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ABSTRACT

INTRODUCTION: Lung cancer remains a leading cause of cancer-related death. The incidence increases with age and the occurrence in young patients is relatively low. The clinicopathological features of lung cancer in younger patients have not been fully explored previously.

METHODS: To assess the age differences in the clinical characteristics of lung cancer, we conducted a retrospective analysis comparing young patients ≤ 65 years of age with an elderly group > 65 years of age. Among 1,232 patients evaluated due to suspicion of lung cancer in our fast-track setting from January-December 2013, 312 newly diagnosed lung cancer patients were included.

RESULTS: Patients ≤ 65 years had a significantly higher representation of females (p = 0.0021), more frequent familial cancer aggregation (p = 0.028) and a lower incidence of squamous cell carcinoma (p = 0.0133). When excluding pure carcinoid tumours, a significantly higher proportion of the younger patients presented with advanced stage disease (p = 0.0392). Combined modality therapy was more common in younger patients (p = 0.0009), while chemotherapy appeared less prevalent among the elderly (p = 0.0015).

CONCLUSIONS: Lung cancer in younger patients comprises a distinct clinicopathological entity with more frequent advanced stage disease and a significantly greater proportion with a family history of cancer. Implementing genetic background assessments and considering lung cancer as a possible diagnosis in younger, symptomatic patients, is of paramount importance.

FUNDING: none.

TRIAL REGISTRATION: The study was approved by the Danish Data Protection Agency.

Lung cancer is among the most common malignancies worldwide. In 2012, the death rate from lung cancer almost reached the combined mortality from breast, prostate and colon cancer [1]. Lung cancer has an overall five-year survival of 17%; however, when diagnosed in early stages, it is possible to offer treatment with a curative intent which raises the five-year survival to > 50% [2].

Lung cancer typically affects elderly individuals. Approximately two out of three patients diagnosed with lung cancer are 65 years or older; fewer than 2% of all cases are found in patients younger than 45 years of age [1]. The average age at diagnosis is about 70 years [1].

As our clinical impression is that younger patients present in more advanced stages, we conducted a retrospective analysis to examine the clinical characteristics and management of a cohort of newly diagnosed lung cancer patients.

METHODS

The medical records of patients referred for evaluation of suspected lung cancer at Vejle Hospital in 2013 were reviewed for epidemiologic data and clinical history. During this period, 1,232 patients were evaluated in our fast-track setting, and in 332 patients the diagnosis was confirmed.

The following parameters were extracted and analysed: age, gender, smoking habits, occupational/environmental exposure to asbestos, previous cancer, self-reported familial history of cancer, symptoms, performance status (PS) as defined by the Eastern Cooperative Oncology Group [3], clinical stage, cytological/histological subtype, diagnostic procedures and treatment. Cyto-histopathology was categorised according to the World Health Organization classification of lung tumours, whereas clinical staging was based upon the international tumour-node-metastasis system as defined in the seventh edition by the The International Union Against Cancer in 2010 [4].

Patients with intrathoracic metastases from extrapulmonary cancer (n = 1) without unambiguous clinical staging or sufficient biopsy verification (n = 19) were excluded from the analysis. Eligible patients were categorised into four groups according to age: ≤ 55 years, 56-65 years, 66-75 years and finally > 75 years (**Table 1**, **Table 2** and **Table 3**).

Statistical analyses were performed on combined age groups, comparing the clinicopathological features of patients ≤ 65 years (defined in the following as younger patients) with patients > 65 years (defined in the following as elderly patients).

We conducted all statistical analyses using 2 × 2 contingency tables in GraphPad software.

p-values were calculated by Fisher's two-tailed exact test due to low numbers in some calculations when absolute numbers were compared. Welch's t-test was utilised for mean value comparisons.

Trial registration: The study was approved by the Danish Data Protection Agency.

