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Risk factors associated with treatment refusal in lung cancer

Won Na Suh[1], Kyoung Ae Kong[2], Yeji Han[1], Soo Jung Kim[1], Su Hwan Lee[1], Yon Ju Ryu[1], Jin Hwa Lee[1], Sung Shine Shim[3], Yookyung Kim[3] & Jung Hyun Chang[1]

1 Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Ewha Womans University School of Medicine, Seoul, South Korea
2 Department of Preventive Medicine, Ewha Womans University School of Medicine, Seoul, South Korea
3 Department of Radiology, Ewha Womans University School of Medicine, Seoul, South Korea

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Correspondence
Jung Hyun Chang, Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Ewha Womans University School of Medicine, 1071 Anyangcheon-ro, Yangcheon-gu, Seoul 07985, South Korea.
Tel: +82 2 2650 5686
Fax: +82 2 2655 2076
Email: hs1017@ewha.ac.kr

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Abstract

Background: The incidence of lung cancer is increasing with longer life expectancy. Refusal of active treatment for cancer is prone to cause patients to experience more severe symptoms and shorten survival. The purpose of this study was to define the factors related to refusal or abandonment of active therapy in lung cancer.

Methods: We retrospectively reviewed the data of 617 patients from medical records from 2010 to 2014. Two groups were formed: 149 patients who refused anti-cancer treatment and allowed only palliative care were classified into the non-treatment group, while the remaining 468 who received anti-cancer treatment were classified into the treatment group.

Results: The groups differed significantly in age, employment, relationship status, number of offspring, educational status, body mass index, presence of chest and systemic symptoms, Charlson Comorbidity Index, Eastern Cooperative Oncology Group score, and tumor node metastasis stage ($P < 0.05$). In logistic regression analysis, age (odds ratio [OR] 1.10, 95% confidence interval [CI] 1.07–1.13), educational status lower than high school (OR 1.95, 95% CI 1.2–3.2), no history of surgery (OR 2.29, 95% CI 1.4–3.7), body mass index < 18.5 (OR 2.49, 95% CI 1.3–4.7), and a high Eastern Cooperative Oncology Group score of 3 or 4 (OR 5.02, 95% CI 2.3–10.8) were significant factors for refusal of cancer treatment.

Conclusion: Individual factors, such as old age, low educational status, low weight, and poor performance status can influence refusal of cancer treatment in patients with lung cancer, and should be considered prior to consultation with patients.

Introduction

Lung cancer remains the most frequent cause of cancer-related death worldwide.[1,2] The American Cancer Society estimates that in 2017 in the United States (US) there will be 222 500 new cases (116 990 in men and 105 510 in women) and 155 870 deaths from lung cancer. Lung cancer accounts for approximately 25% of all cancer deaths in the US and is by far the leading cause of cancer death in men and women.[3] Non-small cell lung cancer (NSCLC) accounts for >85% of these deaths.[4] Prognosis is poor, with a five-year survival rate of 10–12%.[5] In NSCLC, 60–65% of all patients have locally advanced unresectable or metastatic disease when diagnosed.[6] Elderly patients comprise a substantial proportion of NSCLC patients, and this rate is expected to increase to 70% of all patients with cancer by 2030 in the US.[7] In Korea, the lungs are the third most common primary cancer site in men and the fifth in women. However, as in other countries, lung cancer is still the most common cause of cancer-related death in both genders, despite decreasing trends in incidence and mortality.[8]

Despite the high incidence of lung cancer and its high mortality rate in elderly patients, the likelihood of receiving active treatment appears to decrease with increasing age.[9,10] Even with the serious prognosis of lung cancer, some patients with earlier-stage disease can be cured. More than 430 000 people alive today in the US have been diagnosed with lung cancer.[3] Treatment of lung cancer consists of chemotherapy, surgery, radiotherapy, targeted therapy, or combined therapy,[11,12] and requires a prolonged process during which patients continuously experience uncertainty regarding curability and prognosis.[13] In particular, during the terminal stages of cancer, patients may face a fear of death and feel hopelessness.[14]

When patients lose control of their bodies and dignity, they are prone to become depressed and may subsequently choose to refuse or avoid medical treatment.[15,16] Refusal of cancer treatment might result in rapid deterioration, emergence of physical symptoms, and metastasis. A study conducted in Taiwan showed that the mortality risk for lung cancer patients refusing treatment was elevated 2.1-fold.[17] Other studies of breast and colorectal cancer have consistently revealed that patients who delayed or refused therapy had lower five-year survival rates compared to treated patients.[18,19] There is a consensus that untreated cancer patients have a poorer prognosis than treated patients. It is important to discuss which factors can affect treatment refusal of cancer patients.[20] In Korea, most cancer patients pay only 5% of the total cost of treatment, with the remainder covered by national health insurance. Even then, some patients or their families decide not to undergo cancer treatment. This study was designed to investigate the factors that influence refusal of anti-cancer treatment, to guide patients and their families.

