Lung Cancer 131 (2019) 1–5

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Treatment, no treatment and early death in Danish stage I lung cancer patients

Niels Lyhne Christensen[a,b,*], Susanne Dalton[c,d], Jesper Ravn[e], Jane Christensen[a], Erik Jakobsen[f], Torben Riis Rasmussen[b]

[a] Department of Documentation and Quality, Danish Cancer Society, Strandboulevarden 49, 2100 Copenhagen Ø, Denmark
[b] Department of Respiratory Diseases and Allergy, Aarhus University Hospital, Palle Juul-Jensens Blvd, 8200 Aarhus, Denmark
[c] Danish Cancer Society Research Center, Danish Cancer Society, Strandboulevarden 49, 2100 Copenhagen Ø, Denmark
[d] Department of Clinical Oncology & Palliative Care, Zealand University Hospital, Rådmandsengen 5, 4700 Næstved, Denmark
[e] Department of Thoracic Surgery, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark
[f] The Danish Lung Cancer Registry, Department of Thoracic Surgery, Odense University Hospital, Odense, Denmark

ARTICLE INFO

Keywords:
Lung cancer epidemiology
Stage I
Mortality
Treatment
No treatment

ABSTRACT

Background: Stage I lung cancer is curable with surgery as the treatment of choice. Other effective and curative treatments exist. Nevertheless, some patients only receive palliative treatment and some receive no treatment at all.

Materials and methods: Using the Danish Lung Cancer Registry (DLCR), we assessed treatment distribution for a population-based Danish cohort of stage I lung cancer patients diagnosed from 2011 to 2014. We assessed one-year mortality according to treatment. Furthermore, in a nested case-control study based on data from medical records, we assessed the reason for not undergoing treatment among patients in favourable performance status (PS) with no treatment registration in the DLCR.

Results: We identified 2985 patients, 68% (n = 2021) were treated surgically and 17% (n = 508) were managed with curative oncological therapy. The unadjusted odds ratio (OR) for death within one year was 2.5 (95% CI, 1.8–3.3) for the oncologically managed vs. the surgically treated. After adjusting for age, lung function and PS, the OR was 1.2 (95% CI, 0.8–1.9).

Among 129 patients with a PS of 0–1 and no treatment registration, we established the reason for not undergoing treatment in 122 (95%). The majority (70%) were misclassified and did either not have lung cancer, had more advanced disease or were curatively treated. The 36 (30%) patients that did not undergo treatment, had a lower prevalence of adenocarcinomas (17 vs. 51%, p = 0.003), more comorbidites (median Charlson comorbidity index score 2 vs. 1, p < 0.001) and high alcohol intake (19 vs. 7%, p = 0.04) as compared to surgically treated controls. The primary reasons for no treatment were; comorbidity, patient decision and disease progression.

Conclusion: Difference in outcome between the two major treatment groups was confounded by age, lung function and PS. Comorbidity, high alcohol intake and histology were associated with not undergoing curative treatment in spite of a favourable PS.

1. Background

Lung cancer is globally the most common cause of cancer related death [1]. Compared to other developed countries, mortality rates among Danish lung cancer patients have historically been high [2]. Stage at diagnosis is the most significant prognostic factor, and serves as a proxy for disease burden and as a treatment indicator [3–5]. Under consideration of their general condition, it is pivotal for the prognosis that the patients receive the most effective and safest treatment modality [6,7]. For early stage lung cancer, several treatment options exist and surgery is associated with the most favourable outcome [8,9]. However, stereotactic body radiotherapy is an effective alternative, particularly for patients that are medically unfit for surgery [10,11]. More recently, radiofrequency ablation (RFA) and microwave therapy

