

# Patterns of failure in patients with lung carcinoma after treatment by different modalities

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## Abstract

**Background:** Lung cancer is a major health problem worldwide. Patterns of failure can be local (lung parenchyma, bronchial stump, chest wall), regional (mediastinal lymph nodes) or distant (brain, liver and bone). **Aim:** To study the patterns of failure in patients with lung carcinoma after treatment by different modalities. **Material and Methods:** Patients with histologically confirmed Carcinoma Lung, registered between January 2008 to December 2012 and treated by Radiotherapy/Chemotherapy/Surgery or any combined modality were included. Follow up details were thoroughly studied with regard to loco-regional failure, distant failure, overall survival. **Results:** Only 558 (out of 714) patients were available for evaluation after completion of treatment. 34 patients (6.09%) had complete response, 128 patients (22.94%) had partial response and 122 patients (21.86%) had stable disease. 274 patients (49.10%) had progression of disease. 19 patients have recurrence of the disease out of 34 patients who had complete response. 27 patients with squamous cell cancer who had complete response, 16 recurred and out of 6 patients with adenocarcinoma who had complete response, 3 had recurrence. 3 patients had local, 2 had regional, 2 had loco-regional, 6 had distant and 6 had local+ regional +distant failure. **Conclusion:** Educating people about lung cancer, smoking cessation, early diagnosis, early treatment, nutritional support, combined modality of treatment and proper follow-up can help these patients reduce failures and improve survival. **Keywords:** Lung carcinoma, Radiotherapy, Chemotherapy, Surgery, combined treatment modality, pattern of failure.

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## INTRODUCTION

Lung cancer is a major health problem worldwide. The incidence is increasing globally at a rate of 0.5% per year. It is the leading cause of cancer mortality in most of the countries in the world.<sup>1</sup> In Kashmir it ranks second among all cases in males. Non-small cell lung cancer accounts for

nearly 85% and small cell lung cancer accounts for 15% to 20% of cases.<sup>2</sup> In Kashmir, the annual crude incidence rate of lung cancer was 4.005 per 100000 populations, being 6.55/100 000 in males and 1.18/100000 in females.<sup>3</sup> The patterns of failure in lung cancer seem to differ by cell type (histology), pathologic stage and by the treatment modality instituted. Patterns of failure can be local (lung parenchyma, bronchial stump, chest wall), regional (mediastinal lymph nodes) or distant (brain, liver and bone). Locoregional recurrences are reported in up to 85% of the patients after radiochemotherapy for locally advanced non-small cell lung cancer.<sup>4,5</sup> In the present study was conducted to study the patterns of failure in patients with lung carcinoma after treatment by different modalities.

## MATERIAL AND METHODS

Patients with histologically confirmed Carcinoma Lung, registered at Sher-i-Kashmir Institute of Medical Sciences Soura, Srinagar between January 2008 to December 2012 and treated by Radiotherapy/Chemotherapy/Surgery or any combined modality were included in the study. This was a retrospective study in which patient characteristics with regard to gender, age, presentation, locality, investigations, treatment prescribed and treatment received in each case were studied in detail. Follow up details were thoroughly studied with regard to loco-regional failure, distant failure, overall survival and other co-morbid conditions related to treatment.

### Inclusion criteria

- Patients with histologically confirmed Carcinoma Lung.
- Patients who had completed prescribed treatment.
- Patients on follow up for 2 years after completion of treatment.

### Exclusion criteria

- Patients who have not completed treatment i.e. defaulters.
- Second malignancy.

The observations were statistically analyzed by using Descriptive Statistics (in percentage and average).

## RESULTS

Most of the patients were from Srinagar (32.77%) followed by Baramulla (12.09%), Anantnag (11.57%), Budgam (10.81) and Pulwama (9.87%). In Kashmir province, low prevalence of lung cancer in districts Kupwara (4.60%), Shopian (3.06%), Bandipora (3.15%) and Kulgam (3.57%). Out of 1175 patients, 15 (1.28%) patients were 30 or less than 30 years of age. Most number of patients were in the age group 51-60 years (33.87%). 80.43% patients were between 41-70 years of age. Median age for lung cancer was 57 years. 966 patients (82.21%) were males and 209 (17.79%) were females. Male:Female ratio is 4.6:1. Out of 1175 patients, 912 (77.62%) patients' smokers and 263 (22.38%) were non-smokers. 81.57% male patients were smoker and 18.43% were non-smokers, while among female patients, 59.33% were smokers and 40.67% were non-smokers. Out of 1175 patients, histological status was known in 1154 only. Most of the patients have non-small cell lung cancer (81.88%). Only 209 patients (18.11%) have small cell cancer. Among NSCLC, squamous cell cancer was most common (61.44%) and 18.11% patients have adenocarcinoma. Other histologies were only 2%.