Methods

Study population and data source

We retrospectively reviewed the clinical records of patients with a confirmed diagnosis of lung cancer that were treated in one tertiary university hospital from January 2010 to December 2014. The inclusion criteria were: (i) pathological confirmation of lung cancer, and (ii) patients received active anti-cancer treatment in our hospital (cancer surgery, chemotherapy, radiation therapy) or palliative care only.

A total of 704 lung cancer patient records were evaluated, but 87 were excluded because of incomplete data, transfer to another hospital (according to patient preference), or loss to follow-up. Among the remaining 617 patients, 149 (24.2%) had avoided all kinds of anti-cancer treatment except palliative care, such as analgesics or symptomatic relievers, and were classified into a non-treatment group (NTG). The remaining 468 (75.8%) patients who received anti-cancer treatments, including surgery, chemotherapy, and/or radiation therapy, regardless of therapeutic or palliative purpose, were classified into the treatment group (TG). The Institutional Review Board of Mokdong Hospital, Seoul, South Korea approved the study (EUMC 2016-02-022) and waived the need for informed consent.

Study variables

The variables comprised age, gender, history of smoking, history of alcohol consumption, employment, religion, relationship status, number of offspring, educational status, history of surgery, personal history of cancer, familial history of cancer, body mass index (BMI), pathological type of lung cancer, respiratory symptoms (including chest pain, hemoptysis, dyspnea, cough, and sputum), systemic symptoms (including weight loss and fever), Charlson Comorbidity Index (CCI, age-adjusted),[21] Eastern Cooperative Oncology Group (ECOG) performance status (PS) score, and tumor node metastasis (TNM) stage.

Statistical analysis

Demographic and clinical characteristics between the two groups were compared by Student's *t*, chi-square or Fisher's exact test, depending on whether the characteristic was continuous or discrete. To assess the factors associated with a decision to refuse treatment, logistic regression analyses were conducted. Factors associated with treatment refusal with a P value < 0.05 in age-adjusted logistic regression analysis were included in multiple logistic regression analysis. $P < 0.05$ was considered to be statistically significant. SPSS version 22.0 (IBM Corp., Armonk, NY USA) was used for the analysis.

Results

Demographics

Bivariate analysis was conducted to compare the TG and NTG (Table 1). Age, occupation, relationship status, number of offspring, educational status, BMI, systemic and chest symptoms, age-adjusted CCI, ECOG PS score, and TNM stage were significantly different between the groups ($P < 0.05$). The mean age of the NTG (75 ± 9 years) was higher than that of the TG (66 ± 10 years) and the proportion of patients aged >76 was 56% in the NTG versus 15% in the TG ($P < 0.001$). One hundred and thirty-five (91%) patients in the NTG were unemployed compared to 344 (74%) in the TG ($P < 0.001$). Ninety-eight (69%) patients in the NTG were in a relationship compared to 374 (82%) in the TG ($P = 0.002$). One hundred and eight (72%) patients in the NTG had low educational status

