., 2008). Even among patients receiving anticancer treatment, there is gross underutilization of curative treatment modalities. Studies from United States demonstrate that 30-60% of cases of early stage lung cancer don't undergo surgery (Esnaola et al., 2008; Cykert et al., 2010a). Similarly only 36-70% patients receive radiotherapy in contrast to guideline recommendation of radiotherapy use requirement in up to 76% of lung cancer patients (Delaney et al., 2005).

There are many valid reasons because of which optimum treatment can't be administered in lung cancer. Most patients present with advanced disease that is often incurable. This leads clinicians to therapeutic nihilism. Old age, co morbidities, poor performance status and social reasons are other factors which limit the ability to treat patients optimally. There is paucity of data regarding

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treatment utilization rates and patterns in NSCLC from India.

In context of lung cancer, particularly non small cell lung cancer (NSCLC), radical treatment consists of surgery and radical doses of radiotherapy with or without chemotherapy (Ustaalioglu et al., 2013). Majority of the patients present with advanced stage disease which is not amenable to curative treatment modalities. We analyzed records of our patients with NSCLC who were registered at our centre in last 3 years, which is a regional cancer centre registering approximately 8000 new cancer cases every year.

Materials and Methods

We screened case records of 370 consecutive, pathologically confirmed non small cell lung cancer patients, registered at our centre in Lung Cancer Chemotherapy Clinic between July 2008 and June 2011 (a period of 3 years). This clinic is primarily run by medical oncology team in close collaboration with pulmonologists, surgical oncologists and radiation oncologists. Approximately 3-5 new cases of lung cancer are registered at this clinic every week. The cases are referred from various general and speciality hospitals of northern India. Clinical, demographic, treatment and outcome related informations were collected from case record files and entered in a predesigned proforma. Disease was restaged according to AJCC staging system 7th edition based on the available clinical and radiological findings. Patients were treated as per departmental treatment protocols according to disease stage, performance status, co morbidities and patient's preference. Permission for viewing case records was obtained from the institute's committee and the medical record department. Confidentiality of the patient's identity was maintained.

Patients were considered on continuous follow up if the last visit was within 3 months of data censoring. In cases where last visit was more than 3 months ago, attempts were made to contact the patients by telephone and/or a reply letter. Patients were followed from the date of registration to the date of death and were censored at the date they were last known to be alive i.e. date of last follow up (if lost to follow-up) or May 31, 2012, whichever came first.

Statistical analysis

The data was censored on 31st May 2012 or last follow up date (if lost to follow up). Descriptive statistics was used for describing demographic and clinical characteristics. For comparison of two groups (patients receiving or not receiving radical treatment) Chi square and Fischer Exact test were used. Logistic regression was used to estimate odds ratio. The Survival was estimated by the Kaplan–Meier method. Overall survival was defined as duration from registration till death due to any cause and progression free survival was defined as duration from registration till occurrence of disease progression or death. Analysis was done using the Stata software (Release 9.0, Stata Corp.).

Results

A total of 370 pathologically confirmed cases of NSCLC were identified. Only 261 (70.54%) patients received some form of anticancer treatment. Out of these 261 patients, 68 (26.05%) were stage 1-3A who were potentially resectable and 104 (39.8%) were of stage 1-3B who were amenable to radical treatment modalities. Remaining 157 patients were of stage 4 disease and excluded from further analysis. Only 33 out of these 104 (31.7%) patients received curative intent treatment, i.e. surgery or radical radiotherapy. Out of these 33 patients, 14 underwent surgery and 19 received radical doses of radiotherapy as curative treatment modality. The median age of this cohort was 58 years (range 36-78 years) with male: female ratio of 10:1. Squamous cell carcinoma was the most common histological subtype among these patients. Radical radiotherapy was delivered either upfront as primary treatment modality (1 patient) or in a sequential manner (18 patients) after 4-6 cycles of chemotherapy. Most of the patients received radiotherapy doses between 45-60 Gy through conventional fractionation. Two patients underwent stereotactic body radiation (SBRT) and received a dose of 40 Gy in 10 fractions. Most common chemotherapy regimen used was the combination of Paclitaxel and Carboplatin (93.3%). Among 14 patients, who underwent surgery, 5 patients received neo adjuvant chemotherapy, 4 patients received adjuvant chemotherapy and 6 patients received post op radiotherapy.