* Corresponding author at: Department of Respiratory Diseases and Allergy, Aarhus University Hospital, Palle Juul-Jensens Blvd, 8200 Aarhus, Denmark.
E-mail addresses: niechris@rm.dk (N.L. Christensen), sanne@cancer.dk (S. Dalton), jesper.ravn@regionh.dk (J. Ravn), jane@cancer.dk (J. Christensen), erik.jakobsen@rsyd.dk (E. Jakobsen), torbrasm@rm.dk (T.R. Rasmussen).

https://doi.org/10.1016/j.lungcan.2019.03.007
Received 25 December 2018; Received in revised form 6 March 2019; Accepted 8 March 2019

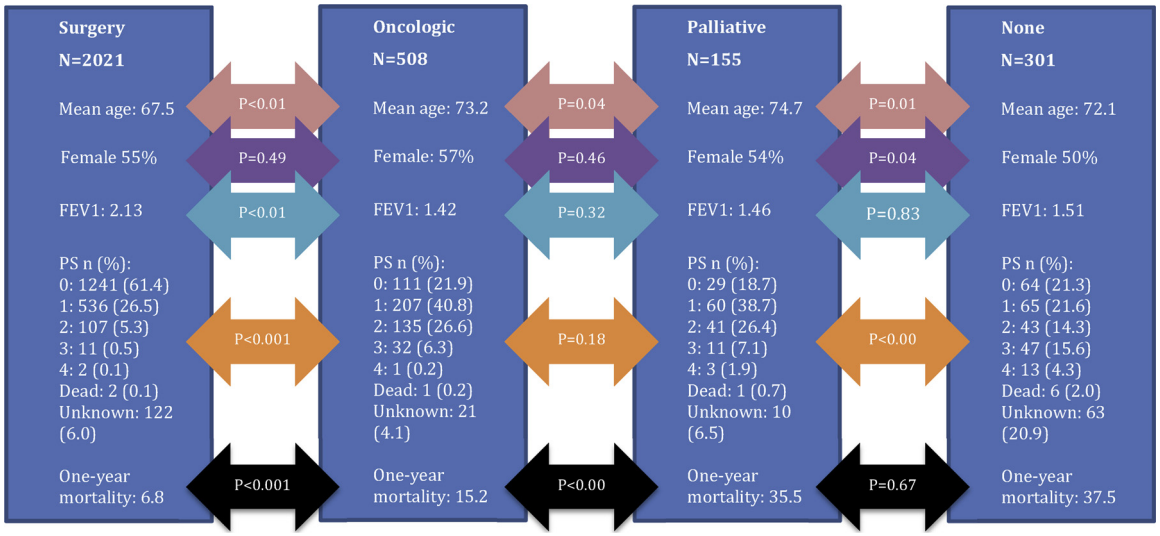

Fig. 1. Treatment patterns of clinical stage I lung cancer patients diagnosed from 2011 to 2014 in Denmark.
Legend: Mean age in years. FEV1 forced expiratory volume (liters) in one second. PS performance status. Differences in age means by student's t-test. Differences in FEV1 By Mann Whitney *U* test gender, performance status and one-year mortality by chi-squared.

(MWA) have been suggested as treatment options [12,13]. After staging, patient-specific factors as age, physical performance and burden of comorbidity including lung function need to be considered in the evaluation of the patient's ability to tolerate the treatment modality of choice [14,15].

In a population-based cohort of recently diagnosed clinical stage I patients identified through the Danish Lung Cancer Registry (DLCR), we aimed to establish treatment patterns and the corresponding association with one-year mortality. Furthermore, by adding data from patients' medical records, we aimed to explore why patients with a Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or I and no treatment registration, did not undergo treatment for their lung cancer, while exploring factors related to not undergoing treatment.

2. Material and methods

Data sources for the present study were the Danish Lung Cancer Registry (DLCR) and medical records. The DLCR has since year 2000 collected data regarding tumour, patient characteristics and treatment details reported to the registry by the departments involved with primary care of lung cancer patients [16]. DLCR has a completeness of more than 95%. Via the DLCR, we identified all patients diagnosed with stage I lung cancer from 2011 - 2014. For this cohort of patients, we assessed the one-year mortality according to treatment modality as registered in the DLCR.

