Factors affecting lung cancer survival: a literature Review

Abstract

Lung cancer is a disease which invades the lung tissue by formation of uncontrolled cell growth, and this may also affect the tissues near the lung. There are a wide range of prognostic factors which determine survival duration of lung cancer patients. Among the most important factors are patient demographics, disease factors, and health care related factors. Lung cancer remains one of the leading causes of the overall cancer burden worldwide. The aim of this review is to investigate the existing knowledge and relevant literature on prognostic factors in lung cancer survival. Literature search was carried on OVID databases (1990-2011) that include Ovid MEDLINE in process and EMBASE. In Ovid, truncations were used. Only papers published in English were included. A total of 315 were found and refined, only 43 papers were reviewed. In conclusion, lung cancer survival is influenced by a number of factors that interact to determine the prognosis of patients. Lung cancer survival is not dependent on a single factor of these prognostics, but is affected by the interaction between them.

Keywords: lung cancer, survival, prognostic factors

Introduction

Lung cancer is a disease which invades the lung tissue by formation of uncontrolled cell growth, and this may also affect the tissues near the lung (Metastasis). The primary type of lung cancer is histologically divided into two main types, which are small cell lung carcinoma and non-small cell lung carcinoma. The former accounts for 20% of lung cancer cases, and it is divided into two stages, limited and extensive, whereas the latter represents 80% of cases ,and it is staged into four stages based on the international Tumour Node Metastases (TNM) staging system, which is used for describing the extent of cancer in the body of the

patient . Both cancers behave differently in terms of treatment response and prognosis. Non-small cell lung carcinoma (NSCLC) is sometimes treated with surgery, while small cell lung carcinoma (SCLC) usually responds better to Chemotherapy and radiation (Schiller et al, 2009). Smoking represents the most direct cause of lung cancer, and leads to 90% of lung cancer deaths (Cancer Research UK, 2011).Nevertheless, there are other causes leading to lung cancer in non-smoking people attributed to genetic factors and air pollutants such as asbestos, radon gas, and passive smoking (Thun et al. 2008).

Lung cancer remains one of the leading causes of the overall cancer burden worldwide. On average, lung cancer accounts for 12.3% of all new cancer cases (Bray et al. 2002) .Buccheri and Ferrigno ,1994 in their comprehensive study on prognostic factors in lung cancer pointed out that the number of potentially associated factors with lung cancer outcomes is certainly more than one hundred . The aim of is to investigate the existing knowledge and relevant literature on prognostic factors in lung cancer survival

Methods: Literature search was carried on OVID databases (1990-2011) that include Ovid MEDLINE in process and EMBASE .Further relevant studies were identified by searching the references in the obtained full text papers. Tables1 shows search terms and results of literature search in Ovid, including relevant studies that were published in English. There were 10 searches for each factor affecting survival separately with specific search terms on sex , age, socioeconomic status, performance status, clinical stage, surgery, chemotherapy, radiotherapy, comorbidity and health care . Truncations were used.

Table 1: Ovid Search terms and number of resulted studies on factors affecting lung cancer survival

Search Number	Search terms : in title (duplicate removed) Limits: English Language and 1990-2011	Relevant results
1	(lung cancer* or lung neoplasm* or lung tumo*r* or respiratory cancer* or respiratory neoplasm* or respiratory tumo*r*) and (sex* or gender*) and survival	25
2	(lung cancer* or lung neoplasm* or lung tumo*r* or respiratory cancer* or respiratory neoplasm* or respiratory tumo*r*) and survival and age	12
3	(lung cancer* or lung neoplasm* or lung tumo*r* or respiratory cancer* or respiratory neoplasm* or respiratory tumo*r*) and survival and (depriv* or socioeconomic* or poverty)	3
4	(lung cancer* or lung neoplasm* or lung tumo*r* or respiratory cancer* or respiratory neoplasm* or respiratory tumo*r*) and survival and performance status	8
5	(lung cancer* or lung neoplasm* or lung tumo*r* or respiratory cancer* or respiratory neoplasm* or respiratory tumo*r*) and (clinical stage or tumo*r size) and survival	21
6	(lung cancer* or lung neoplasm* or lung tumo*r* or respiratory cancer* or respiratory neoplasm* or respiratory tumo*r*) and survival and surgery	34
7	(lung cancer* or lung neoplasm* or lung tumo*r* or respiratory cancer* or respiratory neoplasm* or respiratory tumo*r*) and survival and chemotherapy*	152
8	(lung cancer* or lung neoplasm* or lung tumo*r* or respiratory cancer* or respiratory neoplasm* or respiratory tumo*r*) and survival and radiothrap*	47
9	(lung cancer* or lung neoplasm* or lung tumo*r* or respiratory cancer* or respiratory neoplasm* or respiratory tumo*r*) and co*morbidity* and survival	12
10	(lung cancer* or lung neoplasm* or lung tumo*r* or respiratory cancer* or respiratory neoplasm* or respiratory tumo*r*) and health care* and survival	1