ORIGINAL ARTICLE

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RESULTS

Demographic data

The final retrospective study sample included data on 312 patients. Their age ranged from 21-93 years with a median age of 69 years. Female patients were slightly overrepresented, and the highest female-to-male ratio (1.7) was found in the youngest age group (Table 1).

Most patients (93.6%) were current or ex-smokers with a mean cumulative tobacco consumption of 43.2 pack-years (range: 2-252 pack-years). There were no differences between male and female smokers in the two age groups ($p = 0.4808$ for patients ≤ 65 years; $p = 0.2249$ for patients > 65 years). In 37 patients (11.9%), exposure to asbestos was recorded, whereas 97 medical records failed to address this issue. No significant age differences were found (Table 1).

A total of 115 patients (36.9%) presented a family history of cancer. Familial cancer accumulation proved considerably more prevalent among the younger lung cancer patients ($p = 0.028$ for any family history of cancer, $p = 0.0026$ for a family history of lung cancer and $p < 0.0001$ for ≥ 1 first-degree relative with lung cancer, respectively) (Table 1, **Figure 1**A).

Symptoms

Symptoms were similar in both age groups (Table 1) and included: persistent cough (50%), dyspnoea (34.6%), weight loss (31.4%), pain (most commonly in the chest, shoulder and abdomen) (28.5%) and chronic fatigue (21.8%). Less frequently reported symptoms were haemoptysis (11.5%), fever/recurring pneumonia (10.6%), nocturnal sweating (9.6%) and neurological complaints (16.7%). There were no statistically significant age differences in the duration of predominant symptoms (Table 1).

Of the 312 patients included, 45 (14.4%) were asymptomatic (Table 1). In these patients, lung cancer was primarily discovered as an unsuspected incidental finding on a chest X-ray/computed tomography (CT) during routine medical check-up.

Diagnostic procedures

Diagnostic procedures were overall comparable across the age groups. The majority of patients (99.7%) underwent CT of the chest and abdomen, whereas 91.7% had positron emission tomography (PET)/CTs performed (Table 2).

TABLE 1

Base-line characteristics and symptoms.

	Age, yrs				
	≤ 55	56-65	66-75	> 75	p-value[a]
Base-line characteristics					
Patients, n (%)	29 (9.2)	82 (26.3)	121 (38.8)	80 (25.6)	< 0.0001
Males, n (%)	10 (34.5)	31 (37.8)	66 (54.5)	45 (56.3)	0.0021
Current or former smoker, n (%)	26 (89.7)	76 (92.7)	115 (95)	75 (93.8)	0.4693
Smoking, pack-years, n, mean [range]	32.5 [3-95]	38.8 [2-150]	48.2 [3-252]	43.9 [10-130]	0.0019
Asbestos exposure, n (%)	2 (6.9)	9 (11)	16 (13.2)	10 (12.5)	0.4700
Family history of cancer, n (%)	13 (44.8)	37 (45.1)	44 (36.4)	21 (26.3)	0.028
Family history of lung cancer, n (%)	8 (27.6)	15 (18.3)	12 (9.9)	5 (6.3)	0.0026
Family history of ≥ 1 1st-degree relative with lung cancer, n (%)	4 (13.8)	14 (17.1)	11 (9.1)	4 (5)	< 0.0001
Previous cancer, n (%)	3 (10.3)	15 (18.3)	27 (22.3)	19 (23.8)	0.1885
WHO performance status ≤ 2, n (%)	29 (100)	79 (96.3)	115 (95)	70 (87.5)	0.0827
FEV1, % predicted	79.3	72.4	68.9	70.5	0.0358
COPD, n (%)	10 (35.7)	42 (53.8)	69 (62.2)	50 (64.9)	0.0433
Symptoms					
Duration of predominant symptom, weeks, mean [range]	19.7 [1-114]	13.7 [1-96]	22.2 [1-720]	14.5 [1-58]	0.2097
Haemoptysis, n (%)	2 (6.9)	9 (11)	14 (11.6)	11 (13.8)	0.5813
Pain, n (%)	17 (58.6)	22 (26.8)	39 (32.2)	11 (13.8)	0.0666
Dyspnoea, n (%)	12 (41.4)	26 (31.7)	44 (36.4)	26 (32.5)	1.0000
Cough, n (%)	19 (65.5)	40 (48.8)	61 (50.4)	35 (43.8)	0.4081
Weight loss, n (%)	8 (27.6)	20 (24.4)	40 (33.1)	30 (37.5)	0.0976
Chronic fatigue, n (%)	7 (24.1)	12 (14.6)	28 (23.1)	21 (26.3)	0.1535
Night sweats, n (%)	4 (13.8)	10 (12.2)	13 (10.7)	3 (3.8)	0.2284
Fever/unresolving pneumonia, n (%)	5 (17.2)	7 (8.5)	13 (10.7)	8 (10)	1.0000
Neurologic symptoms, n (%)	7 (24.1)	13 (15.9)	20 (16.5)	12 (15)	0.6372
Asymptomatic, n (%)	2 (6.9)	12 (14.6)	16 (13.2)	15 (18.8)	0.2141