Patients who according to the DLCR had no treatment registration and a PS of 0 or 1 (cases, no treatment group), were matched with three controls according to age, gender and PS that had been surgically treated. In order to obtain more detailed data than can be retrieved from the DLCR regarding patient characteristics and treatment details, we retrieved a copy of the medical records from both the no treatment group and the matched controls.

2.1. Study variables

In the comparison of the entire cohort according to treatment, differences in mean age, female/male ratio and lung function, defined as forced expiratory volume (liters) in one second (FEV1) and performance status and one-year mortality were assessed. There are four main treatment categories in the DLCR: Surgical treatment, curative oncological treatment (including stereotactic body radiotherapy, conventional external beam radiotherapy and concomitant chemo-radiotherapy), palliative treatment and no treatment. Additionally, two categories related to the treatment registration include adjuvant and neoadjuvant treatment also exist.

For patients with no treatment registration in the DLCR, information from the medical records was used to establish the reason for not undergoing curative treatment. This was categorized into either patient decision, due to comorbidity, death prior to treatment or other reasons. Given the potential for misclassification in the DLCR, we also registered whether the patient actually had stage I lung cancer. If the patient had in fact been treated, we registered the type of treatment and whether the treatment had been with curative intent. In case of incorrect stage or disease classification, we did not assess the treatment details.

Based on data from the medical records, we assessed the overall burden of somatic comorbidity by using the Charlson comorbidity index [17], nutritional status, smoking and alcohol drinking habits. We also registered which diagnostic tests were performed during the diagnostic work-up.

2.2. Statistical analyses

Two-sample tests of proportions, Pearson chi squared distributions and Fischer's exact test were used for descriptive statistics as stated. Age means according to treatment groups were compared by the student's t-test, if data were assumed as normally distributed based on Q-Q plots. Differences in FEV1 and CCI were assessed by using the Mann-Whitney *U* test

Comparative analyses of the association between treatment modality and one-year mortality were performed in both an adjusted and unadjusted logistic regression model. The multivariate model was adjusted for age and FEV1 as continuous variables and PS as a categorical variable.

3. Results

3.1. Treatment registration and early death

In the DLCR cohort, 2985 patients were registered with stage I lung cancer from 2011 - 14. The mean age was 69.3 years, 55% were female and the one-year mortality was 13%. Main results regarding treatment distributions are given in Fig. 1. The majority (2529, 85%) received therapy with curative intent, 68% (n = 2021) were surgically treated and 17% received curative oncological therapy. However, there was a

Table 1
Type of misclassification among 86 patients registered in the Danish Lung Cancer Register as diagnosed with stage I lung cancer, performance status 0–1 and no registration of treatment, 2011-2014.

Type of misclassification	No treatment group (n = 86)	
	N	%
No cancer	11	13
Other type of cancer	9	10
Clinical stage	9	10
Surgery	29	34
Oncology	12	14
Radio frequency ablation	13	15
Microwave ablation	2	2
Argon beam	1	1

significant difference in overall one-year mortality between the two treatment modalities, corresponding to an unadjusted odds ratio (OR) for death within the first year in the oncological vs. the surgical group of 2.5 (95% CI, 1.8–3.3). Given the significant differences in age and distribution of PS, we adjusted for these, which resulted an adjusted OR of 1.2 (95% CI, 0.8–1.9). In the comparison of palliative vs. curative oncologic therapy, the unadjusted OR for death within the first year was 3.1 (95% CI, 2.0–4.6).

3.2. Treatment misclassification

Among the patients with no registration of treatment, 64 patients had a PS = 0 and 65 had a PS = 1, and should thus have been potential candidates for curative therapy (Fig. 1). We were able to retrieve the medical records of 122 (95%) of these 129 patients for further review. As seen in Table 1, 86 (70%) were misclassified and 57 (46%) of the patients with no treatment registration had in fact been curatively treated. The most frequent treatment modalities were surgery or curatively intended oncologic treatment. Of the nine patients that had another cancer than lung cancer, eight (89%) had malignant mesothelioma. None of the 108 surgically treated controls were misclassified.