Literature review

1. Patient factors

1.1 Sex

The importance of sex as a prognostic factor was highlighted by some researchers. In a retrospective cohort study conducted in Brazil, researchers analysed data of 253 patients of non-small cell lung cancer and observed 5 year survival rate of 85.5% in females and 46.4% in males(Chatkin et al, 2004). These results were obtained after adjusting for age, smoking habit, haemoglobin, tumour size, tumour-node-metastasis stage, prospective complication and surgery type.

Another cohort study from Taiwan was conducted on 695 patients (315 females and 380 males) who were enrolled in the study between January 2002 and December 2005. The study revealed that the better prognosis was found in females compared to males (685 vs.493days) after adjustment for age, disease stage and smoking history (Hsu et al, 2009). There was substantial evidence of sex being a predictor in lung cancer prognosis.

All these studies reported better survival in women after receiving treatment for lung cancer. However, these studies failed to clarify the reason of difference. It has been suggested in other studies that survival advantage associated with women might be due to different natural history of disease and tumour biology (Wisnivesky and Halm, 2007). Another potential cause of difference in survival may be related to difference in treatment response in both sexes (Ferguson et al, 1990). With considerations to reported findings on lung cancer survival and sex, it appears that further studies are needed to adjust for age related differences in death resulting from unrelated cause (life expectancy) which might have confounded the results.

1.2 Age

Age is a decisive factor in treatment option and outcome of a lung cancer patient. Older age is shown to be associated with poor prognosis. A prospective study on patients of non-small lung cancer showed that elderly patients survived for an average of 39 months after surgery compared to an average of 49 months by younger patients (Schulte et al, 2010).

Similarly, a retrospective study conducted on 519 patients showed results suggesting poor prognosis for older patients compared to younger patients (Agarwal et al. 2010). This is in contrast to other studies that consider age of patients as not an important prognostic factor in lung cancer survival and treatment.

A prospective study by Takigawa et al, (1996) on 185 NSCLC patients found no significant effect of age on survival. Hurria and Kris (2003) in their review pointed out that older patients should not be defined by their chronological age, but assessment of their physiological age should be taken into account to determine their prognosis or treatment decision. In addition, some of the recent studies raised the question of age being a negative prognostic factor in lung cancer treatment outcome.

Recently, a review conducted on lung cancer treatment suggested that as life expectancy and the incidence in old age is increasing, the patients and oncologists face an issue on deciding whether to give or not to give the treatment (Pallis and Gridell, 2010). The review concluded that if the same treatment is given to older fit patients the prognosis is similar to treatment outcome for a younger patient (Pallis and Gridell, 2010). However, it is important to consider that the information included in the review was obtained from retrospective studies, which are prone to selection bias.

The importance of age in lung cancer is not only associated with survival but also with the complications after surgery and other complications associated with co- morbidities (Pagano et al. 2010).

1.3 Socioeconomic status

The prognostic significance of such health influencing factor in survival of cancer patients seems controversial. Some studies reported that patients from the least deprived areas are supposed to have better prognosis compared to the most deprived areas. This disparities in survival explained by inequalities in clinical care and presentation with advanced stage in the most deprived patients. The other argument is that no relationship between socioeconomic status and survival of cancer patients.

A retrospective study on 19702 incident cases of NSCLC patients presented with stage I described low socio-economic status as an independent poor prognostic factor after adjusting for surgery, race and marital status (Ou et al ,2008). Another study was conducted on patients of 13 different cancers, including lung cancer, in Australia, who were diagnosed between 1992 and 2000 and followed until the end of 2001(Yu et al , 2008). This study showed significantly worse survival after adjustment for age, sex, and with and without adjustment for stage of disease in lung cancer patients from the most deprived areas ($p<0.0001$) . The study concluded that the difference in survival in different deprivation categories might be because of the difference in access to health care. Potosky et al (2004) also reported considerable variations in the pattern of initial treatment of NSCLC in the United State.

