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Cost and survival analysis of treating stage IV non -small cell lung cancer

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COST AND SURVIVAL ANALYSIS OF TREATING STAGE IV NON-SMALL CELL LUNG CANCER

by

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DEDICATION

I would like to dedicate this work to all the patients afflicted by lung cancer; especially those whose information was used for the purpose of this study.

ACKNOWLEDGMENTS

I will like to thank my readers Dr. Zaner and Dr. Hartshorn for tolerating my frequent unannounced intrusion to their busy schedule for advice. This study will not have been completed without the help of my co-investigator Dr. Julian Lel and I thank him immensely for his dedication and insight.

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COST AND SURVIVAL ANALYSIS OF TREATING STAGE IV NON -SMALL CELL LUNG CANCER

EDMUND FOLEFAC

ABSTRACT

The United States spends about 17% of its gross domestic product (GDP) on healthcare, the most of any industrialized nation. Oncology care alone accounts for 5–10% of this expenditure. Although the cancer survival data in the US are better than of most industrialized nations, the fact that healthcare expenditure is rising faster than the GDP makes the current situation unsustainable. In 2010 lung cancer accounted for 13% of the 124 billion dollars the USA spent on cancer care. Though survival for some patients with metastatic non-small cell lung cancer is improving with increasing use of targeted therapy, for the majority of patients it is still short but the amount of money spent treating them is quit high. With many different chemotherapy regimens to choose from, different threshold for individual clinicians to initiate and discontinue therapy as well as the lack of firm guidelines to image patients during treatment, we decided to study the cost and cost distribution of treating this patient population at our institution with the goal of identifying areas of waste reduction and improve efficiency.

Methods

We searched the BMC cancer database for all stage IV non-small cell lung cancer patients treated between 2006 and 2011. Information such as demographics, number of clinic visits, days spent in the hospital (both inpatients and ER visits), types of chemotherapy each patient received, number of CT, MRI, PET and bone scans were

extracted from the medical records. The date of death for each patient was identified through the Social Security Administration's Death Master File as well as genealogy bank and ancestry websites. The costs of inpatient stay and ER visits, imaging and pathology were obtained from the appropriate hospital authorities. The costs of chemotherapy (medications) were obtained from the oncology pharmacy while the cost of outpatient labs, chemotherapy administration and charges for services provided by the outpatient clinic staff was obtained from the clinic billing office.

Results

Between the study period, 224 patients were treated at BMC for metastatic non-small cell lung cancer. Of the patients in the study, 57% were whites, 9% were homeless, 43% received chemotherapy. The median survival was 5 months for patients not treated with chemotherapy, 8 months for patients treated with cytotoxic chemotherapy alone and 9.2 months for patients who received targeted therapy as part of their treatment. The mean charge for treatment was $127,000; ranging from $78,000 for patients not treated with chemo to $259,000 for those who received biologic. The charges per month of survival were between $28,000 and $32,000. The charges per month of survival were on average $12,000 less for white patients and $15,000 more for homeless patient. Inpatient treatment accounted for 56% of the charges, imaging 15% and outpatient including chemo 18%.

Conclusion

Metastatic non- small cell lung cancer is expensive to treat with a bulk of the expenditure

in the inpatient setting. Imaging is also responsible for a significant percentage of the expenditure. Significant cost reduction can be made without negatively impacting patient survival if we can find a way of reducing inpatient hospital stay and imaging.

PREFACE

The United States spends about 17% of its gross domestic product (GDP) on healthcare, the most of any industrialized nation. Oncology care alone accounts for 5-10% of this expenditure(1). Although the cancer survival data in the US are better than for most industrialized nations, the fact that healthcare expenditure is rising faster than the GDP makes the current situation unsustainable. Many factors account for this dilemma, most of which are not under the direct control of the healthcare providers.

One area in which healthcare providers can be instrumental is cost effectiveness analysis, the lack of which has created an environment of evidential uncertainty. This leaves providers, payors, policy makers and patients confused when considering the best way to spend the limited resources available to achieve maximum quality care. The UK has attempted to solve this problem by creating the National Institute for Clinical Excellence (NICE), which is charged with evaluating the cost effectiveness of medications and medical procedures in deciding whether their use by patients is justified at the government's expense (2) .Accordingly they have recommended against the use of some expensive oncologic medications that are commonly used in the United States due to lack of cost effectiveness. Examples of these include bevacizumab in combination with a platinum doublet (platinum compound combined with another chemotherapy medication) in metastatic non-small cell lung cancer. Similarly, the use of erlotinib as second line treatment for metastatic non-small cell lung cancer is only recommended on condition the manufacturer provides the drug at a cost comparable to that of docetaxel, which is regarded as standard second line therapy with comparable survival outcomes,

but costs far less.(3, 4). Other countries such as Australia and Canada have created regulatory agencies to control health care cost. In Australia, the Pharmaceutical Benefits Scheme (PBS) and in Canada the single payer system are charged with the responsibility of policing healthcare cost (6); (4). While we have a different health care system in the US, there is no reason why some of these concepts cannot be applied (6).

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LIST OF ABBREVIATIONS

BMC- Boston Medical Centre

CDC Centre for Disease Control

CONCORD; A global study on cancer survival

CT – computed tomography

ECOG- Eastern Cooperative Oncology Group

EGFR – Epidermal growth factor receptor

ER –Emergency Room

FDA- U.S. Food and Drug administration

GDP –Gross national product

GCSF-Granulocyte colony-stimulation factor

JAMA-Journal of the American Medical Association

MD –Medical Doctor

MRI- Magnetic Resonance Imaging

n- Number of patients

NICE –National Institute for Clinical excellence

NIH- National Institutes of Health

NSCLC- Non-small cell lung cancer

OECD; Organization for Economic Co-operation and Development

PBS- Pharmaceutical Benefits Scheme

PET – Positron Emission Tomography

P25 25^{th} percentile

P75 -75th percentile

QALY- Quality adjusted life year

RN – Registered Nurse

SD- Standard deviation

SEER –Surveillance, Epidemiology, and End results

STD- Standard deviation

UK-United Kingdom

USA –United States of America

USD- U.S. Dollars

WHO- World Health Organization

INTRODUCTION

Worldwide lung cancer is the leading cause of cancer in males, accounting for 17% of all new cancer cases and 23% of all cancer deaths. In females it is the fourth leading cause of cancer death. In 2010 an estimated 1.6 million new cases of lung cancer were diagnosed worldwide with approximately 1.4 million deaths .In the same year, there were about 374,000 lung cancer survivors in the USA and this number is expected to rise to 412,000 by 2020(7). Furthermore, according to CDD data, in 2012, there were an estimated 202, 000 new cases of lung cancer and 159,500 lung cancer deaths in the USA. Worldwide tobacco smoking accounts for about 80% of lung cancer in males and about 50% of lung cancer in females. In the United States of America, smoking accounts for approximately 90% of lung cancer cases. The economic impact of lung cancer is staggering not only because it is expensive to treat (the direct cost of cancer care in the USA was about $124 billion in 2010 with lung cancer alone accounting for about 13% of all cancer expenditures), but because it also leads to premature death. The economic burden of premature death due to cancer in the USA is projected to reach $148 billion by 2020 and lung cancer alone will account for 27% of this.

Though the United States cancer expenditure (mostly direct cost) constituted about 5% of total health care costs in 2010 which is comparable with figures from other industrialized nations, studies suggest that increases in costs of cancer treatment could begin to outpace health-care inflation as a whole, and become responsible for a rising percentage of total health-care spending.(8). Moreover, certain factors not properly taken into account when estimating cost of cancer care nonetheless play a role in the rising cost. These include

current cancer incidence, patterns of care, cancer survival and the escalation in the costs of cancer chemotherapy, which has outpaced general medical care inflation. For example, Mariotto, *et al.* argued that the National Institutes of Health (NIH) estimates of direct costs of cancer care at $91 billion were flawed because factors such as changes in incidence trend, survival and population demographics were not accounted for. Using different methods developed specifically to account for these factors, the cancer-associated cost was estimated to be $124.5 billion and $157.7 billion for 2010 and 2020 respectively, representing a 27% increase when they accounted for population changes alone. When adjusted for a 2%/year increase in cost of care for the first and last years of life, the 2020 figure was $170 billion (37% increase). Lung cancer accounted for $12.12 billion in 2010 and will account for $14.74 billion in 2020, second only to breast cancer. Based on Medicare's SEER data, lung cancer care accounted for 20% of Medicare's total expenditures for cancer in 2008(9) .The estimated monthly cost of treating stage IV lung cancer (1992–2003) depended on the phase of treatment, ranging from about $12,000–$16,600 in the staging (diagnosis and treatment planning) phase, $3,400–$9000 in the initial phase, $5,500–$11000 in the continuous phase, and $14000–$16500 in the terminal phase.(10)

Important changes have taken place in the treatment of metastatic non-small cell lung cancer since this study was published. These include the use of platinum doublets, the increased use of targeted therapies and the shift in cancer chemotherapy administration to the outpatient setting. It is also likely that the use of imaging has increased.