Comparison of the baseline characteristics of the patients receiving or not receiving radical treatment despite having stage 1-3 B disease is shown in Table 1. There was no statistically significant difference between the two groups for all factors. Stage differences were of borderline significance (p=0.054).

Table 1. Comparison of Baseline Characteristics of Patients Who Received and Who didn't Receive Radical Treatment

Variable		Received radical treatment (n=33)	Didn't receive radical treatment (n=71)	p	OR (95% CI)
Age	<60	21 (63.64%)	43 (60.56%)	0.76	1
	>60	12 (36.36%)	28 (39.44%)		0.87(0.37-2.06)
Sex	Male	30 (90.91%)	59 (83.1%)	0.29	1
	Female	3 (9.09%)	12 (16.9%)		0.49 (0.12-1.87)
Smoking	No	7 (23.33%)	57 (81.43%)	0.585	1
	Yes	23 (76.67%)	13 (18.57%)		0.74 (0.26-2.11)
PS	≤2	28 (96.55%)	63 (94.03%)	0.61	1
	>2	1 (3.45%)	4 (5.97%)		0.56(0.06-5.26)
Stage	1-3A	26 (78.78%)	42 (59.15%)	0.054	1
	3B	7 (21.21%)	29 (40.84%)		0.38 (0.14-1.01)
Histology					
Squamous		17 (51.52%)	31 (43.66%)		1
Adenocarcinoma		9 (27.27%)	23 (32.39%)	0.46	0.71(0.2-1.88)
Large cell		1 (3.03%)	0		
BAC		1 (3.03%)	1 (1.41%)	0.67	1.82(0.1-31.03)
NOS		5 (15.15%)	16 (22.54%)	0.34	0.5 (0.17-1.82)
Hemoglobin	≥12	11 (44%)	37 (63.79%)	0.09	1
	<12	14 (56%)	21 (36.21%)		2.24 (0.86-5.82)
Albumin	≥3.5	18 (85.7%)	38 (80.85%)	0.62	1
	<3.5	3 (14.29%)	9 (19.15%)		0.70 (0.17-2.91)

*PS-Performance status; BAC-Bronco-alveolar carcinoma; NOS-not otherwise specified)

Table 2. Treatment Received and Responses in Patients who Received and Who didn't Receive Radical Treatment

Variable		Received radical treatment (n=33)	Didn't receive radical treatment (n=71)	p=
Surgery		14 (42.42%)	0	
Stage (if operated)			-	
	1A and B	4 (28.57%)		
	2A	2 (14.29%)		
	2B	3 (21.43%)		
	3A	5 (35.71%)		
RT	Radical RT	19 (57.58%)	0	
	PORT	6 (18.18%)		
	No RT	8 (24.24%)		
	Palliative RT	0	30 (42.2%)	
Chemotherapy				
	No Chemotherapy	6 (18.18%)	20 (28.17%)	<0.001
	Chemotherapy	27 (81.81%)	51 (71.84%)	
	Pre Operative	5 (15.15%)		
	Adjuvant (after Surgery)	4 (12.12%)		
	Pre RT	18 (54.54%)		
Response to Chemotherapy (NACT)				
	CR	4 (17.39%)	0	
	PR	14 (65.22%)	13 (25.49%)	
	SD	4 (17.39%)	9 (17.65%)	<0.001
	PD	0	17 (33.33%)	
	NA	0	12 (23.53%)	