Regarding some existing literature in this field from Scotland, Campbell et al (2000) reported poorer one year survival rate for most deprived lung cancer patients compared with the least deprived (21.2% vs.24%, $p<0.001$). Their study in 2002 suggested that the poorer survival of patients from deprived areas is because they are more likely to present with advanced stage at diagnosis, and not due to differences in treatment rates (Campbell et al, 2002).

By contrast, some studies described the association between socio-economic status and lung cancer prognosis as non-significant. A retrospective study by Hui et al (2005) found no significant difference in survival of patients from different deprivation categories after adjustment for stage of disease, utilisation of different treatment modalities, and health care

services. However, this study had some serious limitations. Although the study showed to be adjusted for disease stage and health care services, the group which was more affluent had an older population compared to the other group, and as mentioned earlier that, older age would be associated with poor prognosis. This might have influenced the analysis to produce non-significant results (p=0.08). In statistical terms the results might not be entirely non-significant as the 'p' value is not much greater than 0.05 and there is existence of 3.3% excess survival for affluent category. There might be an accumulative effect of life style factors, diet and education.

1.4 Co-morbidity

Often co-morbidity is negatively associated with length of survival after the treatment for lung cancer. A study on 1155 patients showed a significant association between co-morbidity and poor survival in both initial and advanced stages of lung cancer after adjustment analysis (Tammemagi et al. 2003). The results of this study significantly explained survival by both common and uncommon co-morbidities. Nineteen common co-morbidities explained 6.1% of survival, while thirteen uncommon co-morbidities explained 3.5% of the survival variation (Tammemagi et al. 2003).

Some of the researchers described co-morbidity as an independent prognostic factor. An analysis conducted on data of 1255 lung cancer patients reported that co-morbidity was significantly associated with the hazard of death [hazard ratio 1.28 ,95% CI 1.09-1.5, p value 0.003](Asmis et al. 2008). However, recently questions have been raised regarding considering co-morbidity as an important prognostic factor for lung cancer treatment. Some of the researchers denied co-morbidity as an independent prognostic factor.

A recently reported study(Regina et al. 2010) used both the indexes (Charlson Co-morbidity Index and simplified Co-morbidity Index) for measuring co-morbidity and obtained that neither of the co-morbidity indexes was significantly associated with survival after lung cancer treatment (p=0.47 and p=0.24 respectively). The study related the co-morbidity with under- treatment and advised consideration of co-morbidity in treatment design rather than a

factor of exclusion for oncologic treatment. But the study itself described the limitation in terms of sample size (83 patients) and described the result's inference as hypothesis-generating rather than conclusive.

From the above discussion it can be inferred that although there are doubts over considering co-morbidity as an independent prognostic factor, the importance of co-morbidity in lung cancer treatment prognosis cannot be declined. The influence of co-morbidity on prognosis might not be solely because of itself , but rather a combination of other factors including age, disease stage, treatment type and design.

1.5 Performance status

Performance status (PS) scoring system such as the Eastern Cooperative Oncology Group (ECOG) is widely used in oncology to estimate the patient's ability to carry out daily activities (Dajczman et al. 2008). The ECOG scale was designed by the World Health Organisation, and it runs from (0 to 4). Performance status information is a crucial prognostic factor of lung cancer survival, and it is useful to determine the appropriate therapeutic course. As an example, patients with (PS 2) are at higher risk of chemotherapy complication, and surgery is not recommended (Blagden et al, 2003).

2. Disease Factors

Certain factors associated with disease are directly linked with prognosis. Discussion and understating of these factors is important in order to comment on treatment and prognosis of the disease. Some of the most important disease -related factors are tumour size, lymph node involvement and distant metastasis or disease staging. These factors are also the important determinant in disease staging. To understand cancer stage, it would be useful to start by discussing the role of tumour size in lung cancer staging and prognosis.

2.1 Tumour size

One of the most important factors in determining the prognosis for a lung cancer patient is the tumour size, especially in the early stages of the disease. A study by Port et al.(2003) conducted analysis on 244 patients and showed that patients with lung tumour size of less than 2 cm had a higher 5-year survival rate than patients with tumour size of 2 to 3 cm. The study concluded that, in order to accurately assess and treat the disease there may be a need of further sub-staging apart from the current lung cancer staging guidelines, which categorise lung tumour as being less than, equal to, or more than the baseline value of 3 cm.