What drives the cost of cancer care in the USA today?

Figure 1 below is borrowed from the proceedings of a Lancet Oncology commission, and may help illustrate the difficulties in providing affordable cancer.

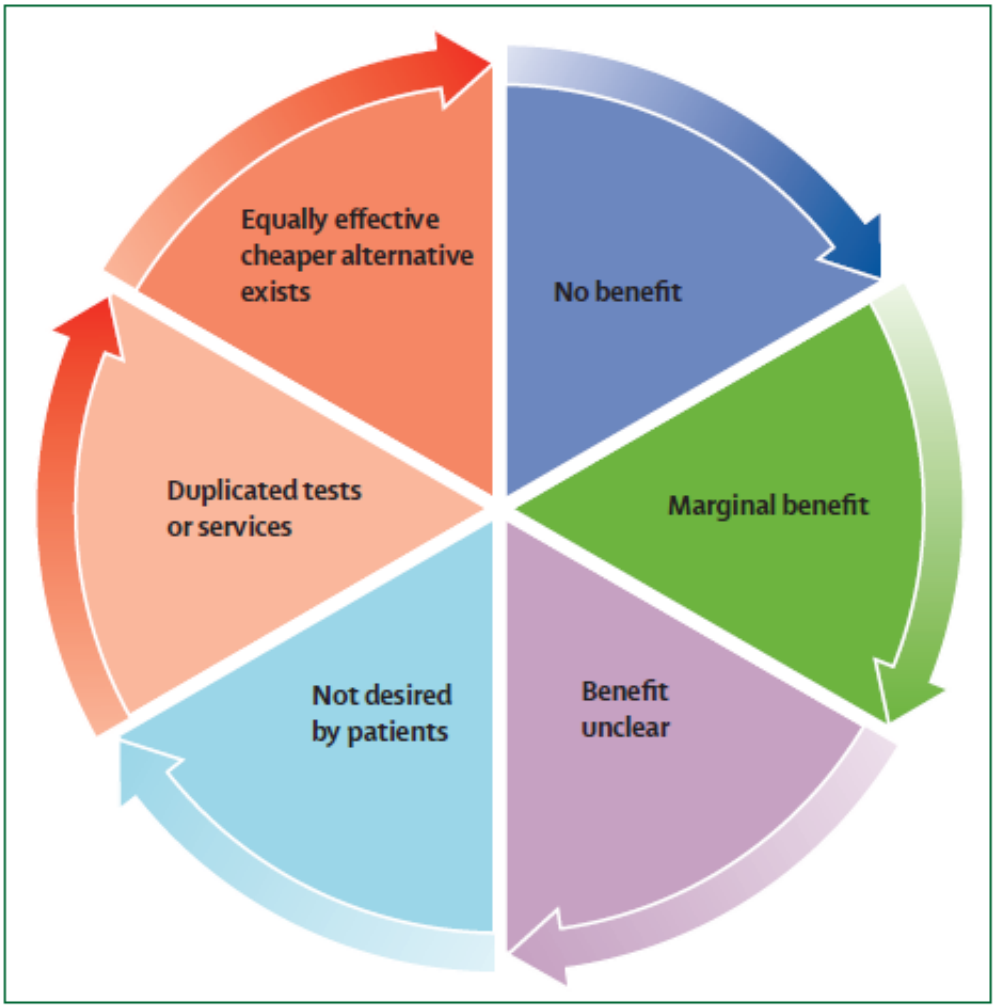


Figure 1: Classes of interventions to target for decreased utilization.

The increase in the cost of cancer care in the USA today can be attributed to many factors, such as the cost of research & development and clinical trials especially in the era of personalized medicine (e.g. testing a lung tumor for the EGFR mutation costs approximately $400). Fortunately, research and development has led to more effective,

though also more expensive therapies that provide significantly improved overall survival and in some cases fewer side effects when compared to cytotoxic chemotherapy commonly used in a majority of the patients today. This increased survival and cost of medications ultimately leads to increased overall costs of care, although they may be more cost effective than cytotoxic chemotherapy in the long run. Given the high cost of these new therapies, their use for certain indications cannot always be justified especially when there are much cheaper alternative therapies that can provide generally similar outcomes. Other factors responsible for rising costs include current cancer incidence/prevalence as well as patterns of care.

Several other reasons account for lack of cost effectiveness in the American health care system. The cost of healthcare administration in the US is high, accounting for approximately 30% of the entire healthcare budget compared to about 16% in Canada (11). The FDA only considers safety and efficacy and does not engage in economic analysis when evaluating medicines or healthcare technologies for approval. There is a lack of well-designed cost and cost effectiveness analysis studies. On the front lines of healthcare spending, oncologists and other providers do not necessarily consider cost analysis as part of the decision making process before recommending specific therapies. The last two factors in addition to the current physician reimbursement have led to the routine use of some expensive therapies by providers despite lack of evidence that these improve outcomes. For example, although GCSF-supported therapy has not been shown in randomized trials to either improve overall cancer survival or quality of life in patients with any of the four most common solid tumors (12) , Smith *et al.* found that its use as

supportive therapy in patients with these cancer types was prevalent and generated substantial profit to medical practices and to drug manufacturers. This study showed that in 2011 GCSF generated $1.25 billion per year in sales and provided substantial profits to large oncology practices in Northern California; the revenue earned from each dose of pegfilgrastim (Neulasta, Amgen) was 6% ($141) for Medicare patients, 25% ($611) from one of their larger commercial insurers, and 53% ($1,312) from another health plan (13). Patients and families may demand more care with unrealistic expectations for various reasons; providers may not have taken the time to educate them about their disease and so patients and families may lack the understanding of the disease process. They are likely unaware of the cost of the care they expect or care little about cost if they are not paying for it directly, hence pushing providers to deliver care at exorbitant prices and with marginal benefit.

While patients with cancer do incur substantial additional costs during their treatment, which should be considered when making treatment decisions, this may not be obvious to the providers and or patients. For example, prior to a cancer diagnosis, health care costs for a 72-year-old patient increased by 20% over 10 years (1992-2003) while the costs for a typical cancer patient showed a 107% increase over the same period. A 72-year-old patient in 2000 receiving an active course of treatment for cancer incurred patient-share costs ranging from $899 to $2,004 per month, (15–22% of total health care costs), though not necessarily paid out-of-pocket if they have third party insurance. Given the increase in the cost of care, this figure is likely much higher today, particularly in lung cancer, where newer chemotherapeutic agents are much more expensive. The lack of early

incorporation of end-of-life discussion and involvement of palliative care consultation into the treatment paradigms for patients with advanced cancer have also contributed to the rising cost of cancer care. Patients and providers may avoid initiating end-of-life discussions due to fear that this will be perceived as surrender in the fight against cancer. In a prospective, multicenter study of 360 patients with advance stage cancer, only 37% of patients and their families could recall having a discussion about impending death with their physician (14). Patients with end-stage cancer likely receive treatment despite futility of such care. One study showed that about 20% of patients were given chemotherapy within the last 2 weeks of life and that the average time spent by lung cancer patients on hospice was only four days (15). About half of the total healthcare expenditures for cancer patients are in the inpatient setting. This suggests that efforts to increase the proportion of care delivered in the outpatient setting may reduce the cost of care, as some of the cost incurred in the inpatient setting could be avoided.

The median survival of patients with metastatic non-small cell lung cancer without a targetable mutation is about 6 months without treatment and about 8-12 months with chemotherapy. There are several different chemotherapy regimens that have been shown to improve both overall survival and quality of life in this patient population. These include cytotoxic chemotherapy and targeted therapy. Most trials leading to the approval or recommendation of most of these regimens did not include an economic analysis. Though many of the regimens are comparatively effective, the price difference for both direct cost and the management of side effects can be substantial.