COPD = chronic obstructive pulmonary disease; FEV1 = forced expired volume in the 1st sec.
a) ≤ 65 vs > 65 yrs.

Histopathology and/or cytopathology specimens were obtained via bronchoscopy (74.4%), endobronchial ultrasound/endoscopic ultrasound (74%), thoracoscopy (3.5%), mediastinascopy (1.6%) and CT-guided percutaneous needle biopsies (42.6%).

Additional invasive procedures included gland extirpation and biopsies from suspected distant metastatic lesions (19.2%).

Several patients underwent multiple invasive investigations.

Lung cancer subtypes

Adenocarcinoma comprised 53.2% of all lung cancers of a defined histological subtype, followed by squamous-cell carcinoma (24.7%) and small-cell lung carcinoma (18.6%). Squamous cell carcinoma was less frequent in the younger population (p = 0.0133; Table 2).

Stages

The majority of patients had advanced stage disease (III-IV) at presentation (69.2%), while local-stage disease (I-II) was found in 96 patients (30.8%). When excluding patients with pure carcinoid tumours from the statistical analyses, a significantly higher proportion of the younger patients had advanced, non-resectable disease at diagnosis (p = 0.0392) (Figure 1B). As depicted in Table 2, 82.1% of the youngest patients presented with advanced stage, while this was the case in 66.3% of the oldest patients.

Treatment

Surgery was performed in 62 patients (19.9%). Four different surgical approaches were utilised: lobectomy (accounting for 67.7% of all operations), followed by segment/wedge resection (25.8%) and pneumonectomy (6.5%).

TABLE 2

Diagnosis, overall clinical stage and use of diagnostic modalities. The values are n (%).