Similarly, another study by Cangir et al.(2004) involving 550 patients, described tumour size as an important prognostic factor. The study presented that the 5 years survival with tumours larger than 5 cm was 31.4%, while for the tumours 3-5 cm is 45.9% which is significantly higher in the latter (P = 0.005). While other studies reported that tumour size is an important survival factor in NSCLC (Mery et al, 2005; Lopez-Encuentra et al, 2002), the association between tumour size and stage distribution is still controversial (Yang et al, 2010).

Tumour size might be linked with the spread of cancer i.e. metastasis that ultimately decides the survival rather than tumour size. However, these views were not supported by researches held to explain the association between tumour size and metastasis. A retrospective study by Heyneman et al (2001) focused on patients with tumour size measuring from less than one centimetre to three centimetres. The researchers concluded from their analysed data that the advanced stage of the lung cancer is not determined by the size of the tumour as data showed that even the smaller tumours could represent an advanced stage of this cancer. They explained that their study suggests that the size of tumours less than or equal to three centimetres plays only a limited role in the metastasis of lung cancer. Regardless of the size of lesion at detection, patients with a primary lesion which is three centimetres or smaller in size will have an approximately 80-85% probability of

having stage I lung cancer ,and an approximately 10% chance of having stage IV lung cancer (Heyneman et al. 2001).

The above discussion underlines the importance of tumour size as a prognostic factor and questions the view that tumour size only decides the metastasis and ultimately the prognosis.

2.**2 Metastasis and/or tumour stage**

The stage of the tumour has a major impact on lung cancer prognosis. Cancer staging is the process of determining tumour size, growth rate, possible metastasis, lymph node involvement, treatment options and prognosis. NSCLC stages range from stage I, in which the cancer has not metastasised, to stage IV, in which the cancer has spread (Heyneman et al. 2001).

A number of studies have concluded that there is strong association between metastasis and survival of the patient after lung cancer treatment. They presented an inverse relation between stage and lung cancer prognosis i.e. more advanced stage is associated with lower survival rate (al-Kattan et al.1996 ;Nykamp 2010) .

A retrospective study by Agarwal et al (2010) estimated survival after surgical treatment and control for age, sex and other factors for NSCLC patients with stage IA, IB, and IIB as 2648 days , 2085 days , and 1405 days , respectively.

2.3 Treatment modalities

Increasing researches have shown a strong association between active treatment and survival improvement of lung cancer, especially in NSCLC. It was estimated that 50% of lung cancer patients are treated with palliative therapy, because they are either presenting with metastatic disease or are medically unfit for active treatments.

Surgical treatment was found to be beneficial for 30% of tumours. Radiotherapy alone or combined with chemotherapy shows a better response in the further 20% of local advanced tumours (Rudd, 1991). A study reported the overall 5-year and 10-year relative survival rates for active treated patients as 14% and 8%, respectively. Whereas for patients who received no cancer directed treatments, these estimations were 5% and 2% respectively (Willard et al, 1999).

Similarly, higher active treatments rates in NSCLC patients were associated with better one year survival rates (23%) compared with (19%) for those received lower treatment rates (Cartman et al, 2002).

A systematic review and meta-analysis of sixteen randomised controlled trials has provided strong evidence on the role of chemotherapy in improving overall survival in all patients with advanced NSCLC , this in addition to supportive care (NSCLC Meta-Analysis Collaborative Group, 2008). A prospective study on lung cancer patients from the South of Scotland reported median survival of patients after treatment with radiotherapy and chemotherapy as 207 days and 251 days respectively (Fergusson et al, 1995).

3. Health care factors

There is availability of different diagnostic and treatment options with advancement in research in the area. These advancements have improved survival time of the lung cancer patients, especially one-year survival. However, the concern stands with the access and timely availability of these options to the population at the risk of lung cancer and/or lung cancer patients. Certain health care factors are quite important determinants of survival of a lung cancer patient. These factors include access to health care, waiting time for treatment after diagnosis and after- treatment needs.

