

Site of Metastases as Prognostic Factors in Unselected Population of Stage IV Non-Small Cell Lung Cancer

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Abstract

Background: Advanced stage non-small cell lung cancer (NSCLC) is a heterogenous disease, yet, with the exception of targeted therapies, most guidelines recommended uniform treatment irrespective of tumor burden or sites of metastases and this may explain, in part, the wide range of responses to same lines of therapy. **Aim of work:** In this work we tried to explore the effect of metastatic sites in on overall survival (OS), in an unselected group of Non-small cell lung cancer patients who received different treatments line. **Methods:** A retrospective analysis was performed on patients with stage IV NSCLC who received systemic treatment at UAB Cancer Center (NCI designated comprehensive cancer center) between 2002 to 2012. The details of sites of metastases, systemic therapy and overall survival were recorded for each patient. **Result:** In 409 patients who received systemic treatment, there was statistically significant lower OS in those presenting with liver metastases ($p<0.001$), adrenal metastases ($p=0.011$) and metastases to abdominal lymph nodes ($p=0.014$). There was no statistically significance difference in OS in patient presenting with pleural metastases or effusion ($p=0.908$), metastases to heart or pericardium ($p=0.654$), metastases to bone ($p=0.281$), brain ($p=0.717$) or skin and subcutaneous tissue ($p=0.642$). **Conclusion:** Intra-abdominal metastases confer a particularly poor prognosis in stage IV NSCLC treated with systemic therapy and may identify patients in whom aggressive treatment beyond first line therapy is not appropriate.

Keywords: Lung cancer- metastases- prognosis

Asian Pac J Cancer Prev, 19 (7), 1907-1910

Introduction

Lung cancer is the most common cancer type with 1.8 million new cases diagnosed annually, accounting for 12.9% of newly diagnosed cancer cases. It is also the first cause of worldwide cancer death with estimated 1.59 million death annually that accounted for 19.4% of total cancer death (Jemal et al., 2011; Ferlay, 2013).

In the United States, lung cancer is the second most common cancer in both males and females after prostate cancer and breast cancer with 115,610 and 105,590 new cases, respectively each year. It is also the first cause of cancer death in both males and females with estimated 158040 deaths each year (Siegel et al., 2016).

The WHO classified lung cancer into two main categories Non-small cell lung cancer (NSCLC), which accounts for 85% of totally diagnosed lung cancers and small cell lung cancer which accounts for 15% of totally diagnosed lung cancers. NSCLC is further subdivided into adenocarcinoma, squamous cell carcinoma and large cell carcinoma (Beasley et al., 2005; Travis et al., 2015).

Unfortunately more than half (57%) of patients' diagnosed NSCLC presented with metastatic disease and nearly one half of patients with early stage lung cancer will progress to metastatic disease within five years with overall survival rate for all stages of 17% and 5-year overall survival for metastatic disease of 4% and 90% of lung cancer death is due to development of metastases (Goldstraw et al., 2016). The mechanism of metastases include: detachment of tumor cells from the extracellular matrix with several proteolytic enzymes then invasion of neighboring tissues and basement membrane then intravasation into the blood stream or lymphatic vessels, by attachment to the endothelial cells with adhesion molecules, infiltration of the vessels, survival and transport through the blood stream and finally arrest and extravasation at a distant site and formation of a metastatic lesion (Mehlen and Puisieux, 2006; Perlikos et al., 2013; Popper, 2016).

The most frequent metastatic sites for NSCLC are the nervous system, bone, liver, respiratory system, and adrenal glands (Nakazawa et al., 2012; Riihimaki et al.,

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2014; Tamura et al., 2015).

The availability of multiple lines of chemotherapy, targeted therapy and immunotherapy for metastatic NSCLC, reveals a wide range of responses, demonstrating the heterogenous nature of advanced NSCLC

In this work we tried to explore the effect of different metastatic sites in unselected group of Non-small cell lung cancer patients who received different lines of treatment, on overall survival at one of NCI designated comprehensive cancer center and one of NCCN member institute.

Materials and Methods

A retrospective analysis was performed on patients with stage IV NSCLC who received systemic treatment at University of Alabama at Birmingham (UAB) from 2002 to 2012. The details of site of metastases, systemic therapy and overall survival were recorded for each patient.