	Age, yrs				
	≤ 55	56-65	66-75	> 75	p-value[a]
Patients	29 (9.2)	82 (26.3)	121 (38.8)	80 (25.6)	< 0.0001
Diagnosis					
Adenocarcinoma	17 (58.6)	48 (58.5)	64 (52.9)	36 (45)	0.1555
Squmaous cell carcinoma	3 (10.3)	15 (18.3)	28 (23.1)	30 (37.5)	0.0133
Small cell carcinoma	6 (20.7)	14 (17.1)	26 (21.5)	13 (16.3)	0.8801
Large cell carcinoma	0 (0)	3 (3.7)	1 (0.8)	0 (0)	0.1306
Other, undifferentiated or mixed tumour	3 (10.3)	2 (2.4)	2 (1.7)	1 (1.3)	0.1381
EGFR mutation	1 (3.4)	2 (2.4)	4 (3.3)	3 (3.8)	1.0000
Overall clinical stage					
IA	4 (13.8)	5 (6.1)	13 (10.7)	10 (12.5)	0.4373
IB	0 (0)	5 (6.1)	10 (8.3)	6 (7.5)	0.3457
IIA	1 (3.4)	6 (7.3)	7 (5.8)	3 (3.8)	0.6118
IIB	1 (3.4)	3 (3.7)	7 (5.8)	7 (8.8)	0.3118
IIIA	4 (13.8)	16 (19.5)	23 (19)	13 (16.3)	0.2451
IIIB	6 (20.7)	9 (11)	9 (7.4)	12 (15)	0.4607
IIII	13 (44.8)	38 (46.3)	52 (43)	28 (35)	0.3380
T1-3 and N0-1 and M0: resectable stages	6 (20.7)	21 (25.6)	42 (34.7)	27 (33.8)	0.0736
T4 or N2-3 or M1: unrectable stages	23 (79.3)	61 (74.4)	79 (65.3)	53 (66.3)	0.0736
T1-3 and N0-1 and M0: resectable stages, excl. pure carcinoids	5 (17.9)	20 (24.7)	42 (34.7)	27 (33.8)	0.0392
T4 or N2-3 or M1: unrectable stages, excl. pure carcinoids	23 (82.1)	61 (74.3)	79 (65.3)	53 (66.3)	0.0392
Diagnostic modality					
CT chest and abdomen	29 (100)	82 (100)	120 (99.2)	80 (100)	1.0000
PET/CT	27 (93.1)	69 (84.1)	115 (95)	75 (93.8)	1.0000
Other, e.g. bone scan and brain imaging	8 (27.6)	25 (30.5)	28 (23.1)	14 (17.5)	0.0967
Bronchoscopy	20 (69)	56 (68.3)	93 (76.9)	63 (78.8)	0.1040
EBUS/EUS	21 (72.4)	57 (69.5)	91 (75.2)	62 (77.5)	0.2818
Biopsy from distant metastasis	9 (31)	21 (25.6)	19 (15.7)	11 (13.8)	0.0110
CT-guided biopsy	8 (27.6)	29 (35.4)	56 (46.3)	40 (50)	0.0852
Thoracocentesis	0 (0)	5 (6.1)	7 (5.8)	3 (3.8)	1.0000
Surgical lung biopsy	1 (3.4)	2 (2.4)	3 (2.5)	5 (6.3)	0.7521
Mediastinoscopy	0 (0)	4 (4.9)	0 (0)	1 (1.3)	0.0558

CT = computed tomography; EBUS/EUS = endobronchial ultrasound/endoscopic ultrasound; EGFR = epidermal growth factor receptor; PET = positron emission tomography.

a) ≤ 65 vs > 65 yrs.

TABLE 3

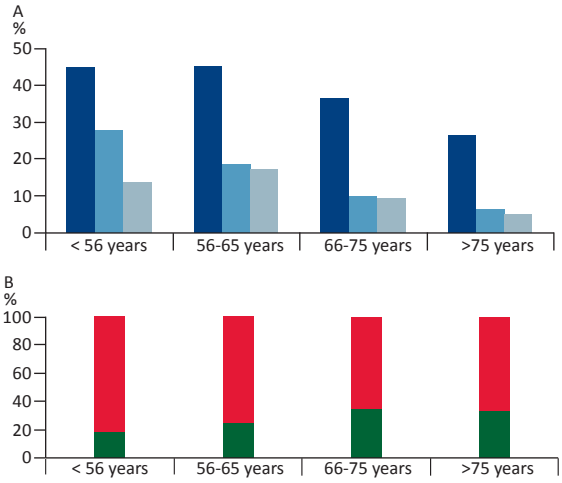
Treatment. The values are n (%).