3.1 Access to health care

There have been some researches indicated that the association between socio-economic status and survival could be described by access to health care, which ultimately affects the

survival in lung cancer patients (Auvinen and Karjalainen, 1997) . However, access to health care might not be linked with the socio-economic status as in countries like the UK, where the treatment is offered even for the population of low socio-economic groups. Campbell et al (2002) found that socioeconomic status is unlikely to lead to any delay in treatment after the referral point .A recently conducted research in Korea found a non- significant association between social class and access to health care in different deprivation categories (Yim et al, 2010).

However, there is *a* need for research in this area to identify the factors which describe the access to health care as being a prognostic factor in survival from lung cancer.

3.2 Waiting time for treatment

Recently, researchers have started focussing on the relationship of waiting time for treatment and survival. The reason behind the research was to ascertain whether delay in delivery or obtaining treatment, which might lead to worsening the condition of the disease, affects the survival after the treatment. Various researchers have come up with contrasting views. One of the researchers described the association between increased waiting time and re-occurrence and ultimately poor survival but the results were not similar for different types of cancer(Chen et al. 2008). However, they highlighted the importance of waiting time in disease prognosis.

3 .3 After treatment needs

It is important to provide support services for improving the quality of life or prognosis of cancer patients after treatment. Although most of the patients adjust to the morbidity after treatment, some feel psychological distress and sometimes feel anxiety and depression. Hence there is interaction between the clinical side and support service side of the patient.There is a need to address the issue of after- treatment needs as we concentrate on the treatment of the disease. There might be a need for interdisciplinary action to meet the demands of such situations. However, at present, the majority of the patients do not obtain

support services after treatment but these services are quite important to deliver, especially to females (Ernstmann et al. 2009).

Conclusion:

There are a wide range of prognostic factors which determine survival duration of lung cancer patients. Lung cancer survival is not dependent on a single factor of these prognostics, but is affected by the interaction between them. Among the most important factors are patient demographics, disease factors, and health care related factors.

References

Agarwal, M., Brahmanday, G., Chmielewski, G.W., Welsh, R.J., & Ravikrishnan, K.P.(2010) Age, tumor size, type of surgery, and gender predict survival in early stage (stage I and II) non-small cell lung cancer after surgical resection. *Lung Cancer*, 68, (3) pp.398-402

Asmis, T.R., Ding, K., Seymour, L., Shepherd, F.A., Leighl, N.B., Winton, T.L., Whitehead, M., Spaans, J.N., Graham, B.C., Goss, G.D., & National Cancer Institute of Canada Clinical Trials Group.(2008). Age and comorbidity as independent prognostic factors in the treatment of non small-cell lung cancer: a review of National Cancer Institute of Canada Clinical Trials Group trials. *Journal of Clinical Oncology,26(1)* pp.54-9,

Al-Kattan, K., Sepsas, E., Townsend, E.R., & Fountain, S.W.(1996).Factors affecting long term survival following resection for lung cancer. *Thorax*, 51, (12) pp.1266-1269

Auvinen, A. & Karjalainen, S.(1997). Possible explanations for social class differences in cancer patient survival. *IARC Scientific Publications*.(138) pp.377-97

Bray, F., Sankila, R., Ferlay, J., & Parkin, D.M.(2002).Estimates of cancer incidence and mortality in Europe in 1995. *European Journal of Cancer,*38(1)pp.99-166

Buccheri, G. & Ferrigno, D. (1994). Prognostic factors in lung cancer: tables and comments. *European Respiratory Journal*, 7, (7) pp.1350-1364.

Blagden, SP., Charman, SC., Sharples, LD., Magee, LRA., & Gilligan, D.(2003).Performance status score: do patients and their oncologists agree?*, British Journal of Cancer* , 89,pp. 1022 – 1027

Cancer Research UK (2011). *Lung cancer and smoking statistics - Key Facts*.Available from: http://info.cancerresearchuk.org/cancerstats/keyfacts/lung-cancer/

Chatkin, J.M., Abreu, C.M., Fritscher, C.C., Wagner, M.B., & Pinto, J.A. (2004). Is there a gender difference in non-small cell lung cancer survival? *Gender Medicine,*1(1)pp.41-7

Campbell, NC. Elliott, AM., Sharp, L., Ritchie, LD., Cassidy, J., Little, J .(2000) .Rural factors and survival from cancer: analysis of Scottish cancer registrations. *Br J Cancer*, 82, pp.1863 – 1866

Campbell, N.C., Elliott, A.M., Sharp, L., Ritchie, L.D., Cassidy, J., & Little, J. (2002). Impact of deprivation and rural residence on treatment of colorectal and lung cancer. *British Journal of Cancer*, 87, (6)pp. 585-590 .