While diagnostic imaging has generally been estimated to constitutes less than 6% of the

total oncology care cost in the past, its utilization has gone up quite significantly .The lack of evidence based guidelines on use of imaging during treatment of metastatic NSCLC contributes to high variability in use and excessive imaging by some, despite the lack of evidence correlating more frequent imaging with improved outcomes. Available data suggest that there is little or no benefit from imaging patients during treatment, except during select clinical decision points. More studies are needed to determine the best use of imaging in this patient population. The American Society of Clinical Oncology has put out guidelines aimed at reducing use of costly imaging in specific situations but practice is still highly variable.

Increased treatment not only results in direct additional cost associated with the therapy but also may lead to more toxicity, hence increasing healthcare utilization through hospitalization (49 % of total cost), ER visits or outpatient clinic visits.

What is considered cost effective in oncology care?

The answer to this question may depend on who is asked the question, who pays the bills and when. Common perceptions suggest upper limits of good value (cost effective) care in general range from $50,000 per quality adjusted life year (QALY) to $100,000 per QALY. Experts suggest that these thresholds are probably too low, outdated, and might be contributing to resistance to cost-effectiveness analysis in the United States. As a result, some researchers and stakeholders have discussed updated thresholds for willingness to pay. Current values for cost-effectiveness were first proposed in the 1970s and 1980s based on cost effectiveness of hemodialysis. Adjusting this value to 2007 USD equates to $197,000 per QALY. The World Health Organization's suggested calculation

sets the threshold at $140,100 per QALY in 2008 USD. Other experts have suggested that the values be set at not more than threefold the per capita income of a country, which in the US will equate to about $150,000 USD.

In 2006, Nadler *et al.* surveyed 139 medical oncologists at two academic hospitals in Boston as part of a cost effectiveness evaluation of bevacizumab and a hypothetical new cancer drug costing $70,000 per year and found that the majority of oncologists did not consider cost when deciding the choice of treatment for their patients as long as they deemed the treatment "effective." The implied cost effectiveness threshold from the oncologists' perspective in this study was over $300,000 USD/QALY, a far cry from current values of $50,000 USD/QALY commonly quoted today or the $130,000–$197,000 USD/QALY if adjusted for inflation and other factors. Interestingly, the oncologists were more willing to consider the patients' out–of –pocket cost in their ultimate recommendations. Physicians in this same study also indicated that they would be more willing to consider cost in 5 years, mainly because they perceived that growing costs would impose greater rationing of care. One could conclude from these responses that as long as a third party pays the bills and there is little threat of "rationing", cost consideration is less of a priority for some oncologists. Sadly the rising cost of care, which has outpaced the growth in GDP, has led to increased cost consciousness in the healthcare industry which may be what the physicians were describing as rationing of care.

With these considerations in mind a retrospective study of the stage IV lung cancer patients treated at Boston Medical Center (BMC) between 2006 and 2011 was conducted.

The objectives of this study were to: (1) estimate the total institutional charges for treating stage IV non-small cell lung cancer patients and to identify drivers of cost in this patient population as well as the cost distribution; (2) estimate the difference in cost and survival between patients treated with cytotoxic chemotherapy only and those treated with targeted therapy at any point during their treatment, either alone or in combination with cytotoxic chemotherapy; and, (3) evaluate healthcare utilization cost and survival difference by patient demographics (gender, marital status, race, English language fluency, homelessness, and medical insurance status).

METHODS

The Boston Medical Center cancer database was searched for all stage IV non-small cell lung cancer patients treated between 2006 and 2011. Two hundred and thirty -five patients matched this search. Eleven of these patients were eliminated from the study as a review of their records revealed that they were not properly characterized (1 patient had a diagnosis of lymphoma, 3 patients had stage III non-small cell lung cancer, 2 patients had stage IA NSCLC, 1 patient had esophageal cancer, 1 patient had metastatic colon cancer, 1 patient had two primaries (pancreas and lung), and tissue biopsies were not available for 2 patients.). Hence in total there were two hundred and twenty-four patients included in the study.

Demographic information was obtained for these patients including gender, age, race, marital status, smoking status, housing status and English language fluency. Histologic diagnosis and ECOG performance status at the start of therapy or at presentation were also obtained.

The date of diagnosis was assumed to be the date the pathologist first read the lung biopsy specimen. The date of the patient's first visit to the oncology clinic was used as the starting point in estimating the outpatient charges. Patients who received chemotherapy and those who did not were identified, and the reasons for not receiving chemotherapy were documented.

For the patients who received chemotherapy, the specific regimens and the number of cycles of chemotherapy each patient received were extracted from the medical records. The total number of clinic visits each patient attended during the course of their

treatment, including those clinic visits for which they did not receive chemotherapy were documented.

Date of death for each patient was identified through the Social Security Administration's Death Master File as well as relevant websites.

From the records the number of computed tomography (CT) scans magnetic resonance imaging (MRI), positron emission tomography (PET) and bone scans performed on each patient from the date of diagnosis until death or censor were calculated. The number of inpatient hospital admissions and total number of days spent in the hospital from date of diagnosis to death or censor were obtained from the records as well as the number of ER visits for each patient. These were then used to calculate the total inpatient and ER visit charges. These charges were provided by the patient financial office. Imaging charges (CT, MRI, PET scan, bone scan) were provided by the Radiology Department billing office.

The cost of medication and drug administration charges were provided by the outpatient chemotherapy pharmacist. The oncology facility charges, provider charges and cost of laboratory tests were provided by the outpatient billing office. Pathology charges were provided by the Pathology Department billing office.

The outpatient chemotherapy charges were calculated as the sum of the cost of medication (provider's retail price), facility charges, charges for administering the drug (based on standard reimbursement depending on the duration of infusion), provider visit charge, and the cost of laboratory tests.

For the purposes of this study, charges for biopsy from the Surgery Department were

inaccessible.

The following assumptions were made:

i) All hospital admissions, ER visits and imaging done from the time of diagnosis till death of patient or censor were assumed to be cancer related.

ii) Total ER charges were estimated based on the actual estimates per ER visit provided by the billing department multiplied by the number of ER visits because a majority of the billing for the individual visits was not found.

iii) The charges for pathology where estimated based on the information provided by the lung pathologist and billing office.

iv) Because the imaging charges were also highly variable (same procedures billed differently for different patients), the charges were estimated based on the unit price per specific study type in order to get more accurate and representative charges.

Subsection One; Statistical Method

We analyzed the data with SAS version 9.3 (SAS Institute, Inc., Cary, NC).

Survival time was calculated as the duration from diagnosis date to date of death. Six patients were alive at the time of censor and 27 had unknown survival status. The 6 living patients were censored at 9/25/2012. The 27 patients with unknown survival status were assigned dates of death at the median survival time (151 days). For these 27 patients, date of death was calculated as 151 days after diagnosis date.

Twenty-six patients are excluded from analysis for the following reasons:

• 23 patients lived <30 days after diagnosis

• 2 patients had missing diagnosis dates

• 1 patient had an inpatient cost of $2.4 million

Independent variables included in survival analysis were age at diagnosis (<65 years vs. ≥65 years), sex, race (white vs. non-white and unknown), English fluency, marital status, homelessness, smoking status, and treatment group (any biologic vs. no treatment, only cytotoxic vs. no treatment, and any biologic vs. only cytotoxic). A Cox regression model was created with backward elimination, starting with all independent variables and removing the variable with the highest p-value at each iteration until all variables remaining in the model had a p-value <0.10.

Linear regression was used to assess predictors of cost per month of survival. Cost per month of survival was a continuous dependent variable. Independent variables were age at diagnosis (<65 years vs. ≥65 years), sex, race (white vs. non-white and unknown), English fluency, marital status, homelessness, smoking status, and treatment group. A multivariate linear regression model was created with backward elimination, starting with all variables, removing the variable with the highest p-value each iteration until all variables remaining in the model had a p-value <0.10.