	Age, yrs				
	≤ 55	56-65	66-75	> 75	p-value[a]
Patients	29 (9.2)	82 (26.3)	121 (38.8)	80 (25.6)	< 0.0001
Surgery	6 (20.7)	16 (19.5)	24 (19.8)	16 (20)	1.0000
Lobectomy	6 (20.7)	10 (12.2)	15 (12.4)	11 (13.8)	0.7310
Segment/wedge resection	0 (0)	4 (4.9)	7 (5.8)	5 (6.3)	0.4326
Pneumonectomy	0 (0)	2 (2.4)	2 (1.7)	0 (0)	0.6179
Radiotherapy	22 (75.9)	44 (53.7)	70 (57.9)	43 (53.8)	0.6330
Chemotherapy	25 (86.2)	63 (76.8)	89 (73.6)	35 (43.8)	0.0015
Single modality treatment	8 (27.6)	24 (29.3)	55 (45.5)	44 (55)	0.0005
Combined modality treatment	21 (72.4)	50 (61)	63 (52.1)	25 (31.3)	0.0009
No treatment	0 (0)	8 (9.8)	3 (2.5)	11 (13.8)	1.0000

a) ≤ 65 vs > 65 yrs.

FIGURE 1

A. Phenotypic genetics: The differences between the younger patients ≤ 65 years and elderly patients > 65 years are statistically significant with p-values of 0.028, 0.0026 and < 0.0001 for family history of any cancer ■, family history of lung cancer ■ and for ≥ 1 first-degree relative with lung cancer ■, respectively. **B.** Non-resectable ■ versus resectable ■ patients: The differences between the younger patients ≤ 65 years and older patients > 65 years are statistically significant (p = 0.0392).



Other treatment modalities included radiotherapy (57.4%) and various chemotherapy regimens (67.9%). Combined-modality therapy was administered in 159 patients (51%) and was significantly more frequent in the younger patients (p = 0.0009) (Table 3).

A total of 22 patients (7.1%) had no active treatment. Reasons for not receiving treatment included low PS/comorbidities (n = 10), post-biopsy complications (n = 1), early death before initiation of planned therapy (n = 5) or refusal of treatment (n = 6).

DISCUSSION

In comparison to younger patients we found the incidence of squamous cell carcinoma to be significantly higher in the elderly (Table 2). Squamous cell carcinoma is epidemiologically more closely associated with smoking than adenocarcinoma [5]. This is peculiar considering that the proportion of smokers was similar for the two age groups and genders (Table 1). However, elderly patients had a higher accumulated smoking history than younger patients, which can explain this finding. Also, it is reasonable to assume that the consumption of high-tar unfiltered cigarettes was higher in this more advanced age category. Since adenocarcinoma appears to be more prevalent in women [6], another possible explanation for the higher percentage of squamous cell carcinoma in the elderly could be the skewed gender distribution including a significantly higher female-to-male ratio in the younger population.

Finally, as patients ≤ 65 years presented with a higher number of familial cancer incidences, genetic predisposition rendering younger individuals more susceptible to lung cancer development could also offer a possible explanation as to why adenocarcinoma was the leading cell type in younger patients, whereas squamous cell carcinoma proved more common among the elderly.

Even after adjusting for smoking habits, several epidemiologic and clinical studies have identified familial aggregation of lung cancer, particularly in families with adenocarcinoma [7-9]. Furthermore, a large proportion of early-onset lung cancers (< 50 years at diagnosis) appears to be heritable, suggesting that the risk due to cigarette smoking is further amplified by genetic factors [8]. Increasing evidence has shown that genes coding for carcinogen metabolism and DNA repair contribute significantly to familial clustering of lung cancer [10, 11].

Although in our study genetic background appears to be a preponderant factor, one must also consider the possibility of recall bias. Younger patients have a more recent memory of familial cancer than older patients do, and since cancer today is diagnosed in later stages of life than previously, the parents of elderly patients may very well have had undiagnosed cancer.