Cangir, A.K., Kutlay, H., Akal, M., Gungor, A., Ozdemir, N., & Akay, H. (2004). Prognostic value of tumor size in non-small cell lung cancer larger than five centimeters in diameter.[Erratum appears in Lung Cancer. 2005 Nov;50(2):281-2]. *Lung Cancer,46(3)*pp325-31

Cartman, M.L., Hatfield, A.C., Muers, M.F., Peake, M.D., Haward, R.A., & Forman, D. (2002). Lung cancer: district active treatment rates affect survival. *Journal of Epidemiology and Community Health*, 56, (6)pp. 424-429 .

Chen, Z., King, W., Pearcey, R., Kerba, M., & Mackillop, W.J.(2008). The relationship between waiting time for radiotherapy and clinical outcomes: A systematic review of the literature. *Radiotherapy and Oncology.*87 (1) pp 3-16

Dajczman, E., Kasymjanova, G., Kreisman, H., Swinton, N., Pepe, C., & Small, D. (2008). Should patient-rated performance status affect treatment decisions in advanced lung cancer? *Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer*, 3, (10) pp.1133-1136

Ernstmann, N., Neumann, M., Ommen, O., Galushko, M., Wirtz, M., Voltz, R., Hallek, M., & Pfaff, H.(2009). Determinants and implications of cancer patients' psychosocial needs. *Supportive Care in Cancer,*17(11)pp.1417-23

Ferguson, MK., Skosey, C., Hoffman, PC, and Golomb, HM.(1990).Sex-associated differences in presentation and survival in patients with lung cancer, *JCO .(8)*pp.1402-1407

Fergusson, R., McLean, C., Dodds, R., & Gregor, A. (1995). Palliative care of patients with lung cancer: Management practices and outcomes in South East Scotland. *European Respiratory Journal*, 8, (SUPPL. 19) 183S.

Hurria, A. & Kris, M.G. (2003). Management of Lung Cancer in Older Adults. *CA: A Cancer Journal for Clinicians*, 53, (6) pp.325-341.

Hsu, LH., Chu, NM., Liu, CC., Tsai, SY., You, DL., and Ko, JS .(2009). Sex-associated differences in non-small cell lung cancer in the new era: is gender an independent prognostic factor? *Lung Cancer,* 66 (2) pp. 262-7

Hui , AC., Vinod, SK., Jalaludin, BB., Yuile, P., Delaney, GP., & Barton, MB. (2005). Socio-economic status and patterns of care in lung cancer. *Australian & New Zealand Journal of Public Health,* 29, (4) pp. 372-7

Heyneman, L.E., Herndon, J.E., Goodman, P.C., & Patz, E.F. (2001). Stage distribution in patients with a small (< 3 cm) primary nonsmall cell lung carcinoma. *Cancer*, 92, (12) pp.3051-3055 .

Lopez-Encuentra, A., Duque-Medina, JL., Rami-Porta, R., Camara, AG., & Ferrando, P. (2002). Staging in lung cancer: is 3 cm a prognostic threshold in pathologic stage I non-small cell lung cancer? A multicenter study of 1020 patients. *Chest*, 121, pp.1515-1520

Mery, CM., Pappas, AN., Burt, BM., Bueno, R., Linden, PA., Sugarbaker, DJ., & Jaklitsch, M.(2005) . Diameter of non-small cell lung cancer correlates with long-term survival. Implications for T stage. *Chest,* 128, pp.3255-3260.

Nykamp, V. (2010). Surgical treatment of non-small cell lung cancer. [Review] [9 refs]. South Dakota Medicine.The Journal of the South Dakota State Medical Association.,Spec No:57-9

NSCLC Meta-Analysis Collaborative Group. (2008). Chemotherapy in Addition to Supportive Care Improves Survival in Advanced NonGÇôSmall-Cell Lung Cancer: A Systematic Review and Meta-Analysis of Individual Patient Data From 16 Randomized Controlled Trials. *Journal of Clinical Oncology*, 26, (28)pp. 4617-4625