3.3. Non-treated vs matched surgically treated

Thirty-six patients (30%) of the 122 stage I patients with no treatment registration that were included in the review of medical records, were correctly registered as not having received treatment (Table 2). These patients thus constituted 1.2% of the DLCR entire cohort. The primary cause for no treatment was comorbidity in 16 cases (44%), patient's decision in 10 cases (28%), disease progression in four cases (11%), death before treatment in three cases (8%), and tumour location, high PS at time of treatment, or unknown reason respectively in one case each (3%, 3%, 3% respectively). As seen in Table 2, patients that did not receive treatment generally had a higher burden of comorbidity, more frequently had high-risk alcohol intake, and fewer had PET scans performed as part of their diagnostic work up. There were significant differences in the distribution of histologic subtypes as compared to the surgically treated controls. Histologic subtypes according to reason for not undergoing treatment are provided in Table 3. Due to small numbers no conclusions can be drawn from the data (Fischer's exact p-value = 0.42).

We conducted a subgroup analysis of the 16 patients who were not treated due to comorbidity. The mean age was 71.4 years, 69% were male and the median CCI score was 4.5 (range 1–9) vs. 1 (range 0–4) among the surgically treated controls (p = 0.0001). The primary type of comorbidity related to no treatment was another cancer (n = 8), severely reduced lung function (n = 6) and physical inability to cooperate to radiotherapy (n = 2).

For the 10 patients who declined treatment, the mean age was 75.5 years (range 55–84), 40% were male and the mean CCI was 2.1 vs. 1.3 among their matched controls (P = 0.12).

Table 2
Descriptive characteristics of patients correctly registered as not treated and patients treated surgically in the Danish Lung Cancer Register from 2011 to 2014.

Characteristics	No treatment (n = 36) %	Surgically treated controls (108) %	P-value
Patient-related			
Age years mean (range)	72.6 (51–86)	72.3 (50–89)	0.86
Female/male %	47/53	47/53	1
CCI median (range)	2 (0-9)	1 (0-4)	< 0.001
Never-smoker	3	6	0.50
Smoking at diagnosis	58	40	0.07
High-risk alcohol intake	19	7	0.04
Diagnostic work-up			
Discussed at MDT	100	100	1
PET/CT	83	99	< 0.001
Biopsy	81	84	0.61
Bronchoscopy	75	88	0.06
EBUS	61	74	0.14
EUS	17	19	0.71
Cancer histology			
Adenocarcinoma	17	51	0.003
Squamous	25	28	0.75
NSCLC	11	14	0.67
Small-cell	14	2	0.04
Other	14	4	0.03
Unknown	19	2	0.002

CCI, Charlson comorbidity index. MDT, multidisciplinary team conference, PET/CT positron emission tomography - computed tomography. EBUS, endobronchial ultrasound. EUS, endoscopy, NSCLC, non-small-cell lung cancer. Other histology includes: Carcinoid tumours and not otherwise speficied (NOS) histology.

4. Discussion

According to the DLCR, 85% of Danish stage I lung cancer patients diagnosed from 2011 to 2014 were curatively treated. Surgery was associated with the best short-term prognosis, probably due to both an effective treatment modality and selection of younger patients with a good lung function and a favourable performance status into this treatment group. The weakened association between the surgical and oncological treatment and one-year mortality in the adjusted analysis supports this mechanism, and is in accordance with the findings of several other retrospective studies as concluded in a review by Shultz et al [18]. Not surprisingly, the palliative group had significantly higher one-year mortality as compared to the group that received curatively intended oncologic therapy.