We excluded patients originally treated with adjuvant treatment who did not receive systemic treatment upon progression and patients who did not receive any active treatment.

Statistical analysis was performed using SPSS version 23 and calculated using log-rank testing.

Results

Four hundred and nine patients received systemic treatment were identified. There were 232 patients <65 years old (56.7% of total study population) and 177 patients > 65 years old (43.3% of total study population). As regard to gender, 230 patients were males (56.2%) and 179 were females (43.8%). Most of patients identified had adenocarcinoma (50.9%), followed by non-small cell lung cancer not otherwise specified (28.6%), followed by squamous cell carcinoma (17.1%) (Table 1).

Pleural effusion or deposits were represented in 22.5% of patients, metastases to bone in 28.6%, to brain in 22.7%, to liver in 14.4%, to adrenals in 13%, to abdominal lymph nodes in 5.4%, to subcutaneous tissue

Table 1. Demographic and Pathological Characters of the Patients

	Number	Percent
Age		
>65	177	43.3
<65	232	56.7
Gender		
Female	179	43.8
Male	230	56.2
Histology		
Adenocarcinoma	208	50.9
NSCLC NOS	117	28.6
SCC	70	17.1
Large cell carcinoma	7	1.7
Adenosqamous carcinoma	7	1.7

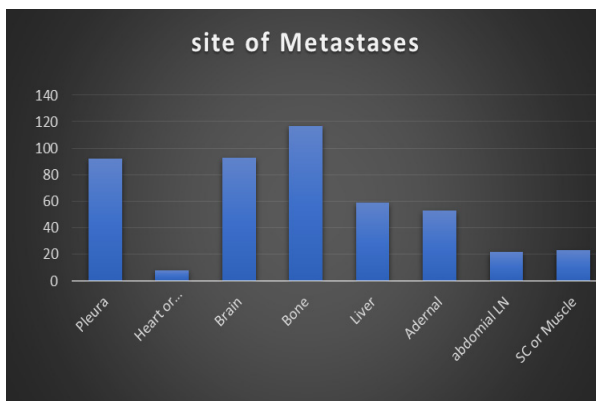


Figure 1. Site of Metastases in Study Population

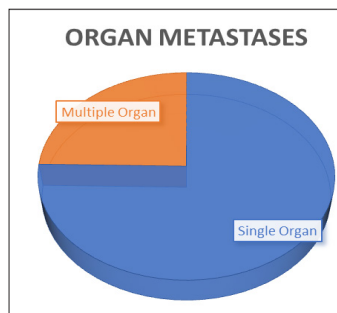


Figure 2. Organ Metasetes in Study Population

or muscle in 5.6%, to other abdominal viscera in 1.2% and cardiac involvement in 2% of patients. Single organ metastases were represented in 75.3% while multiple organ metastases were represented in 24.5% of patients. (Figure 1 and 2).

Regarding site of metastases, there was a statistically significant lower OS in patients presenting with liver metastases (p<0.001), adrenal metastases (p=0.011) and metastases to abdominal lymph nodes (p=0.014). However, there was no statistically significance difference in OS in patients presenting with pleural metastases or effusion (p=0.908), metastases to heart or pericardium (p=0.654), metastases to bone (p=0.281), brain (p=0.717) or skin and subcutaneous tissue (p=0.642) (Table 2).