Table 1: Treatment Received

Treatment Modality	Year					Total	%
	2008	2009	2010	2011	2012		
EBRT	11	14	18	18	21	82	8.68
Chemotherapy	10	13	16	17	20	76	8.04
Surgery	3	3	4	4	5	19	2.01
R+C	46	60	74	75	91	346	36.61
R+S	1	2	3	3	3	12	1.27
C+S	9	12	14	15	17	67	7.09
R+C+S	15	20	24	24	29	112	11.85
No Rx	21	27	33	34	41	156	16.51
Defaulters	8	10	11	11	11	51	5.40
Palliative Rx	3	4	5	5	7	24	2.54
<b>Total</b>	<b>127</b>	<b>165</b>	<b>202</b>	<b>206</b>	<b>245</b>	<b>945</b>	

Treatment modalities received by patients were:

- Radiotherapy only (45Gy + 15Gy; 2Gy/#, 5#/week) - 82 (8.68%) patients received this modality.
- Chemotherapy only - Type of chemotherapy given depends on the histology.
- Combinations include: Paclitaxel and Cisplatin, Gemcitabine and Cisplatin/Carboplatin and Pemetrexed and Cisplatin. 76 (8.04%) patients received chemotherapy only.
- Surgery only - Surgeries done were wedge resection, lobectomy, and pneumonectomy. 19 (2.01%) patients underwent surgery only.
- Radiotherapy (45Gy + 15Gy; 2Gy/#, 5#/week) + Chemotherapy- Either concurrent or sequential. 346 (36.61%) patients received this modality.
- Radiotherapy (45Gy; 2Gy/#, 5#/week) + Surgery - 12 (1.27%) patients received this.
- Chemotherapy + Surgery- Either adjuvant or neo-adjuvant. 67 (7.09%) patients received this.
- Radiotherapy (45Gy; 2Gy/#, 5#/week) + Chemotherapy + Surgery- 112 (11.85%) patients received triple modality of treatment.

Out of 1154 patients, 945 were available for follow up and 714 patients completed the treatment and rest of the patients either didn't want to receive any treatment or defaulted. 24 patients (2.54%) received palliative treatment (EBRT) to metastatic sites only. Most of the patients (36.61%) received Radiotherapy + Chemotherapy. 11.85% patients received triple modality i.e. Radiotherapy + Chemotherapy + Surgery, 8.68% EBRT only and 8.04% chemotherapy only. 19 patients (2.01%) underwent surgery only.

**Table 2: Response Evaluation After Definitive Treatment**

Modality	Response				Total
	Complete	Partial	Stable	Progressive	
EBRT	0	16	17	26	59
Chemotherapy	1	14	20	23	58
Surgery	2	7	0	1	10
C+S	7	1	4	26	38
R+C	7	71	70	141	289
R+S	2	0	0	6	8
R+C+S	15	19	11	51	96
Total	34	128	122	274	558
%age	6.09	22.94	21.86	49.10	

Only 558 (out of 714) patients were available for evaluation after completion of treatment. 34 patients (6.09%) had complete response, 128 patients (22.94%) had partial response and 122 patients (21.86%) had stable disease. 274 patients (49.10%) had progression of disease.