We retrieved additional information regarding patients that based on performance status were *a priori* candidates for curative therapy, but had no treatment registration and found that the majority of these patients were misclassified. Consequently, we identified an additional 57 patients (2% of all stage I patients) that received curatively intended therapy. A subgroup of the curatively treated patients received either radio frequency ablation or microwave therapy and at time for entry into the DLCR, there was no registration code for these procedures, which explains our findings regarding these patients. Concerning misclassified patients, there was no obvious reason for misclassification. Thus, simply failing to report treatment details to the DLCR, correcting or informing the DLCR about patients who were initially wrongfully suspected of having lung cancer but were later found to have another disease (mesothelioma) are the most feasible explanations. This study was not designed to assess the overall data validity of the DLCR and the overall rate of misclassification. We have reported the types of misclassification encountered in a highly selected group of patients, with opposing registrations of PS and treatment. Furthermore, among the 108 matched controls, none were misclassified, thus the overall rate of

Table 3
Histologic subtypes according to the primary reason for not undergoing therapy in Danish stage I lung cancer patients diagnosed between.2011–2014.

Reason	Unknown histology	Adeno	NOS	NSCLC	Carcinoid	Squamous	Small-cell	Total
Patient decision	4	0	0	1	0	4	1	10
Co-morbidity	3	4	2	1	1	3	2	16
Tumor location	0	0	1	0	0	0	0	1
Disease progress	0	1	0	1	0	1	1	4
Death	0	1	0	1	0	1	0	3
High PS	0	0	0	0	0	0	1	1
Unknown	0	0	0	0	1	0	0	1
Total	7	6	3	4	2	9	5	36

Adeno: Adenocarcinoma. PS Performance status. NOS Not otherwise specified. NSCLC non-small-cell lung cancer.

misclassification in the DLCR is arguably much lower.

In general, fewer diagnostic procedures were undertaken among the non-treated patients as compared to the surgically treated controls. Albeit only reaching statistical significance in terms of PET-scans, this association is in accordance with the Danish lung cancer guidelines that recommend that a PET scan should be undertaken if the patient is a candidate for curative therapy. Hence curability may have been questioned in these patients already during the staging phase. Furthermore, there was a significant difference in burden of comorbidity between the no-treatment group and the controls. Limited utilization of diagnostic procedures and comorbidity has to our knowledge not been studied in depth, however a retrospective cohort study of several cancers including 14,096 patients by Gurney et al. found that a high burden of comorbidity was associated with not receiving a final stage designation [19]. Furthermore, the CCI has in addition to being a validated prognostic marker [20,21] also been found to be a predictor for receiving guideline-consistent treatment [22,23], which our findings support. In addition to the CCI, we specifically assessed the reason for not undergoing treatment. The primary non-malignant disease relating to not receiving curative treatment was severe COPD, which has been linked to an adverse outcome in surgically lung cancer patients [24]. For patients who had another cancer, the primary reasons for not undergoing treatment for the lung cancer were either dissemination of or severe treatment complications to the second cancer, and probably merely reflect a prioritized and individually assessed order of treatments.

A history of high-risk alcohol intake and cigarette smoking were also associated with not being treated. Our findings corroborate those of other studies of surgically treated patients where high alcohol intake was adversely related to outcome [25,26]. Furthermore, our findings regarding alcohol and smoking could also indirectly reflect a lower socioeconomic position among patients not treated [27,28] or even point to a causal link between low socioeconomic position and treatment refusal, which for instance was observed in a retrospective cohort study by Na Suh et al. where age, stage, sociodemographic factors and performance status were significant predictors of treatment refusal among 617 lung cancer patients [29]. In our stage - and performance status-restricted study, only 10 patients declined treatment and these patients tended to be older than those who did not receive treatment for other causes, but the burden of comorbidity was not significantly higher than their age, gender and performance status-matched controls.