Table 1 Demographic data of enrolled patients

	Non-treatment group (NTG) (n = 149)	Cancer treatment group (TG) (n = 468)	P
Age	75 ± 9	66 ± 10	<0.001†
31–65	19 (13%)	202 (43%)	<0.001‡
66–75	47 (31%)	195 (42%)	
76–94	83 (56%)	71 (15%)	
Gender			
Male	100 (67%)	316 (68%)	0.926‡
Female	49 (33%)	152 (32%)	
Smoking (pack year)			
<10	90 (60%)	283 (60%)	0.988‡
≥10	59 (40%)	185 (40%)	
Alcohol			
Non-drinker	97 (65%)	287 (61%)	0.408‡
Drinker	52 (35%)	181 (39%)	
Occupation			
Unemployed	135 (91%)	344 (74%)	<0.001‡
Employed	14 (9%)	124 (26%)	
Religion			
Absent	88 (59%)	264 (56%)	0.569‡
Present	61 (41%)	204 (44%)	
Relationship status			
None	44 (31%)	83 (18%)	0.002‡
In a relationship	98 (69%)	374 (82%)	
Offspring			
0	6 (4%)	33 (7%)	0.003‡
1–2	53 (36%)	227 (49%)	
>3	90 (60%)	208 (44%)	
Education			
Less than high school	108 (72%)	241 (52%)	<0.001‡
More than high school	41 (28%)	227 (48%)	
History of surgery			
Absent	98 (66%)	269 (58%)	0.073‡
Present	51 (34%)	199 (42%)	
Personal history of cancer			
Absent	135 (91%)	408 (87%)	0.262‡
Present	14 (9%)	60 (13%)	
Cancer family			
Absent	145 (97%)	441 (94%)	0.194§
Present	4 (3%)	27 (6%)	
BMI			
18.5–25	87 (58%)	320 (68%)	<0.001‡
>25	27 (18%)	113 (24%)	
<18.5	35 (24%)	35 (8%)	
Pathology			
Small cell carcinoma	22 (18%)	65 (14%)	0.270‡
Non-small cell carcinoma	101 (82%)	402 (86%)	
Chest symptoms			
Absent	41 (28%)	177 (38%)	0.022‡
Present	108 (72%)	291 (62%)	
Systemic symptoms			
Absent	64 (43%)	309 (66%)	<0.001‡
Present	85 (57%)	158 (34%)	
CCI, age adjusted	7.3 ± 3.7	5.1 ± 3.9	< 0.001†
ECOG			
0	16 (11%)	189 (40%)	<0.001‡
1	46 (31%)	185 (40%)	
2	33 (22%)	49 (10%)	
3–4	54 (36%)	45 (10%)	
TNM			
Stage 1	9 (6%)	92 (20%)	<0.001‡
Stage 2	6 (4%)	35 (8%)	
Stage 3	23 (15%)	86 (18%)	
Stage 4	111 (75%)	255 (54%)	

†Student's *t*-test; ‡Pearson's χ^2 test; §Fisher's exact test. Chest symptoms: chest pain, hemoptysis, dyspnea, cough or sputum. Systemic symptoms: weight loss or fever. BMI, body mass index; CCI, Charlson comorbidity index; ECOG, Eastern Cooperative Oncology Group; TNM, tumor node metastasis.

compared to 241 (52%) in the TG ($P < 0.001$). Thirty-five (24%) patients in the NTG had BMI < 18.5 (which reflected poor nutrition) compared to 35 (8%) in the TG, whereas 27 (18%) patients in the NTG had BMI > 25 (which indicated obesity) compared to 113 (24%) in the TG ($P < 0.001$). One hundred and eight (72%) patients in the NTG had chest symptoms compared to 291 (62%) in the TG, and 85 (57%) patients in the NTG had systemic symptoms compared to 158 (34%) in the TG ($P < 0.001$). The CCI score indicative of comorbidity was higher in the NTG than in the TG ($P < 0.001$). Poor ECOG PS was more common in the NTG compared to the TG ($P < 0.001$). A more advanced stage of lung cancer was observed in the NTG than in the TG ($P < 0.001$). Other factors of gender, history of smoking, history of alcohol consumption, religion, history of surgery, personal history of cancer, familial history of cancer, and pathological type of lung cancer (NSCLC and small cell cancer) did not differ significantly between the groups.

Analyses of risk factors related to refusal of cancer treatment

In age-adjusted univariate analysis, age (odds ratio [OR] 1.12, 95% confidence interval [CI] 1.09–1.14, $P < 0.001$), low educational status (OR 1.62, 95% CI 1.05–2.51; $P = 0.03$), no history of surgery (OR 1.92, 95% CI 1.25–2.94; $P = 0.003$), BMI < 18.5 (OR 3.36, 95% CI 1.86–6.07; $P < 0.001$), presence of systemic symptoms (OR 2.52, 95% CI 1.67–3.80; $P < 0.001$), CCI (OR 1.17, 95% CI 1.11–1.23; $P < 0.001$), a high ECOG PS score of 3 or 4 (OR 8.07, 95% CI 4.08–15.94; $P < 0.001$), and higher cancer stage (stage 4) (OR 4.45, 95% CI 2.01–9.59;