For abdominal metastases the presence of one or

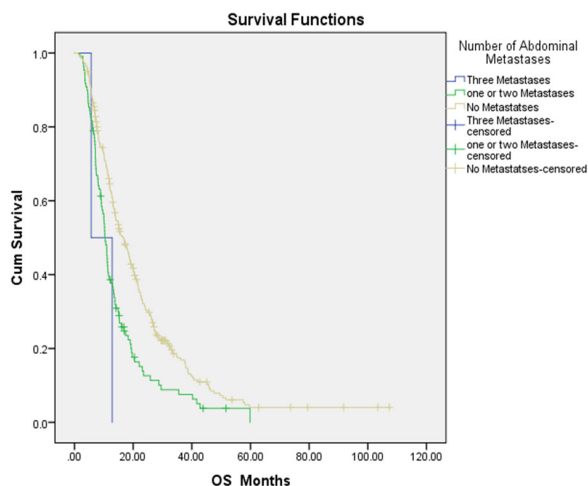


Figure 3. Kaplan Marie Survival Curve for Abdominal Metastases

Table 2. Log Rank Test of Site of Metastases

	Medians for Survival Time								Chi-Square	df	Sig.
	No metastases				Yes						
	Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval				
		Lower Bound	Upper Bound			Lower Bound	Upper Bound				
Pleura	13.839	0.714	12.439	15.240	12.990	2.678	7.741	18.240	0.013	1	0.908
Heart or Pericardium	13.793	0.718	12.387	15.200	14.849	3.942	7.122	22.576	0.201	1	0.654
Brain	13.793	0.725	12.372	15.215	14.092	1.670	10.819	17.364	0.132	1	0.716
Bone	14.161	1.098	12.009	16.312	12.416	1.212	10.041	14.792	1.163	1	0.281
liver	15.285	1.184	12.964	17.606	10.259	.881	8.532	11.986	16.944	1	0.000
Adrenals	14.849	0.989	12.911	16.787	10.259	1.003	8.294	12.224	6.468	1	0.011
abdominal LN	14.000	0.681	12.665	15.335	9.203	2.643	4.022	14.384	6.093	1	0.014
Skin or SC	13.839	0.702	12.463	15.215	12.416	2.529	7.459	17.374	0.216	1	0.642

Table 3. Log Rank Test for Abdominal Metastatic Sites

Number of Abdominal Metastases	Median			
	Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound
Three Metastases	5.669			
one or two Metastases	10.351	0.489	9.392	11.310
No Metastases	16.525	1.280	14.015	19.034
Overall	13.793	0.675	12.470	15.117

two or three abdominal metastases were associated with inferior survival compare to absent of metastatic site in the abdomen (Table 3) (Figure 3).

Discussion

Although advanced stage NSCLC is a heterogenous disease, most treatment guidelines recommend standardized treatments irrespective of tumor burden or site of metastases (Novello et al., 2016; Hanna et al., 2017; Members, 2017).

Many authors report inferior survival with specific sites of metastases. In one abstract reported by Naito and his colleagues' pleural effusion found to be a poor prognostic factor for survival (Naito et al., 1997).

In another Japanese data reported by Sugiura et al., (1997) on 197 patients with advanced stage NSCLC, pleural effusion was selected as a poor prognostic factor in the multivariate analysis.

Hilsenbeck and colleagues sought to determine the prognostic significance of stage, race, gender, age, and treatment in each histologic subtype in lung cancer. The presence of liver metastases, was an important prognostic factor in all subtypes except large cell carcinoma in univariate but not in multivariate analysis (Hilsenbeck et al., 1993).

In a paper by Maeda and his colleague, in 261 patient with advanced NSCLC who had been enrolled in clinical trials conducted by the Okayama Lung Cancer Study Group between 1978 and 1992, the presence of lung, liver and bone metastases all were associated with poor survival (Maeda et al., 2000).

In the present study, a statistically significant lower

OS was seen in patients presenting with liver ($p < 0.001$), adrenal ($p = 0.011$) and abdominal lymph node metastases ($p = 0.014$). However, there was, however, no statistically significant difference in OS in patient presenting with pleural metastases or effusion ($p = 0.908$), metastases to heart or pericardium ($p = 0.654$), metastases to bone ($p = 0.281$), brain ($p = 0.717$) or skin and subcutaneous tissue ($p = 0.642$).

Our findings support previously reported findings that certain sites of metastatic disease confer a poor prognosis on patients diagnosed with NSCLC and identifies abdominal lymph nodes metastases as a poor prognostic factor. These sites of metastases may help identify patients for whom aggressive salvage therapy may be inappropriate, particularly if the patient failed to respond to first line therapy. In addition, our data suggests that these sites of disease should be considered in the stratification of patients participating in randomized clinical trials and the failure to do so may distorted the validity of a study.

In conclusion, intra-abdominal metastases confer a poor prognosis in stage IV NSCLC treated with systemic therapy. This is highly relevant in both clinical practice and in the conduct of clinical trials and should be considered in the selection of therapies and design of randomized clinical trials.

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