Furthermore, we saw a significant difference in the distribution of histologic subtypes among the non-treated patients. Due to the limited diagnostic work-up in the no-treatment group, the proportion of patients with unknown histology was expectedly higher. In terms of the predominantly non-adenocarcinoma histology associated with not undergoing treatment, our findings are in accordance with a register-based study of 190,539 non-treated advanced-stage lung cancer patients [30]. However, due to the limited size of our study population our findings do not readily point to any specific causality and larger studies are needed in order to address these findings further.

Among the oncologically treated, patients that were treated with palliative intent were slightly older than those who were treated with curative intent, but they had similar distribution in terms of PS. Further studies should be undertaken in order to address the reasons for not receiving curative therapy.

4.1. Strengths and limitations

We assessed the treatment patterns among recently diagnosed stage I lung cancer patients in a population-based setting. For the subgroup of patients with no registration of treatment, we validated the register-based data with highly detailed data from the medical records for both the cases and controls, thus avoiding the inherent risk of selection and information bias associated with case-control studies.

Limitations to our study apply. The majority of the patients with no registration of treatment were misclassified, thus reducing the size of the study population and the power to identify significant associations. Having based our study population on stage I patients alone, makes comparisons to otherwise similar studies difficult. A few patients had a PS of 5 (dead), thus performance status could have been reported to the DLCR at different times during the course of disease. We did not have data on socioeconomic factors (civil status, education and household income) and CCI for the entire DLCR cohort and including these could have provided further information. However these factors may be of less significance in a Danish setting, where access to health care is free of charge due to the tax financed health care system. We did not have data regarding comorbidity (CCI) for the entire cohort, but only for the subgroup of patients subjected to review of medical records. The CCI-score, smoking and drinking habits were based on data from the medical records without validation, facilitating a potential for misclassification regarding these variables. We believe however, that this potential misclassification bias is non-differential and have not affected the direction of the observed associations.

5. Conclusion

Differences in one-year mortality between surgically and curative oncologic therapy were mainly driven by differences in age and performance status between the two treatment groups. The majority of stage I lung cancer patients in a favourable performance status who had no registration of treatment were misclassified and either did in fact receive curative treatment, did not have lung cancer or had a higher stage than what was registered. Only 1.2% did not undergo treatment, the primary reasons for not receiving treatment included comorbidity and patient decision. Compared to the surgically treated patients, high-risk alcohol intake, smoking and non-adenocarcinoma histology were associated with not undergoing treatment. Whether the treatment distribution and proportion of non-treated are in line with those of other countries with similar health-care systems and/or better one-year mortality needs to be confirmed in future comparative studies.

Acknowledgements

The study was funded by the Danish Cancer Society under grant

number: 52271004. Thank you to all departments that provided data to the study. To Linda Aagaard Thomsen, Lotte Linnemann, Anne Mette Kejs and the Danish Lung Cancer Group for support.

References

[1] A. Jemal, F. Bray, J. Ferlay, Global Cancer Statistics, CA Cancer J. Clin. 61 (2) (2011) 69–90, https://doi.org/10.3322/caac.20107.

[2] S. Walters, C. Maringe, M.P. Coleman, et al., Lung cancer survival and stage at diagnosis in Australia, Canada, Denmark, Norway, Sweden and the UK: a population-based study, 2004-2007, Thorax 68 (6) (2013) 551–564, https://doi.org/10.1136/thoraxjnl-2012-202297.

[3] P. Goldstraw, J. Crowley, K. Chansky, et al., The IASLC lung cancer staging project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumours, J. Thorac. Oncol. 2 (8) (2007) 706–714, https://doi.org/10.1097/JTO.0b013e31812f3c1a.

[4] F.C. Detterbeck, D.J. Boffa, A.W. Kim, L.T. Tanoue, The eighth edition lung cancer stage classification, Chest 151 (1) (2017) 193–203, https://doi.org/10.1016/j.chest.2016.10.010.