Table 2 Risk factors for treatment refusal in lung cancer

	Age adjusted analysis			Multivariate analysis		
	Odds ratio	95% CI	P	Odds ratio	95% CI	P
Age	1.12	1.09–1.14	<0.001	1.10	1.07–1.13	<0.001
Gender						
Female	Reference					
Male	1.03	0.67–1.60	0.880			
Smoking (pack year)						
<10	Reference					
≥10	1.21	0.80–1.83	0.359			
Alcohol						
Non-drinker	Reference					
Drinker	1.07	0.71–1.64	0.738			
Occupation						
Unemployed	Reference					
Employed	0.83	0.43–1.60	0.581			
Religion						
Absent	Reference					
Present	0.88	0.58–1.32	0.532			
Relationship status						
None	Reference					
In a relationship	0.87	0.54–1.42	0.581			
Offspring						
0	Reference					
1–2	1.28	0.46–3.58	0.638			
≥3	1.14	0.41–3.14	0.800			
Education						
More than high school	Reference			Reference		
Less than high school	1.62	1.05–2.51	0.030	1.95	1.20–3.17	0.007
History of surgery						
Present	Reference			Reference		
Absent	1.92	1.25–2.94	0.003	2.29	1.42–3.69	0.001
Personal history of cancer						
Present	Reference					
Absent	1.71	0.89–3.29	0.108			
Cancer family						
Absent	Reference					
Present	0.73	0.24–2.23	0.583			
BMI						
18.5–25	Reference			Reference		
>25	1.06	0.63–1.78	0.839	1.38	0.77–2.46	0.278
<18.5	3.36	1.86–6.07	<0.001	2.49	1.32–4.71	0.005
Pathology						
Small cell carcinoma	Reference					
Non-small cell carcinoma	0.68	0.38–1.20	0.181			
Chest symptoms						
Absent	Reference					
Present	1.43	0.92–2.21	0.113			
Systemic symptoms						
Absent	Reference			Reference		
Present	2.52	1.67–3.80	<0.001	1.26	0.76–2.10	0.377
CCI, age adjusted	1.17	1.11–1.23	<0.001	1.02	0.95–1.10	0.511
ECOG						
0	Reference			Reference		
1	1.87	0.99–3.52	0.052	1.42	0.73–2.77	0.301
2	3.64	1.76–7.55	0.001	2.37	1.07–5.23	0.033
3–4	8.07	4.08–15.94	<0.001	5.02	2.32–10.84	<0.001

Table 2 Continued

	Age adjusted analysis			Multivariate analysis		
	Odds ratio	95% CI	P	Odds ratio	95% CI	P
TNM						
Stage 1	Reference			Reference		
Stage 2	1.63	0.50–5.32	0.422	1.18	0.33–4.27	0.804
Stage 3	2.92	1.21–7.01	0.017	1.86	0.72–4.82	0.202
Stage 4	4.45	2.01–9.59	<0.001	2.21	0.92–5.34	0.078

BMI, body mass index; CCI, Charlson comorbidity index; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; TNM, tumor node metastasis.

$P < 0.001$) were significantly related to refusal of cancer treatment (Table 2). In multivariate analysis, age (OR 1.10, 95% CI 1.07–1.13; $P < 0.001$), low educational status (OR 1.95, 95% CI 1.20–3.17; $P = 0.007$), no history of surgery (OR 2.29, 95% CI 1.42–3.69; $P = 0.001$), low BMI (< 18.5) (OR 2.49, 95% CI 1.32–4.71; $P = 0.005$), and a high ECOG PS score of 3 or 4 (OR 5.02, 95% CI 2.32–10.84; $P < 0.001$) were significantly related to refusal of cancer treatment in the NTG (Table 2).

Discussion

The treatment of lung cancer is still a challenging issue as malignant tumors in adults carry a relatively poor prognosis, and the elderly are reluctant to undergo treatment because of concerns about adverse events. This study revealed that age, low education reflecting inferior socioeconomic status, low nutrition, and poor PS significantly influenced the decision whether to accept treatment for lung cancer.

Possible factors influencing treatment refusal in cancer patients include concerns about adverse events, underlying comorbidity, poor familial support, transport difficulty, and use of alternative medicine. Cancer patients might also refuse treatment because of inadequate channels of communication with the medical team, resulting in lack of awareness about their medical condition and treatment options.[22] The attitude of the physicians and the content of their explanations are usually the key factors that help patients to decide whether to receive treatment. Budkaew and Chumworathayi reported that adequate medical knowledge, a good attitude of patients, physicians' awareness of patient concerns, and physicians' timely clarification of doubts increase patients' willingness to receive treatment.[23,24]