RESULTS

Within the study period, 224 patients were seen at Boston Medical Center for Stage IV lung cancer. Of the 224 patients seen at BMC for Stage IV lung cancer, 26 patients were excluded from the final analysis, 2 because diagnosis date was missing, 1 because of an inpatient cost ($2.4 million) that was more than 3 STD from the mean and 23 survived less than 30 days from diagnosis hence the final analysis was done on 198 patients

Of the 198 patients included in the final analysis, 43% were minority, 57 % were whites and 11% were homeless. 43% of the patients were treated with pharmacotherapy while 57 % of the patients did not receive any form of pharmacotherapy. The median overall survival was 5 months amongst all patients included in the analysis, 7.8 months for patients treated with cytotoxic chemo only and 9.2 months for patients who received targeted therapy as part of their treatment. See tables 1–4 below

Table 1: Patient Characteristics

	All Patients	After exclusions*
	n=224	n=198
Male	125 (56%)	110 (56%)
Race – White	131 (58%)	113 (57%)
Race – Black	69 (31%)	63 (32%)
Race – Hispanic	12 (5%)	11 (6%)
Race – Asian	8 (4%)	7 (4%)
Race – Other/Unknown	4 (2%)	4 (2%)
Smoking	195 (87%)	173 (87%)
Homeless	21 (9%)	21 (11%)
Treatment – only Cytotoxic	49 (22%)	48 (24%)
Treatment – only Biologic	2 (1%)	2 (1%)
Treatment – Cytotoxic and Biologic	35 (16%)	35 (18%)
No Treatment – Neither Cyt nor Bio	138 (62%)	113 (57%)
Alive at time of censor – Yes	6 (3%)	6 (3%)
Alive at time of censor – No	191 (85%)	165 (83%)
Alive at time of censor – Unknown	27 (12%)	27 (14%)

Excluding 2 patients with missing diagnosis dates
Excluding 23 patients who lived <30 days after diagnosis
Excluding 1 patient with inpatient cost of $2.4 million

Table 2: Months of Survival at Death or Censor

	n	mean	Median
All	198	8.3	5.0
Any chemo (cytotoxic and/or biologics) (groups 2, 3, 4)	85	9.5	7.8
Biologics (with or without cytotoxic) (groups 2, 4)	37	10.6	9.2
Cytotoxic without biologics (group 3)	48	8.6	7.0
No chemo (group 1)	113	7.4	5.0

NB: If alive, censor at 9/25/12. If unknown survival status, assume median survival time (diagnosis date + median survival). Median survival is 151 days.

Table 3: Charges

Median charges in parenthesis		Total charges with Estimated Imaging			
	n	**Mean**	**Median**	**P25**	**P75**
All	198	127,652	97,542	52,225	172,037
Any chemo (cytotoxic and/or biologics) (groups 2, 3, 4)	85	193,839	164,004	98,601	266,730
Biologics (with or without cytotoxic) (groups 2, 4)	37	258,562	247,251	164,005	301,634
Cytotoxic without biologics (group 3)	48	143,948	112,350	75,601	180,442
No chemo (group 1)	113	77,866	70,278	29,319	101,390

Table 4: Charges per Month with Estimated Imaging

	n	Mean	Median	P25	P75
All	198	28,318	18,367	7,831	40,603
Any chemo (cytotoxic and/or biologics) (groups 2, 3, 4)	85	28,608	21,240	12,771	42,159
Biologics (with or without cytotoxic) (groups 2, 4)	37	32,877	25,853	13,283	45,760
Cytotoxic without biologics (group 3)	48	25,317	18,762	9,700	33,492
No chemo (group 1)	113	28,101	13,934	3,793	36,371

Controlling for treatment type, the hazard ratio of death for white patients was 0.683 relative to that of non-white patients and patients with unknown race, indicating that white patients were less likely to die compared to non–whites.

Controlling for race, the hazard ratio for patients receiving treatment with only cytotoxic chemotherapy was 0.705 relative to that of patients not receiving pharmacotherapy, indicating that cytotoxic chemotherapy alone was associated with improved survival

Controlling for race, the hazard ratio for patients receiving treatment with targeted chemotherapy was 0.486 relative to that of patients not receiving pharmacotherapy, indicating that treatment with targeted chemotherapy was associated with reduced risk of death greater than with cytotoxic chemotherapy alone.

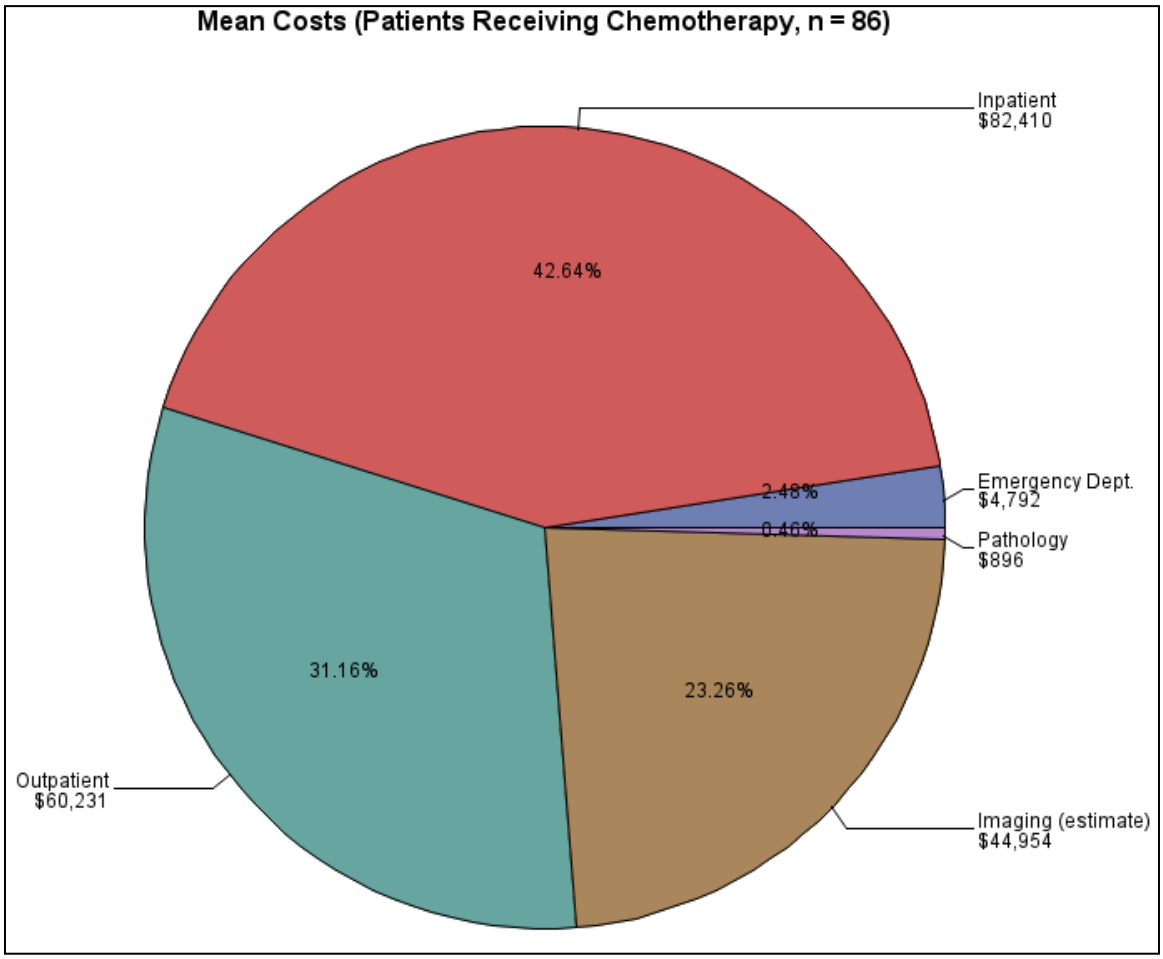
Controlling for age at diagnosis, an increase of $1,000 in charges per month of survival is associated with an increase in the hazard by a factor of 1.024, implying that higher monthly charges was associated with increased risk of death.