[5] P.E. Postmus, K.M. Kerr, M. Oudkerk, et al., Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow-up, Ann. Oncol. 28 (January) (2017) iv1–iv21, https://doi.org/10.1093/annonc/mdx222.

[6] H. Wao, R. Mhaskar, A. Kumar, B. Miladinovic, B. Djulbegovic, Survival of patients with non-small cell lung cancer without treatment: a systematic review and meta-analysis, Syst. Rev. 2 (1) (2013) 10, https://doi.org/10.1186/2046-4053-2-10.

[7] R.H. Nanda, Y. Liu, T.W. Gillespie, et al., Stereotactic body radiation therapy versus no treatment for early stage non-small cell lung cancer in medically inoperable elderly patients: a national cancer data base analysis, Cancer 121 (23) (2015) 4222–4230, https://doi.org/10.1002/cncr.29640.

[8] V. Puri, T.D. Crabtree, J.M. Bell, et al., Treatment outcomes in stage I lung cancer a comparison of surgery and stereotactic body radiation therapy, J. Thorac. Oncol. 10 (12) (2015) 1776–1784, https://doi.org/10.1097/JTO.0000000000000680.

[9] F.C. Detterbeck, S.Z. Lewis, R. Diekemper, D. Addrizzo-Harris, W.M. Alberts, Executive Summary: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines, Chest 143 (5 Suppl) (2013) 7–37, https://doi.org/10.1378/chest.12-2377.

[10] F. Soldà, M. Lodge, S. Ashley, A. Whitington, P. Goldstraw, M. Brada, Stereotactic radiotherapy (SABR) for the treatment of primary non-small cell lung cancer; systematic review and comparison with a surgical cohort, Radiother. Oncol. 109 (1) (2013) 1–7, https://doi.org/10.1016/j.radonc.2013.09.006.

[11] L. Ceniceros, J. Aristu, E. Castañón, et al., Stereotactic body radiotherapy (SBRT) for the treatment of inoperable stage I non-small cell lung cancer patients, Clin. Transl. Oncol. 18 (3) (2016) 259–268, https://doi.org/10.1007/s12094-015-1361-4.

[12] T.J. Vogl, Nour-Eldin N-EA, M. Albrecht, et al., Thermal ablation of lung tumors: focus on microwave ablation, Fortschr Röntgenstr 189 (2017) 828–843, https://doi.org/10.1055/s-0043-109010.

[13] D.E. Dupuy, H.C. Fernando, S. Hillman, et al., Radiofrequency ablation of stage IA non-small cell lung cancer in medically inoperable patients: results from the American College of Surgeons Oncology Group Z4033 (Alliance) trial, Cancer 121 (19) (2015) 3491–3498, https://doi.org/10.1002/cncr.29507.

[14] M. Kovarik, M. Hronek, Z. Zadak, Clinically relevant determinants of body composition, function and nutritional status as mortality predictors in lung cancer patients, Lung Cancer 84 (1) (2014) 1–6, https://doi.org/10.1016/j.lungcan.2014.01.020.

[15] M. Alexander, R. Wolfe, D. Ball, et al., Lung cancer prognostic index: a risk score to predict overall survival after the diagnosis of non-small-cell lung cancer, Br. J. Cancer 117 (5) (2017) 744–751, https://doi.org/10.1038/bjc.2017.232.

[16] E. Jakobsen, A. Green, K. Oesterlind, T.R. Rasmussen, M. Iachina, T. Palhof, Nationwide Quality Improvement in Lung Cancer Care: the Role of the Danish Lung Cancer group and Registry, (2013), pp. 1238–1247.

[17] M.E. Charlson, P. Pompei, K.L. Ales, C.R. MacKenzie, A new method of classifying prognostic comorbidity in longitudinal studies: development and validation, J. Chronic Dis. 40 (5) (1987) 373–383, https://doi.org/10.1016/0021-9681(87)90171-8.