*PORT-post operative radiotherapy; NACT-neo adjuvant chemotherapy, CR-complete response, PR-partial response, SD-stable disease, PD-progressive disease, NA-not available

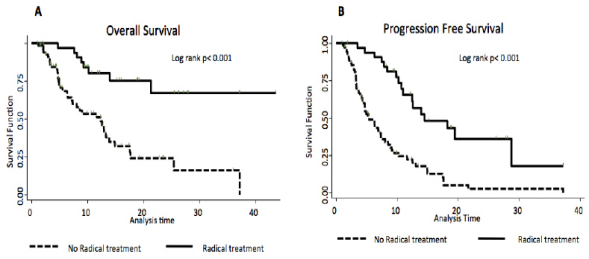

Figure 1. A) Overall Survival of Patients Who Received and Who Didn't Receive Radical Treatment; B) Progression Free Survival of Patients Who Received and Who Didn't Receive Radical Treatment

Details of treatment received are shown in Table 2. Out of 71 patients who didn't receive radical treatment, 20 (28.17%) didn't receive any chemotherapy. They were treated either with TKI (tyrosine kinase inhibitors) with or without palliative radiotherapy or palliative radiotherapy alone. In this group of patients who didn't receive radical treatment, 51 (71.8%) received chemotherapy but 29 (56.8%) of these patients either had progressive disease or not evaluated for response (lost to follow up). On the other hand, in radical treatment arm, 27 out of 33 (81.8%) received chemotherapy and none of them had disease progression after chemotherapy.

After a median follow up time of 18.4 months, the median PFS was 14.47 months for the patients who received radical treatment and 5.36 months for the patients who did not received (p<0.001). Median OS for the patients who didn't received radical treatment was 12.3 months while for patients who have received radical treatment, median hasn't reached (p<0.001).

Discussion

Majority of the patients of NSCLC usually present in advanced stage and generally are not suitable for curative treatment. The management of NSCLC involves multidisciplinary approach and optimal use of the available treatment modalities. Guidelines recommend surgery or radical doses of radiotherapy along with chemotherapy for stage 1-3A, radical radiotherapy with chemotherapy for stage 3B and palliative chemotherapy with or without palliative radiotherapy or TKIs for stage 4 disease (Crino et al., 2010; Peters et al., 2012a; 2012b). In actual practice, not all patients receive the optimum treatment (Vinod et al., 2010). The reasons may be poor PS, advance age, co morbidities, social factors and patient's preference.

We demonstrated in this study that in our practice 29.46% patients of NSCLC didn't receive any anticancer treatment and out the patients who were amenable to radical treatment approach, only 31.7% could receive the curative intent treatment. Treatment utilization rates in lung cancer varies worldwide and so the optimal treatment rates. In our cohort only 15% of potentially resectable patients could undergo surgery. These figures vary from 40-70% in studies from United States. Racial differences in proportion of patients undergoing surgery, apart from disease related factors and co morbidities have been observed in these studies (Esnaola et al., 2008; Cykert et al., 2010b). It is estimated that 61-76% patients would require radiotherapy at some point of time, if used optimally in lung cancer but in actual practice up to 40% receive it (Tyldesley et al., 2001; Delaney et al., 2003). In our group of patients only 18.26% (19/104) patients could receive radical doses of radiotherapy.

Underutilization of treatment strategies results in poor survival in lung cancer (Fry et al., 1999). This is evident from our analysis also which demonstrate a clear difference in survival of patients treated adequately with curative intent versus remaining patients. Major reasons for inferior survival observed in this population were progressive disease or lost to follow up while being on chemotherapy and many patients (28.17%) were treated with palliative intent only with palliative radiotherapy or TKI. In our analysis we found that patients who didn't receive chemotherapy or had progressive disease or lost to follow up had more likelihood of not receiving radical treatment. Patients who have progressive disease on one treatment modality are anyway more likely to have inferior outcome but on the other hand if the curative modalities are instituted early in the course of the disease, some of these patients could be salvaged. We didn't found any difference in terms of age, performance status, stage, histology, haemoglobin or serum albumin. This may be due to selection and referral bias in hospital based data which is reflected by the fact that majority of the patients of this cohort had a good performance status.