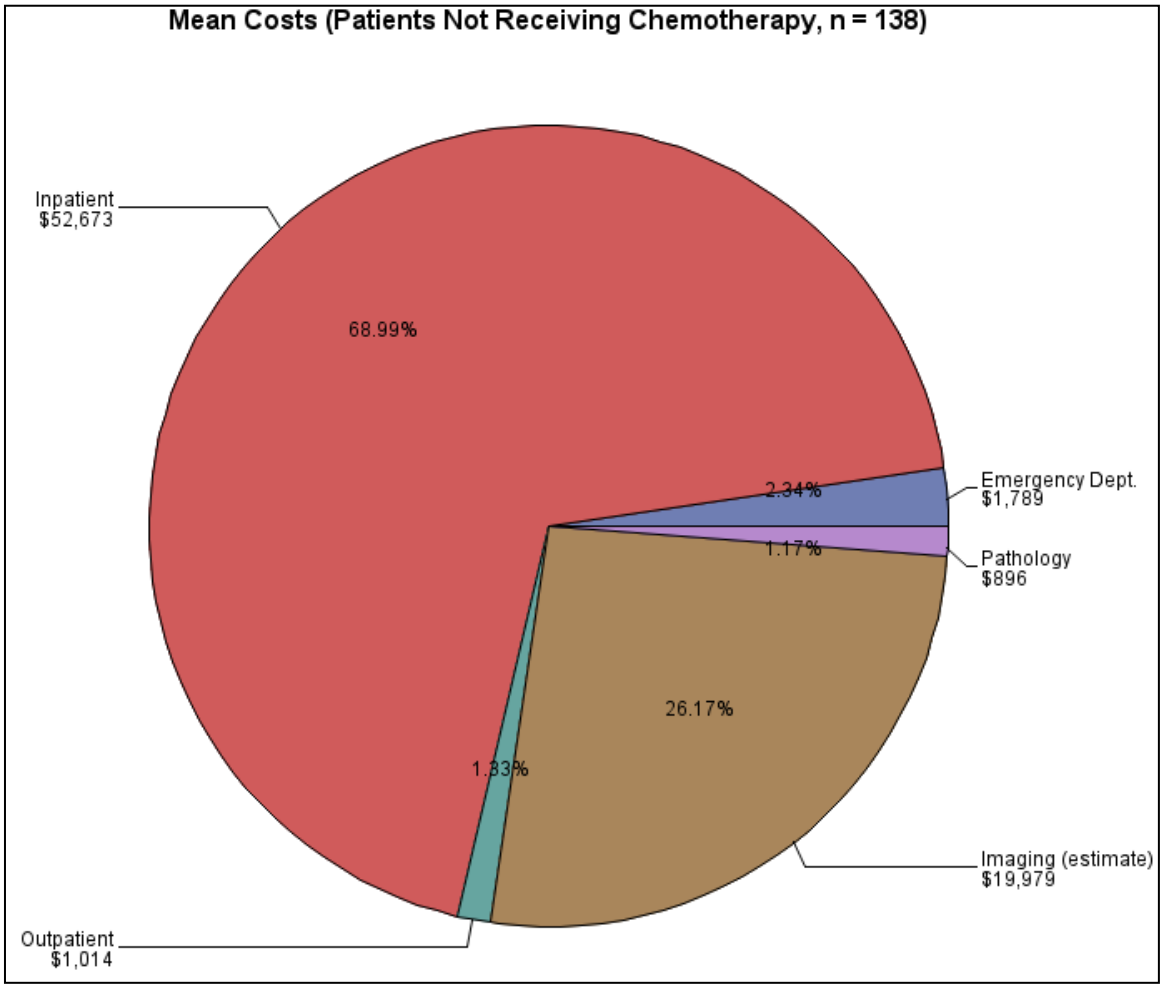
Controlling for charges per month of survival, patients 65 years or older had a hazard ratio of 1.365 that of patients younger than 65 years at diagnosis, implying that the risk of death was higher for older patients

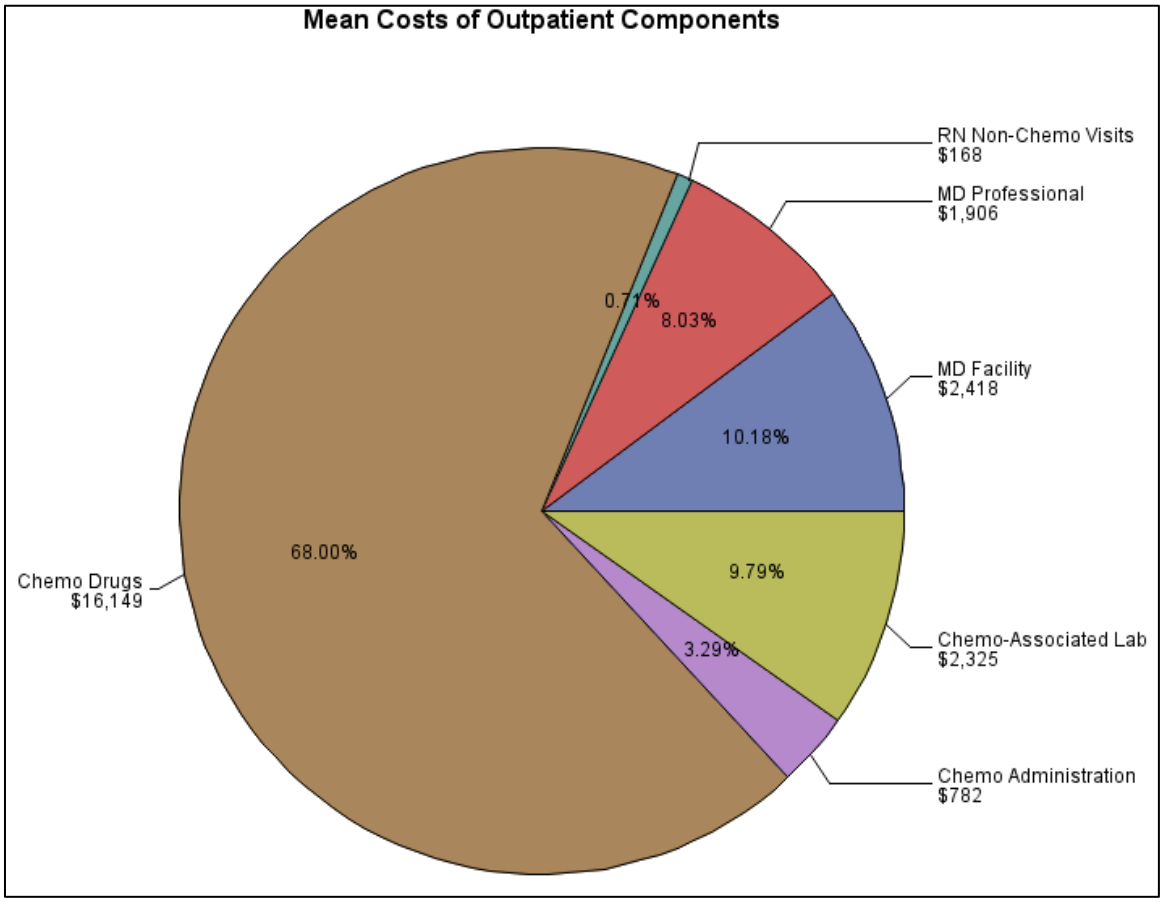
Controlling for homelessness, charges per month of survival for white patients is, on average, $12,305 less than for non-white patients and patients with unknown race.

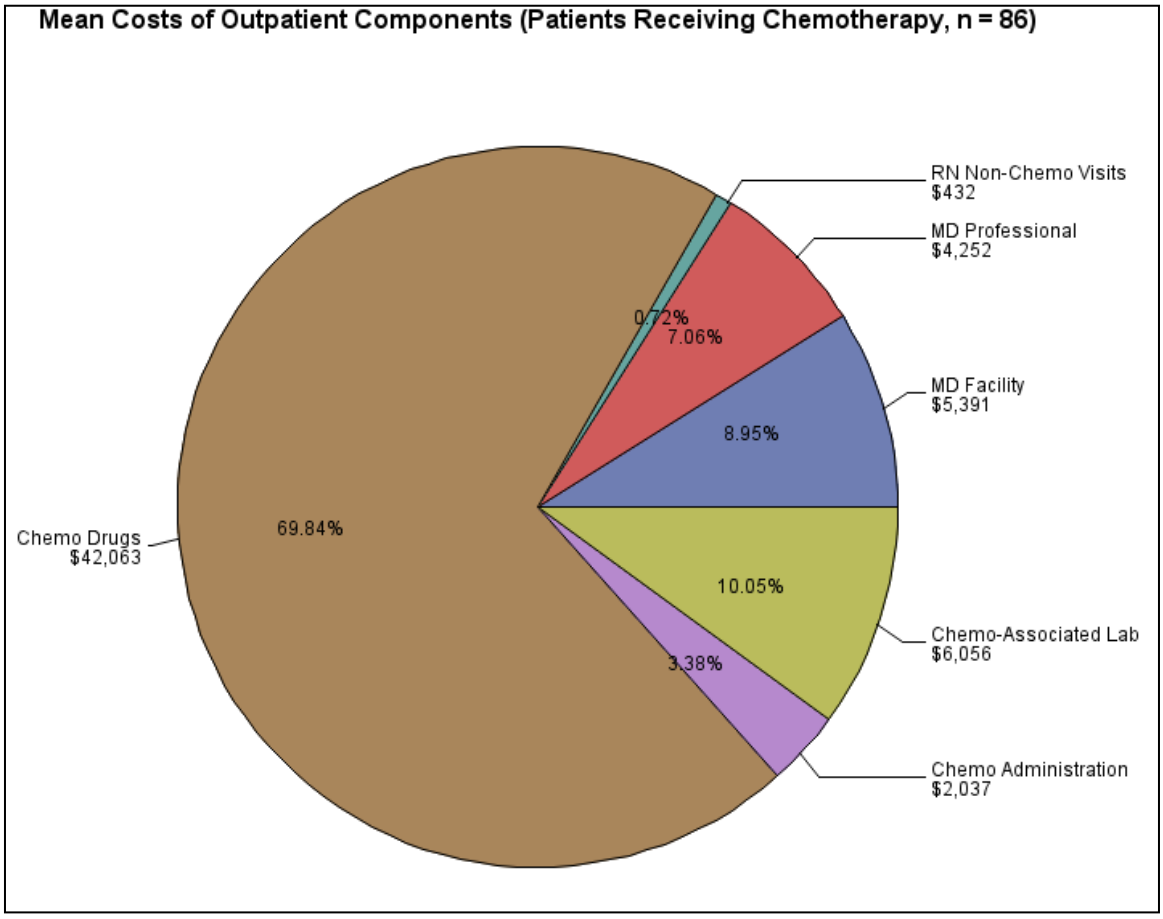
Controlling for race, charges per month of survival for homeless patients is, on average, $15,296 more than for non-homeless patients.