We showed that refusal rates of treatment in lung cancer increased with age, consistent with previous studies in colorectal and breast cancer.[2,17–19,24–27] According to a national cohort study of lung cancer in Taiwan, the treatment refusal rate increased proportionally for each 10-year age increment and the rate of treatment refusal among patients ≥75 years old was increased 2.6-fold compared to those aged ≤44 years.[17] In colorectal cancer patients, the treatment refusal group was on average 4.6 years older than the treated group.[18,19] In the US, 3% of patients, primarily elderly, non-black/non-white, and unmarried female patients refuse palliative radiation for metastatic NSCLC.[28] In our study, the mean age difference between the TG and NTG was nine years. Lung cancer occurs mainly in elderly patients and mortality increases with age,[29] particularly in Asian and Caucasian populations. According to South Korean national statistics, the incidence of lung cancer has markedly increased from 33.7 per 100 000 in 2004 to 47.3 in 2014.[30] In particular, the proportion of patients aged ≥70 was 42.4% in 2004 and 53.6% in 2014,[30] suggesting that lung cancer tends to occur more often in elderly patients and has increased with the aging population in Korea. In China, lung cancer has replaced liver cancer as the leading cause of death in patients with malignant tumors, and lung cancer mortality has increased 4.6 times during the past 30 years because of tobacco consumption and environmental pollution.[31] Lung cancer has reached an age-specific peak incidence in patients aged 80–84 in China.[32] Similar findings have been reported in Caucasian populations.[33,34] An English study found that lung cancer was common in elderly people, with 43% of patients aged ≥75 at presentation.[25]

Our results showed that there was no significant difference in treatment refusal between genders, similar to previous studies in Taiwan.[17,19] One US study reported that men refused treatment for NSCLC twice as often as women.[35] Conversely, a report from the Netherlands suggested that men prefer to receive cancer treatment more often than women.[36] These different findings are likely a result of different study designs and sampling bias.

Data on non-treated cancer patients in Canada indicated that the rate of treatment refusal increased among residents in low urbanized areas. Patients with low income or who were unemployed exhibited a 1.3–1.5-fold higher rate of treatment refusal.[24] Concurrently, Lin *et al.* conducted a study on treatment adherence in breast cancer patients and indicated that medical

expenses contributed to non-adherence.[37] Another study revealed that unemployment and low educational status were predictive factors of treatment refusal.[20] In contrast, other studies have shown that urbanization is not a significant factor related to refusal of cancer treatment.[17,18] We did not directly examine the financial and residential status of our patients; however, low educational status, suggesting low economic status, was a significant variable in treatment refusal, while unemployment was not. A US study showed an association between race and patient refusal of surgery for lung cancer, as well as age and unmarried status, suggesting cultural differences in recognizing cancer.[38] The will to overcome cancer might differ according to cultural background and socioeconomic status in a particular country.

Our data showed that absence of surgical history was a significant factor in treatment refusal for cancer. This suggests that a lack of clinical experience or information about clinical circumstances may cause patients to act negatively or passively. However, further investigation is required to confirm this point.

Low BMI, weight loss, and PS have long been regarded as major prognostic factors in lung cancer.[39,40] Our study found that low BMI as well as poor PS were risk factors for treatment refusal in cancer. This suggests that BMI (representing nutritional status) and poor PS should be taken into consideration as predictive factors of cancer treatment decisions.[20]

Huang *et al.* and Huchcroft & Snodgrass found that multiple cancer diagnoses or advanced cancer contributed to refusal or discontinuation of treatment.[17,24]. Chen *et al.* and Liu *et al.* also found that cancer staging and concomitant catastrophic illnesses were closely associated with treatment refusal.[18,19] Advanced lung cancer stage was significantly different between our two groups in bivariate but not in multivariate analysis. After multiple variable adjustments, this variable lost its individual impact on treatment refusal.

Because of a demographic shift toward an older population and improved survival of patients with cardiovascular diseases, more elderly people are at risk of developing lung cancer.[27] The increase in mean age consequently results in more patients being in a situation of polypharmacy,[41,42] decline in physiological function,[43,44] and various comorbidities,[45,46] with a consequent increase in cancer incidence. These factors increase the risk of mortality and may lead to serious complications during surgical and systemic treatment.[47–50] CCI in our study was not a risk factor for refusal of cancer treatment in multivariate analysis, even though it had significance in univariate analysis.

The strategy to overcome treatment abandonment, especially in weak groups such as the elderly, and patients with poor nutrition, low education, or poor PS should include full details of current cancer status and possible treatment options from medical teams. Active attitudes of physicians positively influence patients and their families.[23,24] Communication with the hospital specialist team, as well as deep familial support, can affect treatment decisions.[22] The management of lung cancer is becoming increasingly complex, and comprehensive measures and a strategy for lung cancer need to be established, with consideration of such individualized conditions.

This study had some limitations. This was a non-randomized observational study with a small sample; however, clinical trials are ethically unfeasible in such a setting.[51] Data from one institution and selection bias in dividing the patients into two groups were also limitations.

Despite the limitations of sample size and possible selection bias, this study revealed which factors influence refusal of cancer treatment in patients with newly diagnosed lung cancer. Advanced age, low education, low weight, and poor PS could affect patients and clinicians when determining treatment of cancer.

Disclosure

No authors report any conflict of interest.

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