When comparing the two age categories the percentage of patients with non-resectable, advanced-stage disease was significantly higher in the younger group provided that a small subset of patients with pure carcinoid tumours was excluded from the statistical analyses (Figure 1B). This exclusion seemed reasonable since typical low-grade malignant carcinoid tumours comprise a rare and distinct spectrum of pathological, epidemiological, clinical and prognostic features and are often perceived as a separate biological entity [12]. Even when calculations incorporated all patients, including the two carcinoid cases, a clear-cut trend towards statis-

tical significance was generated (Table 2). Previous retrospective studies have confirmed the high rate of advanced stage disease in young patients [13-16], which may reflect an intrinsically more aggressive malignant behaviour of lung cancer in young patients, a higher incidence of adenocarcinoma or simply a delayed diagnosis due to the low prevalence of cancer in younger populations.

In our study, the two age groups featured a similar duration of predominant symptoms as well as a similar proportion of asymptomatic patients (Table 1). Very young patients ≤ 55 years were nonetheless more likely to be symptomatic at presentation than were elderly patients (6.9% asymptomatic patients ≤ 55 years versus 18.8% in the age category > 75 years). This supports the notion that symptoms in young patients may often be overlooked or ascribed to benign conditions until the disease has reached an advanced, symptomatic stage.

There is some evidence of certain cytochemical differences, including a significantly higher nuclear protein content and nuclear-protein-to-nuclear-DNA-ratio in lung cancer cells obtained from young patients compared with cells from elderly, indicating a higher tumour proliferation rate as well as lower degrees of tumour differentiation in young patients [17, 18]. Although common sites of metastatic involvement were not specifically assessed in this register study, younger patients had a significantly higher number of biopsies from distant metastatic lesions than elderly patients did (Table 2), which is in line with the greater prevalence of advanced stage disease in this age-category, but may also reflect a greater metastatic capacity.

Combined-modality therapy was significantly more common in younger patients, whereas older patients were more likely to undergo single-modality therapy and also less likely to receive chemotherapy (Table 3). Some previous studies have corroborated these age-based treatment trends [9, 16, 19], which may relate to less comorbidity in younger patients and thus to better tolerability of anticancer treatment.

Interestingly, there were no significant differences in PS when comparing the two age groups (Table 1). This finding may indicate a general trend towards more aggressive, multimodal approaches in the younger age categories. However, as comprehensive geriatric assessment adds substantial prognostic information even among elderly characterised by good physical and mental conditions [20], PS as an isolated marker of functional status is perhaps too simplistic and may require supplemental assessments.

Limitations

There are some important limitations to this study including the relatively small number of patients analysed as well as the restriction of data to one medical centre which limits the generalisability of our study. However, despite the limited number of patients, we found several highly significant differences between younger and elderly patients. Also, we had access to a wide range of clinical information, which is often very limited in large cancer registries.

Certain variables such as pack-years and exposure to asbestos had missing/incomplete information. Nonetheless, the proportion of missing data fields was similar across the age groups studied (p = 0.8101).

The difficulty in comparing the results with those of former studies lies in the variability of age cutoffs used to define "young" populations. For the present study, 65 years of age was selected as it represents the normal age of retirement in Denmark, and thus a reasonable cutoff between younger and elderly patients.

CONCLUSIONS

The present study confirms that lung cancer in younger patients is characterised by female overrepresentation, higher frequency of familial cancer aggregation, less prevalence of squamous cell carcinoma, more advanced stage disease and a significantly greater likelihood of receiving multimodal therapy.

Moreover, since a higher proportion of the youngest patients ≤ 55 years tended to be symptomatic at diagnosis, it is paramount to consider lung cancer as a possible diagnosis in younger patients presenting with symptoms that are consistent with lung disease. Also, early genetic background assessments should be included when evaluating young smokers or young/middle-aged, symptomatic patients.

These contemplations are important, especially since younger patients, as demonstrated in our study, often present with late-stage, advanced disease.

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CONFLICTS OF INTEREST: Disclosure forms provided by the authors are available with the full text of this article at www.danmedj.dk

In the article Dan Med J 2016;63(7):A5248 there has been the following correction on 11 July 2016.

The explanation for Figure 1B has been changed to:

Non-resectable ■ versus resectable ■ patients.

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