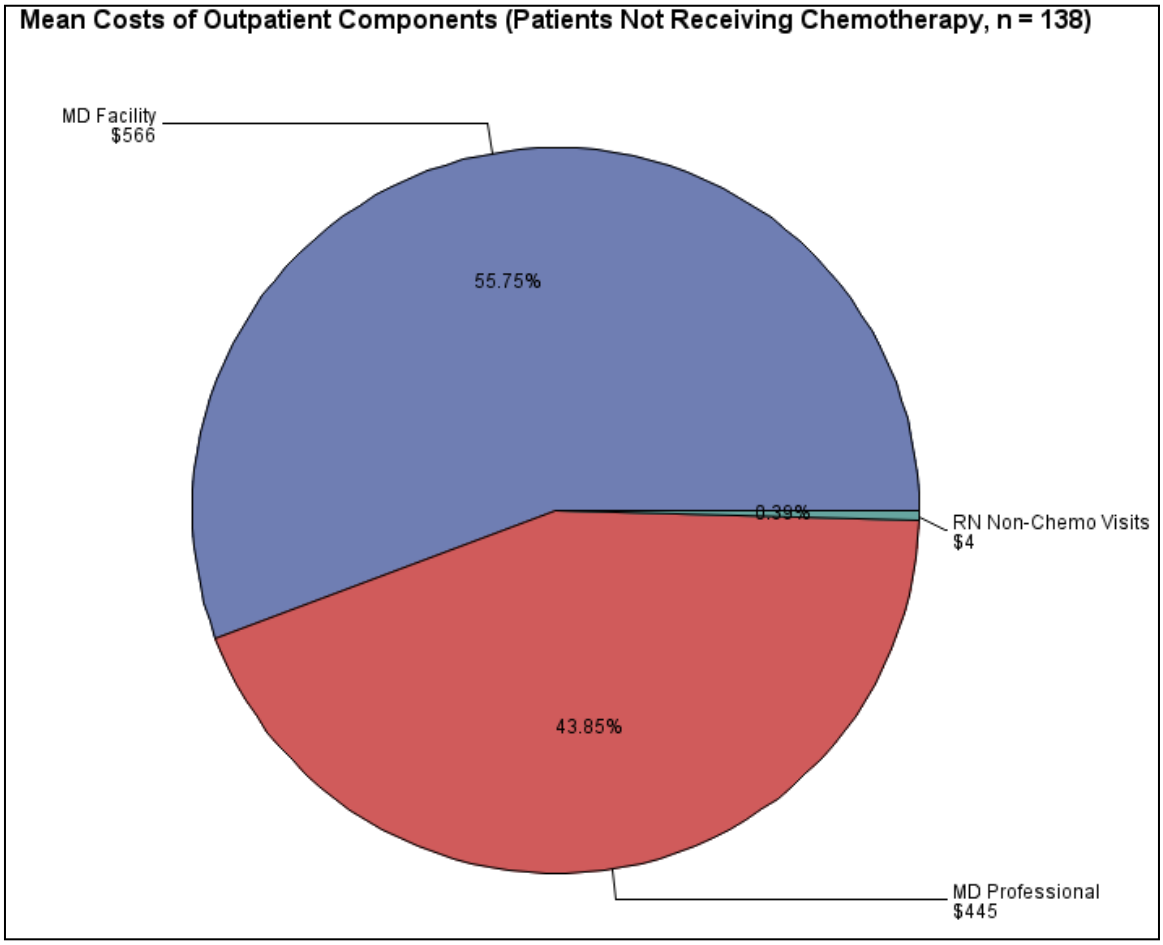
Figure 2. Mean charges distribution for all subjects in the study




Mean Costs (Patients Not Receiving Chemotherapy, n = 138)
Inpatient
$52,673
68.99%
Emergency Dept.
$1,789
2.34%
Pathology
$896
1.17%
26.17%
1.33%
Imaging (estimate)
$19,979
Outpatient
$1,014


Mean Costs of Outpatient Components
RN Non-Chemo Visits
$168
MD Professional
$1,906
MD Facility
$2,418
Chemo-Associated Lab
$2,325
Chemo Administration
$782
Chemo Drugs
$16,149
0.71%
8.03%
10.18%
9.79%
3.29%
68.00%


Mean Costs of Outpatient Components (Patients Receiving Chemotherapy, n = 86)
RN Non-Chemo Visits
$432
MD Professional
$4,252
MD Facility
$5,391
Chemo-Associated Lab
$6,056
Chemo Administration
$2,037
Chemo Drugs
$42,063
0.72%
7.06%
8.95%
10.05%
3.38%
69.84%


Mean Costs of Outpatient Components (Patients Not Receiving Chemotherapy, n = 138)
MD Facility
$566
55.75%
0.39%
RN Non-Chemo Visits
$4
43.85%
MD Professional
$445

DISCUSSION

Between 2005 and 2011, 224 patients were evaluated at Boston Medical Center for stage IV non-small cell lung cancer, 23 patients died within 30 days of diagnosis; these were excluded from the analysis because most of the cost incurred by these patients was not for treating their cancer.

In total 43% were treated with pharmacotherapy; of whom 22% were treated with cytotoxic chemotherapy only, 1% were treated with targeted therapy only, 16% were treated with both cytotoxic and targeted therapy while 57% did not receive any form of pharmacotherapy for various reasons. The percentage of patients who did not receive chemotherapy in this study is higher than figures from the National Cancer Data Base within the study period. The reason for this discrepancy is unclear. One reason may be that until recently patients with unresectable Non-small cell lung cancer including stage IIIB was classified as an advance stage disease, which will inflate the percentage of patients with real stage IV disease receiving chemotherapy. Another reason may be that our patient population is different. BMC treats a lot of underserved population, many of whom present to the provider not only with advanced disease but who also have multiple concurrent comorbidities, limited resources and in some case limited understanding of their disease, all of which may impact survival. These factors may in many cases make the risk of chemotherapy outweigh the potential benefit; hence it is also possible that these providers did a good job at screening out the patients who did not stand to benefit from chemotherapy. It is also possible that some patients needing treatment did not receive it but this is beyond the scope of this study .The percentage of patients treated

with targeted therapy in this study was also smaller than would be expected currently as more targeted drug choices have become available and the laboratory testing to identify eligible patients has also improved and become more available. There is little contemporaneous data on use of targeted therapy in order to do a fair comparison.

The median overall survival was 8 months amongst all study participants treated with any form of pharmacotherapy compared to 5 months for those who did not receive any pharmacotherapy. Of the patients treated with pharmacotherapy, the median overall survival was as expected better for those who received biologics as part of their therapy compared to those who did not (9.2 months vs. 7 months). The number of patients treated with targeted therapy alone was too small to do an independent analysis.

The survival data are similar to contemporaneous national survival data, which range from about less than 6 months for untreated patients to between 8 and 10 months for patients who received chemotherapy. Survival for this patient population (stage IV disease) should be better now given that a higher proportion of patients are treated with targeted therapies than during the period of the study. It may not be unreasonable to expect some patients with non –small cell lung cancer with identifiable driver mutations treated with targeted therapy to survive more than three years today.