[18] D.B. Shultz, M. Diehn, B.W. Loo, To SABR or not to SABR? Indications and contraindications for stereotactic ablative radiotherapy in the treatment of early-stage, oligometastatic, or oligoprogressive non–small cell lung cancer, Semin. Radiat. Oncol. 25 (2) (2015) 78–86, https://doi.org/10.1016/j.semradonc.2014.11.005.

[19] J. Gurney, D. Sarfati, J. Stanley, The impact of patient comorbidity on cancer stage at diagnosis, Br. J. Cancer 113 (9) (2015) 1375–1380, https://doi.org/10.1038/bjc.2015.355.

[20] T. Deleuran, R. Werbich Thomsen, M. Nørgaard, J. Bonde Jacobsen, T. Riis Rasmussen, M. Søgaard, Comorbidity and survival of Danish lung cancer patients from 2000–2011 : a population-based cohort study, Clin. Epidemiol. 5 (Suppl 1) (2013) 31–38.

[21] M. Lüchtenborg, E. Jakobsen, M. Krasnik, K.M. Linklater, A. Mellemgaard, H. Møller, The effect of comorbidity on stage-specific survival in resected non-small cell lung cancer patients, Eur. J. Cancer 48 (18) (2012) 3386–3395, https://doi.org/10.1016/j.ejca.2012.06.012.

[22] M. Iachina, A. Green, E. Jakobsen, The direct and indirect impact of comorbidity on the survival of patients with non-small cell lung cancer: a combination of survival, staging and resection models with missing measurements in covariates, BMJ Open 4 (2) (2014), https://doi.org/10.1136/bmjopen-2013-003846.

[23] M.L. Janssen-Heijnen, R.M. Schipper, P.P. Razenberg, Ma. Crommelin, J.W. Coebergh, Prevalence of co-morbidity in lung cancer patients and its relationship with treatment: a population-based study, Lung Cancer 21 (2) (1998) 105–113, https://doi.org/10.1016/S0169-5002(98)00039-7.

[24] R. Zhai, X. Yu, A. Shafer, J.C. Wain, D.C. Christiani, The impact of coexisting COPD on survival of patients with early-stage non-small cell lung cancer undergoing surgical resection, Chest 145 (2) (2014) 346–353, https://doi.org/10.1378/chest.13-1176.

[25] M. Poullis, J. McShane, M. Shaw, et al., Prediction of in-hospital mortality following pulmonary resections: improving on current risk models, Eur. J. Cardio-thoracic Surg. 44 (2) (2013) 238–243, https://doi.org/10.1093/ejcts/ezs658.

[26] A. Green, J. Hauge, M. Iachina, E. Jakobsen, The mortality after surgery in primary lung cancer: results from the Danish lung cancer registry, Eur. J. Cardio-Thoracic Surg. (2015) 1–6, https://doi.org/10.1093/ejcts/ezv107.

[27] S.E. Collins, Associations between socioeconomic factors and alcohol outcomes, Alcohol Res. 38 (1) (2016) 83–94 http://www.ncbi.nlm.nih.gov/pubmed/27159815%5Cnhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC4872618.

[28] R. Hiscock, L. Bauld, A. Amos, J.A. Fidler, M. Munafò, Socioeconomic status and smoking: a review, Ann. N. Y. Acad. Sci. 1248 (1) (2012) 107–123, https://doi.org/10.1111/j.1749-6632.2011.06202.x.

[29] W.N. Suh, K.A. Kong, Y. Han, et al., Risk factors associated with treatment refusal in lung cancer, Thorac. Cancer 8 (5) (2017) 443–450, https://doi.org/10.1111/1759-7714.12461.

[30] E.A. David, M.E. Daly, C.S. Li, et al., Increasing rates of No treatment in advanced-stage non–small cell lung cancer patients: a propensity-matched analysis, J. Thorac. Oncol. 12 (3) (2017) 437–445, https://doi.org/10.1016/j.jtho.2016.11.2221.