This is a single centre data from India, which reflects inadequacy of treatment utilization in patients with NSCLC. A bigger population based data including all patients whether treated or not, could show the actual scenario of treatment utilization rates and pattern in this country. Another limitation of this study was its

retrospective nature because of which we could not analyze various other factors like social factors, treatment delay, distance from patient's residence etc which might have resulted in sub optimum treatment utilization.

In conclusion, in actual practice, there is gross underutilization of curative treatment options in the management of NSCLC. The use of radical treatment modalities is associated with significantly better outcome. Every attempt should be made for optimum utilization of all the treatment modalities in the management of NSCLC.

References

Crino L, Weder W, van Meerbeeck J, et al (2010). Early stage and locally advanced (non-metastatic) non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*, **21**, 103-15.

Cykert S, Dilworth-Anderson P, Monroe MH, et al (2010). Factors associated with decisions to undergo surgery among patients with newly diagnosed early-stage lung cancer. *JAMA*, **303**, 2368-76.

Delaney G, Barton M, Jacob S, Jalaludin B (2003). A model for decision making for the use of radiotherapy in lung cancer. *Lancet Oncol*. **4**, 120-8.

Delaney G, Jacob S, Featherstone C, Barton, M (2005). The role of radiotherapy in cancer treatment: estimating optimal utilization from a review of evidence-based clinical guidelines. *Cancer*, **104**, 1129-37.

Erridge SC, Murray B, Price A, et al (2008). Improved treatment and survival for lung cancer patients in South-East Scotland. *J Thorac Oncol*, **3**, 491-8.

Ettinger DS (2012). NCCN Clinical Practice Guidelines in Oncology for Non Small Cell Lung Cancer, Ver 2.2012.

Esnaola NF, Gebregziabher M, Knott K, et al (2008). Underuse of surgical resection for localized, non-small cell lung cancer among whites and African Americans in South Carolina. *Ann Thorac Surg*, **86**, 220-6.

Fry WA, Phillips JL, Menck HR (1999). Ten-year survey of lung cancer treatment and survival in hospitals in the United States: a national cancer data base report. *Cancer*, **86**, 1867-76.

Mahmud SM, Reilly M, Comber H (2003). Patterns of initial management of lung cancer in the Republic of Ireland: a population-based observational study. *Lung Cancer*, **41**, 57-64.

Parkin DM FJ, GLOBOCAN (2008). Cancer Incidence and Mortality Worldwide.

Peters S, Adjei AA, Gridelli C, et al (2012). Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*, **23**, 56-64.

Stevens W, Stevens G, Kolbe J, Cox B (2007). Lung cancer in New Zealand: patterns of secondary care and implications for survival. *J Thorac Oncol*, **2**, 481-93.

Tyldesley S, Boyd C, Schulze K, Walker H, Mackillop WJ (2001). Estimating the need for radiotherapy for lung cancer: an evidence-based, epidemiologic approach. *Int J Radiat Oncol Biol Phys*, **49**, 973-85.

Ustaalioglu BBO, Unal OU, Turan U , et al (2103) Prognostic factors for lymph node negative stage I and IIA non-small cell lung cancer: multicenter experiences. *Asian Pac J Cancer Prev*, **14**, 6287-92

Vinod SK, O'Connell DL, Simonella L, et al (2008). Gaps in optimal care for lung cancer. *J Thorac Oncol*, **3**, 871-9.

Vinod SK, Sidhom MA, Gabriel GS, Lee MT, Delaney GP (2010). Why do some lung cancer patients receive no anticancer treatment? *J Thorac Oncol*, **5**, 1025-32.