Mean overall treatment charges at Boston Medical Center amongst all study participants was $127,652. For those who did not receive pharmacotherapy the mean overall treatment charges was $77,866 compared to $193,839 for those treated with any pharmacotherapy which is similar to published data. As expected among those who received pharmacotherapy, the overall charges for treated patients were higher for those

treated with targeted therapy compared to those who were not ($258,562 vs. $143,948). Though the mean overall charges were higher for patients who received pharmacotherapy compared to those who did not, the mean monthly treatment charges were similar at about $28,000 owing to the inferior survival outcome among the untreated patients. Among those patients treated with pharmacotherapy, the mean monthly charges were lower for those who received cytotoxic chemotherapy only compared to those treated with targeted therapy alone or in combination with cytotoxic chemotherapy ($25,000 vs. $33,000).

The charge distribution among all patients in the study showed the highest charges were incurred in the inpatient setting (56%), with imaging accounting for 23% of the total charges. Though the charge distribution was consistent with other published data, the percentage of inpatient charges in our study was higher (56% compared to 49% in some studies. Furthermore the percentage of imaging as a function of the overall charges (23%) was higher in our study compared to published national estimates .An analysis of the data separated into untreated and treated patients showed that the percentage contribution of inpatient charges and imaging charges were significantly higher among untreated patients compared to treated to patients (69%, 26% vs. 43%, 23 %, respectively). Further breakdown of the outpatient charges for patients treated with chemotherapy showed that close to ¾ of the charges were for chemotherapeutic agents, with MD fees (both professional and facility), labs, chemotherapy administration cost and non-chemotherapy RN visit costs accounting for slightly more than ¼ of the total charges. This cost breakdown is very important as it will enable hospital policy makers to

better target and eliminate areas of waste within the section of hematology-oncology. Currently about 75% of non-small cell lung cancer patients have an identifiable driver mutation, though targeted therapy is yet to be developed for most of them. These advances are likely to increase certain components of the cost of care such as drug prices and cost of diagnosis (screening for driver mutation and other mitigating factors necessary for personalized treatment). These advances will likely also lead to increase survival, which means the overall cost of care per patient will increase. On the other hand, inpatient cost, and cost of chemotherapy administration, and probably cost of managing side effect may decrease. With more patients treated with targeted therapy, the overall cost of treating stage IV lung cancer patients may likely increase but because survival is also improving, more side effects are prevented and patient /care giver time wasted is reduced to bare minimum, the cost effectiveness is expected to improve. It is therefore expected that the cost distribution shown above may change significantly in the near future.

The few studies that have been done in this field have either used different study characteristics (advanced lung cancer, elderly patients, total healthcare utilization, etc.) or different methodologies (mostly looking at the SEERS database or claims from HMO or insurance providers), making comparison difficult. Nevertheless, the estimated charges of treating stage IV non-small cell lung cancer at Boston Medical Center is similar to cost estimates from other published studies, although expenditure breakdown was different. For example, Vera-Llonch *et al.* estimated the mean cost of care for this patient population at $125,849 (study conducted between 2000–2006), but unlike this study and

other published studies, which show that in-patient expenditure accounts for the majority of the expenditure, their study suggested that out-patient expenditure accounted for the greater share of the cost. Yebroff *et al.* and Lang *et al.* put the estimate at about $85,000. Lang's study excluded the cost of chemotherapy; however these two studies are consistent with this study's finding that most of the expenditure is incurred in the inpatient setting.

This study attempted to address certain predictors of survival and increased cost, which have rarely been addressed in previous studies with the following findings.

From other studies, predictors of improved survival were white race (HR 0.68) and treatment with any form of chemotherapy (HR 0.70 with cytotoxic chemo and 0.49 with targeted therapy)

Predictors of inferior survival outcomes were non-White race, patients who did not receive any pharmacotherapy, age older than 65 Years (HR 1.37) and homelessness. Marital and smoking status did not significantly affect the outcome. While it may be obvious why the elderly and the untreated patients have inferior outcomes, the rationale for superior outcome among Whites compared to non-Whites was not so clear. It is not clear whether it is due to the difference in biology of disease as reported in some other cancer types or disparity in care. Despite the inferior survival amongst the minority patients, the White patients were on average charged $12,305 less than their non-White counterparts. The charges per month of survival were on average $15,296 higher for homeless patients compared to those who were not homeless, possibly due to higher health services utilization such as prolonged inpatient stay and ER visits. Finally higher

monthly charges were associated with increased risk of death (HR 1.024 per $1000 increase in average monthly charges). We were unable to find any published studies on predictors of cost and survival to compare our study's findings. Results from this study suggest that this to be a relevant research area as this will help in resource allocation. Most studies have not separated the cost distribution into patients who received chemotherapy and those who did not. From this study the percentage of inpatient cost is even higher (70%) for patients who did not receive chemotherapy.

This separation is important because treatment goals are different and may enable stake-holders to better allocate scarce resources. For example, the BMC and similar institutions with robust geriatric programs could develop creative ways of minimizing the amount of time spent in the hospital by elderly patients with terminal cancer who are not candidates for chemotherapy. One such program may include early transition to the geriatric home care program with a periodic oncologist home visits or phone calls. This will offer support and allow the patient and family not feel "abandoned" by their oncologists. This may be especially useful to the group of patients who are reluctant to consider hospice or outpatient palliative care as an option. Early involvement of the palliative care has been shown not only to improve patients' quality of life but also to improve survival and in some cases reduced cost of care. One could deduced from the significant expenditure incurred by patients in the inpatient setting as well as the high percentage of patients who did not receive chemotherapy in this study that probably early involvement of palliative care and or hospice care may have been beneficial both patients and the healthcare system. If similar studies are reproduced at other institutions, it may

go a long way to not only compare survival data from various institutions, but more importantly, compare the cost of treatment necessary to achieve reported survival at different institutions. An efficiency index may then be developed incorporating patient survival, cost of care, patient's quality of live among other measures to better assess performance of different healthcare providers and institutions.

The limitations of our studies were the following;

i) The sample size for this study was small which may make the interpretation of the P value and confidence interval difficult. Hence it is entirely possible that if there was a larger sample size, some of the variables that were included in this analysis like smoking, marital status etc. might have shown different results. The fact that this study was conducted at a single institution also makes it less generalizable.

ii) This study is retrospective in nature with all inherent limitations of retrospective studies; we were only able to work with data documented in the system, some of which was missing. We also had to assume that all the recorded data was accurate but as evident by the one patient whose inpatient charges were more than 3SD from the mean, it is possible that some of the data could have been wrongly entered, which will affect the validity of our results. Being a retrospective study, we could only show an association between variables and not cause and effect. Examples include association between white race and lower charges per month of survival, homelessness and higher charges per month of survival as well as higher charges and inferior survival. Whether there was a cause and effect is not clear.

iii) Some of the charges had to be estimated because the actual charges could not be found; this was especially true for ER visits with less than 30% of the billing data available; meanwhile not only was some of the billing data for imaging missing but in some circumstances there was also a lot of discrepancy in the billing; for example there were many cases where patients were charged different amounts for the same type of imaging, sometimes as much as 3-4 times. This reduces the precision or power of our

results.

iv) Charges were used as a surrogate for actual cost but charges do not necessarily translate to actual cost (the amount paid to the hospital) because different insurance companies pay different rates which make it very difficult to estimate actual cost of treatment. For example MEDICARE pays about 31 cents on the dollar at BMC, MEDICAID about 21 cents on the dollar while the major commercial companies pay between 39 cents to 49 cents on the dollar as of 2013, however these figures were different for each year within the study period.

Despite these limitations this study is very useful as it may enable the section of Hematology /oncology at BMC, where the study was conducted, to eliminate waste and reallocate resources to more specifics areas likely to yield better outcomes. If these studies are replicated in all institutions around the country, then it will allow stake holders to be able to compare not only outcomes like survival but also cost effectiveness. Though there are several quality measures including currently in use to compare cancer care across different institutions, the most commonly used in oncology today is survival data. This may be a flawed comparison because of the discrepancy in patients characteristics treated by different institutions and the difference in resources utilization is not always accounted for hence making it difficult to reliably evaluate efficiency across institutions. In this era of cost consciousness these types of studies will be very useful to policy makers, payors and patients in making informed choices about where to seek quality care. It also helps providers to compare the cost effectiveness of the care they provide their patients with other institutions.

