

# Effects of Amifostine on Acute and Late Toxicity of Radiotherapy and Concurrent Chemotherapy for Local Advanced Non-small-cell Lung Cancer

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## Backgrounds

Lung cancer is the second common cancer and a leading cause of death in the United States. Non-small cell lung cancer accounts for 80% to 85% of all lung cancer cases. Chemoradiation therapy is a standard treatment in patients with local advanced non-small cell lung cancer. Although concurrent chemotherapy and radiotherapy have led to increased survival in patients with inoperable local advanced non-small cell lung cancer, this was made at the expense of increased toxicities as well. Treatment-related toxicity is often dose-limiting factors that significant affect treatment outcomes, patients' quality of life and can also result in treatment interruptions. We, therefore, retrospectively reviewed the patients who treated by concurrent chemoradiation therapy with and without amifostine at the University of Texas M. D. Anderson Cancer Center to evaluate amifostine reduces the major acute and late toxicities.

## Purpose

To compare the acute and late toxicities of patients with local advanced non-small-cell lung cancer treated by radiation treatment and concurrent chemotherapy with or without Amifostine.

## Methods and Materials

Clinical data were retrospectively analyzed for 193 LANSCLC patients treated with definitive three-dimensional conformal radiotherapy and concurrent chemotherapy from 1998 to 2006 at U.T. MD. Anderson Cancer Center. 71 patients were on Amifostine group and 122 patients were on control group. Total dose at the isocenter was 60 - 70 Gy, 18 - 2.0 Gy /fx, 30 - 37 fractions, 5 days/week for once daily group and 60 - 69.6 Gy, 1.2 Gy/fx, 50-58 fractions, 5 days/week with a minimal interaction interval of 6 hours for twice daily group (71 patients on protocols), respectively. Amifostine was given to 37 off protocol patients with larger gross tumor volume (GTV) to prevent normal tissue toxicities. The overall survival was analyzed using the Kaplan-Meier model. Test or chi-square was used to analyze among of the following clinical variables: gender, age, ethnic group, weight loss, performance status (KPS), smoking history, clinical stage, and total dose. Acute toxicities were analyzed including weight loss, esophagitis, pneumonitis, and skin reaction. And late toxicities were cardiac toxicity and lung fibrosis. Patients' characteristics are shown in Table 1.

Table 1. Patients characteristics

Patient & Treatment Characteristics	Control n=122		Amifostine n=71		p-value	Test
	Mean	Median	Mean	Median		
Age					0.105	t-test
Mean	60.5	62.8	61.5	65		
Median	61.5	65	62.8	65		
Range	36-80	34-81	34-81	34-81		
Ethnic Group					0.728	chi-square
White	101	60	60	60		
Black	12	6	6	6		
Hispanic	7	3	3	3		
Asian	1	2	2	2		
Othera	1	0	0	0		
Gender					0.313	chi-square
F	51	35	35	35		
M	71	36	36	36		
Stage					0.458	chi-square
3A	48	23	23	23		
3B	76	48	48	48		
Weight Loss					0.374	chi-square
<5%	97	51	51	51		
>=5%	25	18	18	18		
KPS					<0.001	chi-square
>=90	67	31	31	31		
<=90	50	3	3	3		
Unknown	6	37	37	37		
Total Dose JRT					0.0258	t-test
Mean	64.7	66.0	66.0	66.0		
Median	63.0	64.8	64.8	64.8		
Range	60-69.6	60-70	60-70	60-70		
Ever Smoked					0.616	chi-square
Yes	114	64	64	64		
No	6	6	6	6		
Unknown	2	1	1	1		

## Statistical Analysis

The endpoints of this study were weight loss, normal tissue acute toxicity (skin reaction, esophagitis and pneumonitis), normal tissue late toxicity (lung fibrosis and cardiac toxicity) and overall survival (OS). The survival with both treatments was described using Kaplan-Meier survival curves. The logrank test was used to compare overall survival between both groups. A p-value < 0.05 was considered statistically significant.

## Results

### Survivals

The median survival was 23.1 months in Amifostine arm vs. 23.0 months in control arm, and the overall 3 years survival rate was 37.8% in Amifostine group vs. 35.7% in control group, respectively,  $P = 0.7678$  (Figure 1).

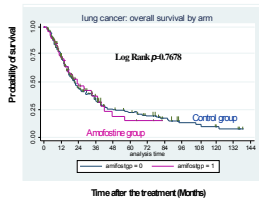
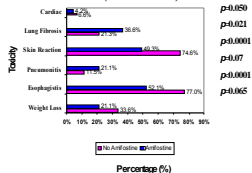


Figure 1. Overall survival for all the patients

## Toxicity

Analysis of toxicity data treated with and without Amifostine, there was significantly less any grade esophagitis (52.1% vs. 77.0%,  $p=0.0001$ ), skin reaction (49.3% vs. 74.6%,  $p=0.0001$ ) and grade 3 or higher esophagitis (11.3% vs. 23.0%,  $p=0.045$ ). Amifostine also has a trend to reduce any grade weight loss (21.1% vs. 33.6%,  $p=0.065$ ). However Amifostine group has shown significantly higher lung fibrosis (36.6% vs. 21.3%,  $p=0.021$ ) and had more pneumonitis (21.1% vs. 11.5%,  $p=0.07$ ) with borderline significance (Figure 2 and 3).

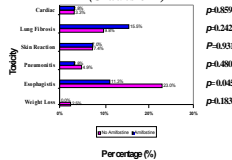
## Percent of Cases with Any Grade Treatment Toxicity by Group (Grades 1-4)



By Common Terminology Criteria for Adverse Events (CTC) v2.0

Figure 2. Any grade treatment toxicity by group

## Percent of Cases with High Grade Treatment Toxicity by Group (Grades 3-4)



By Common Terminology Criteria for Adverse Events (CTC) v2.0

Figure 3. High-grade treatment toxicity by group

## Conclusions

Amifostine had no apparent effect on survival in these patients with inoperable local advanced non-small-cell lung cancer, suggesting that it does not have a tumor-protective effect. Amifostine significantly reduced esophagitis for inoperable local advanced non-small-cell lung cancer patients. Our data showed that there was slightly higher rate of pneumonitis and significantly higher lung fibrosis in Amifostine group which might be related to larger GTV among off protocol patients. Further research is needed to identify the effect of Amifostine on pulmonary toxicity stratified by the GTV.