Ou, S.H., Zell, J.A., Ziogas, A., & Anton-Culver, H. (2008). Low socioeconomic status is a poor prognostic factor for survival in stage I nonsmall cell lung cancer and is independent of surgical treatment, race, and marital status. *Cancer,*112(9)pp.2011-20

Pallis, AG., and Gridelli, C. (2010). Is age a negative prognostic factor for the treatment of advanced/metastatic non-small-cell lung cancer?. *Cancer Treatment Reviews,* 36, (5) pp.436-41

Pagano, E., Filippini, C., Di Cuonzo, D., Ruffini, E., Zanetti, R., Rosso, S., Bertetto, O., Merletti, F., & Ciccone, G. (2010). Factors affecting pattern of care and survival in a population-based cohort of non-small-cell lung cancer incident cases. *Cancer Epidemiology.*34(4)pp. 483-9

Potosky, AL., Saxman, S., Wallace ,RB., Lynch, CF.(2004). Population variations in the initial treatment of non-small-cell lung cancer. *J Clin Oncol,* 22 (16) pp.3261–3268.

Port, J.L., Kent, M.S., Korst, R.J., Libby, D., Pasmantier, M., & Altorki, N.K. (2003). Tumor size predicts survival within stage IA non-small cell lung cancer. *Chest,*124(5)pp.1828-33,

Regina, G. s., Dolores, T., Jos, G., Inma, M., Jose, M., & Rafael, R. (2010)Prognostic impact of comorbidity in elderly lung cancer patients: Use and comparison of two scores. *Lung cancer,72*(1) pp.108-13

Rudd R. (1991). Chemotherapy in the treatment of non-small cell lung cancer*. Respiratory Disease in Practice*, 7, pp.12-14

Schiller, J., Parles, K., Cipau, A. (2009).*100 Questions & Answers about Lung Cancer.* Second Edition. United Sate of America :Jones & Bartlett Learning:

Schulte, T., Schniewind, B., Walter, J., Dohrmann, P., chler, T., & Kurdow, R. (2010). Age-related impairment of quality of life after lung resection for non-small cell lung cancer*. Lung Cancer,* 68, (1) pp.115-20

Thun, M.J., Hannan, L.M., Adams-Campbell, L.L., Boffetta, P., Buring, J.E., Feskanich, D., Flanders, W.D., Jee, S.H., Katanoda, K., Kolonel, L.N., Lee, I.M., Marugame, T., Palmer, J.R., Riboli, E., Sobue, T., Avila-Tang, E., Wilkens, L.R., & Samet, J.M. (2008). Lung cancer occurrence in never-smokers: an analysis of 13 cohorts and 22 cancer registry studies. *PLoS Medicine / Public Library of Science*, 5, (9) e185

Takigawa, N., Segawa, Y., Okahara, M., Maeda, Y., Takata, I., Kataoka, M., & Fujii, M. (1996). Prognostic factors for patients with advanced non-small cell lung cancer: univariate and multivariate analyses including recursive partitioning and amalgamation. *Lung Cancer*, 15, (1)pp. 67-77.

Tammemagi, C.M., Neslund-Dudas, C., Simoff, M., & Kvale, P. (2003). Impact of comorbidity on lung cancer survival. *International Journal of Cancer,*103(6) pp.792-802

Wisnivesky, JP., & Halm, EA (2007) .Sex Differences in Lung Cancer Survival: Do Tumours Behave Differently in Elderly Women? *.J Clinical Oncology*,13(25), pp.1705-1711.

Willard, AF. Jerri, LP. , & Herman, RM. (1999). Ten-Year Survey of Lung Cancer Treatment and Survival in Hospitals in the United States. *Cancer,* 86, pp. 1867-1876

Yu, XQ., O'Connell, DL., Gibberd, RW., & Armstrong, BK. (2008). Assessing the impact of socio-economic status on cancer survival in New South Wales, Australia 1996-2001. *Cancer Causes & Control,* 19, (10) pp.1383-1390.

Yang, F., Chen, H., Xiang, J., Zhang, Y., Zhou, J., Hu, H., Zhang, J., & Luo, X.(2010). Relationship between tumor size and disease stage in non-small cell lung cancer. *BMC Cancer*, 10, (1) p. 474 .

Yim, J., Hwang, S.,Yoo, K.,& Kim, C. (2010). Contribution of income-related inequality and healthcare utilisation to survival in cancers of the lung, liver, stomach and colon. *Journal Epidemiol Community Health.*