APPENDIX

Testing Global Null Hypothesis: BETA=0			
Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	15.6117	3	0.0014
Score	15.1573	3	0.0017
Wald	14.9996	3	0.0018

Analysis of Maximum Likelihood Estimates							
Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Label
race2	1	-0.38116	0.15508	6.0409	0.0140	0.683	race: white
onlycyt	1	-0.34936	0.18007	3.7640	0.0524	0.705	only cytotoxic
bio	1	-0.72147	0.20772	12.0632	0.0005	0.486	biologic

Outcome: Survival Time

All (n=198)

Log Rank Test

Variable	Chi-Square	P-value
Age at diagnosis (<65 years vs. ≥65 years)	3.29	0.07
Sex	0.32	0.57
Race	2.01	0.16
English Fluency	0.0005	0.98
Marital Status	0.10	0.75
Homelessness	0.25	0.62
Smoking	1.86	0.17
Any Biologic vs. No Treatment (n=150)	8.49	0.0036
Only Cytotoxic vs. No Treatment (n=161)	2.27	0.13
Any Biologic vs. Only Cytotoxic (n=85)	2.92	0.09

Cox Regression[1]

Testing Global Null Hypothesis: BETA=0			
Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	15.6117	3	0.0014
Score	15.1573	3	0.0017
Wald	14.9996	3	0.0018

Analysis of Maximum Likelihood Estimates							
Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Label
race2	1	-0.38116	0.15508	6.0409	0.0140	0.683	race: white
onlycyt	1	-0.34936	0.18007	3.7640	0.0524	0.705	only cytotoxic
bio	1	-0.72147	0.20772	12.0632	0.0005	0.486	biologic

[1] Backwards elimination, starting with all variables, removing the variable with the highest p-value each iteration until all variables remaining in the model have a p-value <0.10.

Outcome: Survival Time

Treated (n=85)

Log Rank Test

Variable	Chi-Square	P-value
Age at diagnosis (<65 years vs. ≥65 years)	0.38	0.54
Sex	0.25	0.62
Race	0.43	0.51
English Fluency	1.28	0.26
Marital Status	0.0000	0.9969
Homelessness	0.42	0.52
Smoking	0.66	0.42
Any Biologic vs. Only Cytotoxic	2.92	0.09

Cox Regression[2]

Testing Global Null Hypothesis: BETA=0			
Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	2.8651	1	0.0905
Score	2.8521	1	0.0913
Wald	2.8188	1	0.0932

Analysis of Maximum Likelihood Estimates						
Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
biovcyt	1	-0.38443	0.22898	2.8188	0.0932	0.681

[2] Backwards elimination, starting with all variables, removing the variable with the highest p-value each iteration until all variables remaining in the model have a p-value <0.10.

Outcome: Survival Time

Untreated (n=113)

Log Rank Test

Variable	Chi-Square	P-value
Age at diagnosis (<65 years vs. ≥65 years)	1.58	0.21
Sex	0.07	0.79
Race	5.98	0.01
English Fluency	4.29	0.04
Marital Status	0.04	0.85
Homelessness	0.13	0.72
Smoking	1.35	0.24

Cox Regression[3]

Testing Global Null Hypothesis: BETA=0			
Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	5.2642	1	0.0218
Score	5.6450	1	0.0175
Wald	5.5501	1	0.0185

Analysis of Maximum Likelihood Estimates							
Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Label
race2	1	-0.48104	0.20419	5.5501	0.0185	0.618	race: white

[3] Backwards elimination, starting with all variables, removing the variable with the highest p-value each iteration until all variables remaining in the model have a p-value <0.10.

Outcome: Survival Time

Including cost per month of survival time

Cox regression
Only cost per month of survival as predictor of survival time

Testing Global Null Hypothesis: BETA=0			
Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	80.1422	1	<.0001
Score	147.1694	1	<.0001
Wald	98.5635	1	<.0001

Analysis of Maximum Likelihood Estimates							
Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Label
costsurvmonth1000	1	0.02404	0.00242	98.5635	<.0001	1.024	Cost per month of survival (in thousands of dollars)

Cox regression
Multivariate model [4]

Testing Global Null Hypothesis: BETA=0			
Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	84.5858	2	<.0001
Score	156.4801	2	<.0001
Wald	101.8771	2	<.0001

Analysis of Maximum Likelihood Estimates							
Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Label
costsurvmonth1000	1	0.02404	0.00243	97.6794	<.0001	1.024	Cost per month of survival (in thousands of dollars)
agediag3	1	0.31105	0.14784	4.4265	0.0354	1.365	Age at diagnosis (<65 years vs. 65 years and older)

[4] Backwards elimination, starting with all variables, removing the variable with the highest p-value each time until all variables remaining in the model have a p-value <0.10.

Outcome: Cost per Month of Survival (estimated imaging)

Treatment types (n=198)

Univariate

Variable	β estimate	P-value
Any Biologic vs. No Treatment (n=150)	4777	0.49
Only Cytotoxic vs. No Treatment (n=161)	-2783	0.65
Any Biologic vs. Only Cytotoxic (n=85)	7560	0.15

Multivariate model of three treatment types (dummy variables) is not significant.

Number of Observations Read	198
Number of Observations Used	198

Analysis of Variance					
Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	1206756444	603378222	0.53	0.5901
Error	195	2.224292E11	1140662429		
Corrected Total	197	2.236359E11			

Root MSE	33774	R-Square	0.0054
Dependent Mean	28318	Adj R-Sq	-0.0048
Coeff Var	119.26375		

Parameter Estimates						
Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	Intercept	1	28101	3177.16191	8.84	<.0001
bio	biologic	1	4776.82869	6397.11436	0.75	0.4561
onlycyt	only cytotoxic	1	-2783.45185	5818.77637	-0.48	0.6329

Outcome: Cost per Month of Survival (estimated imaging)

All (n=198)

Univariate

Variable	β estimate	P-value
Age at diagnosis (<65 years vs. ≥65 years)	-3622	0.45
Sex	5896	0.22
Race	-12615	0.01
English Fluency	-5445	0.43
Marital Status	2251	0.65
Homelessness	15942	0.04
Smoking	6563	0.36
Any Biologic vs. No Treatment (n=150)	4777	0.49
Only Cytotoxic vs. No Treatment (n=161)	-2783	0.65
Any Biologic vs. Only Cytotoxic (n=85)	7560	0.15

Multivariate model[5]

[5] Backwards elimination, starting with all variables, removing the variable with the highest p-value each iteration until all variables remaining in the model have a p-value <0.10.

Number of Observations Read	198
Number of Observations Used	198

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	12107916203	6053958101	5.58	0.0044
Error	195	2.11528E11	1084759046		
Corrected Total	197	2.236359E11			

Root MSE	32936	R-Square	0.0541
Dependent Mean	28318	Adj R-Sq	0.0444
Coeff Var	116.30451		

Parameter Estimates

Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	Intercept	1	33719	3682.72987	9.16	<.0001
race2	race: white	1	-12305	4731.31596	-2.60	0.0100
homeless	homeless	1	15296	7605.61532	2.01	0.0457

Outcome: Cost per Month of Survival (estimated imaging)

Treated (n=85)

Univariate

Variable	β estimate	P-value
Age at diagnosis (<65 years vs. ≥65 years)	-3420	0.51
Sex	-3525	0.50
Race	-5564	0.28
English Fluency	-985	0.89
Marital Status	-3736	0.48
Homelessness	-1676	0.84
Smoking	-1831	0.81
Any Biologic vs. Only Cytotoxic	7560	0.15

Outcome: Cost per Month of Survival (estimated imaging)

Untreated (n=113)

Univariate

Variable	β estimate	P-value
Age at diagnosis (<65 years vs. ≥65 years)	-3819	0.62
Sex	13509	0.08
Race	-19174	0.01
English Fluency	-10190	0.39
Marital Status	6949	0.38
Homelessness	31580	0.01
Smoking	13129	0.25

Multivariate model[6]

[6] Backwards elimination, starting with all variables, removing the variable with the highest p-value each iteration until all variables remaining in the model have a p-value <0.10.

Number of Observations Read	113
Number of Observations Used	113

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	3	25992810402	8664270134	6.28	0.0006
Error	109	1.503853E11	1379681818		
Corrected Total	112	1.763781E11			

Root MSE	37144	R-Square	0.1474
Dependent Mean	28101	Adj R-Sq	0.1239
Coeff Var	132.18235		

Parameter Estimates

Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	Intercept	1	33216	6357.20115	5.22	<.0001
race2	race: white	1	-22592	7529.94215	-3.00	0.0033
marital2	married	1	17393	7752.87195	2.24	0.0269
homeless	homeless	1	37767	12148	3.11	0.0024

All data included (n=224)

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CURRICULUM VITAE