**Table 3: Patterns of Failure**

Site	Treatment Modality					Total
	Surgery	C+S	R+C	R+S	R+S+C	
Local	-	4	3	-	4	11
Regional Nodes	-	-	-	-	-	-
Supraclavicular	-	-	1	-	1	2
Mediastinal	-	1	-	-	1	2
Tracheal	-	-	-	-	1	1
Distant Sites	-	-	-	-	-	-
Brain	1	2	-	-	1	4
Contralat.Lung	-	1	-	-	2	3
Liver	-	-	-	-	1	1
Adrenals	-	1	-	-	-	1
Axillary Nodes	-	-	1	-	-	1
Bones	-	-	-	-	-	-
Sternum	1	-	-	-	-	1
Ribs	-	-	-	-	1	1
Dorsal spine	-	-	-	1	-	1
Lumbar spine	-	2	-	-	-	2

19 patients have recurrence of the disease out of 34 patients who had complete response. 27 patients with squamous cell cancer who had complete response, 16 recurred and out of 6 patients with adenocarcinoma who had complete response, 3 had recurrence. 16 squamous cell cancer patients who recurred, 2 had underwent surgery, 4 received chemotherapy + surgery, 3 received radiotherapy + chemotherapy and 7 had received triple modality. Out of 3 adenocarcinoma patients, 1 had received chemotherapy + surgery, 1 received radiotherapy + surgery and 1 received triple modality. 3 patients had local, 2 had regional, 2 had loco-regional, 6 had distant and 6 had local+ regional +distant failure. 3 patients who had local recurrence, 1 received chemotherapy + surgery, 1 received radiotherapy + chemotherapy and 1 received triple modality. Both the patients who had regional recurrence, received triple modality. Patients with loco-regional recurrence, 1 had received chemotherapy + surgery and 1 had received radiotherapy + chemotherapy. Among patients with distant failure, 2 received surgery, 1 received chemotherapy + surgery, 1 received radiotherapy + surgery and 2 received triple modality. Out of 6 patients with local + regional + distant failure, 3 received triple modality, 1 received radiotherapy + chemotherapy and 2 received chemotherapy + surgery.

**Table 4: Overall survival: Treatment wise**

Treatment	1 year	2 year	3 year	5 year
EBRT	40.24	14.63	0	0
Chemotherapy	59.21	18.42	5.26	0
Surgery	68.42	36.84	15.89	5.26
R + C	80.06	23.99	4.91	0.29
R + S	41.67	25	0	0
C + S	71.64	22.38	8.96	0
R + S + C	85.71	55.37	14.29	1.79

## DISCUSSION

A total of 14401 cancer patients were registered from 1st January 2008 to 31 December 2012, out of which 1761(12.23%) were lung cancers which is compatible with study by Jemal A *et al.*<sup>6</sup> Out of 1761 lung cancer patients records of only 1175 were available for analysis. In present study, 945 (81.89%) patients had non-small cell lung carcinoma (NSCLC) while 209 (18.11%) had small cell carcinoma, which was comparable to study by NA Khan *et al.*<sup>2</sup> Among NSCLC patients, 709 (61.44%) had squamous cell carcinoma and 214 (18.54%) had adenocarcinoma. Other histologies were large cell carcinoma (1.21%) and adenoid cystic cell carcinoma (0.69%). 574 (80.96%) patients with squamous cell Ca were smokers and 135 (19.04%) were non-smokers, while 121 (56.54%) patients with adenocarcinoma were smokers and 93 (43.46%) were non-smokers. 607 (85.61%) patients with squamous cell cancer were males and 102 (14.39%) were females while among patients with adenocarcinoma 153 (71.50%) were males and 61 (28.50%) were females. Out of 945 patients only 714 completed the prescribed treatment, rest of the patients either refused the treatment or defaulted. Out of those 714 patients, 558 were available for evaluation of response. Follow up investigations include chest X-ray, CECT chest/abdomen, bone scan CT/MRI head and PET-CT. Response was evaluated by using Responsive Evaluation Criteria in Solid Tumors (RECIST) Criteria (version 1.1). 34 (6.09%) patients had complete response, 128 (22.94%) had partial response, 122 (21.86%) had stable disease and 274 (49.10%) had progression of disease. Among 34 patients who had complete response, 1 (2.94%) received chemotherapy only, 2 (5.88%) underwent surgery only, 7 (20.59%) received chemotherapy and surgery, 7 (20.59%) received radiotherapy and chemotherapy, 2 (5.88%) received radiotherapy and underwent surgery and 15 (44.12%) patients received triple modality i.e., chemotherapy, radiotherapy and surgery. There was no complete response in any of the 59 patients who received radiotherapy only and median survival was 6 months only with this modality and 1 year and 2 years overall survival was 40.24% and 14.63% respectively which was in contrast to the results of studies by Schytte *et al.*<sup>7</sup> and JD Bradley *et al.*<sup>8</sup>

Among 34 patients who had complete response, 19 (55.88%) had recurrence of disease at one or more sites, with total number of failure sites 31. Out of those 19 patients, 3 (15.79%) had local failure, 2 (10.53%) had regional, 2 (10.53%) had loco-regional, 6 (31.58%) had distant and 6 (31.58%) had loco-regional plus distant failure. 8 patients had failure at more than one site. Among distant failures, most common site involved was bone in 5 patients followed by brain in 4 patients, followed by contralateral lung in 3 patients. Other distant sites were liver in 1 patient, adrenal gland in 1 patient and axillary nodes in 1 patient. Among bones, spine was most commonly involved in 3 patients, ribs in 1 and sternum was involved in 1 patient.

In our study, in chemotherapy alone group, only 1 (1.72%) out of 58 had complete response and remained disease free i.e. did not develop failure, results may be biased due to smaller sample size and 1 year, 2 years, 3 years and 5 years survival was 59.21%, 18.42%, 5.26% and 0% respectively. In surgery alone, 2 (20%) out of 10 patients had complete response and both patients developed failures and both patients had distant failure. In surgery plus chemotherapy, 7 (18.42%) out of 38 had complete response and 5 (71.43%) out of those 7 patients had failure. 2 (40%) had local, 1 (20%) had distant and 2 (40%) had loco-regional plus distant. In surgery alone, one, two and three-year overall survival was 68.42%, 36.84% and 15.89% respectively and 5 years survival was 5.26%. In surgery plus chemotherapy, one, two and three-year survival was 71.64%, 22.38% and 8.96% respectively and 5 years survival was 0%. These results show that surgery plus chemotherapy is better than surgery only, as shown by the study by Arriagada *et al.*<sup>9</sup> but results in terms of survival and disease free survival were in contrast to this study. In chemo-radiation group, 7 (2.42%) out of 289 had complete response and 3 (42.86%) out of those 7 patients had failure. 2 (66.67%) patients had loco-regional and 1 (33.33%) had loco-regional plus distant failure. These results were in contrast to study by Patel S *et al.*<sup>10</sup> In surgery plus chemo-radiation, 15 (15.63%) out of 96 patients had complete response and 8 (53.33%) out of those 15 patients developed failures. It was comparable to study by Patel S *et al.*<sup>10</sup> Three (37.5%) had loco-regional, 2 (25%) had distant and 3 (37.5%) had loco-regional plus distant



failure. In chemo-radiation group two, three and 5 years survival was 23.99% and 4.91% and 0.29% respectively and in surgery plus chemo-radiation 2, 3 and 5 years survival was 55.37% 14.29% and 1.79%. 2-years survival was comparable but 3 years and 5 years survival was less than in the study by Patel S *et al.*<sup>10</sup>

In surgery plus radiotherapy, 2 (25%) out of 8 had complete response and 1 (50%) out of those 2 patients had failure (distant) and one, two, three and five-years overall survival was 41.67%, 25%, 0.0% and 0.0% respectively. It was in contrast to the results of the study by Emami B *et al.*<sup>11</sup>

Median survival was 9 months (range 3-66 months). Survival was calculated from date of diagnosis to last follow up. Survival is better with combined treatment modalities i.e. R +S + C, R + C and C + S. The results of our study are in contrast to most of the other studies. This may be due to small sample size, poor compliance of patients to treatment and follow up.

## CONCLUSION

While the outcomes of patients with lung cancer appears to be improving with the advent of new chemotherapeutic agents, targeted therapy and advanced radiotherapy techniques, this disease continues to be associated with poor prognosis and high treatment failures. Better survivals were observed with combined treatment modalities. Triple modality treatment had highest survival rates followed by chemo-radiation. But the survival rates were lower and failure rates were higher than the other studies. Median survival was also low. This can be attributed to late presentation, poor compliance of patients to treatment and follow up, nutritional deficiencies and lack of well balanced diet. Educating people about lung cancer, smoking cessation, early diagnosis, early treatment, nutritional support, combined modality of

treatment and proper follow-up can help these patients reduce failures and improve survival.

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