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Factors associated with delayed treatment initiation in an unselected cohort of patients with small-cell lung cancer.

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ABSTRACT

Background: Small-cell lung cancer (SCLC) is an aggressive, rapidly progressive malignancy. Thus, expedient diagnosis and treatment initiation is important. This study identifies and quantifies factors associated with delayed diagnosis and treatment initiation in patients with SCLC and compares time to treatment in SCLC with a cohort of patients with non-small cell lung cancer (NSCLC).
Materials and Methods: The study included all patients diagnosed with SCLC at a hospital in southern Norway in a ten-year period (2007–2016), and all NSCLC patients during the period 2013–2016. Total time to treatment (TTT), was defined as the number of days from date of referral due to suspicion of lung cancer to first day of treatment. Factors associated with prolonged TTT were estimated using multivariate median regression analysis.
Results: The median TTT and interquartile range (IQR) for the 183 patients with SCLC was 16 (10–23) days. Factors associated with delayed TTT included outpatient versus inpatient evaluation (+8.4 days), number of diagnostic procedures (+4.3 days per procedure), stage I-III versus stage IV (+3.6 days) and age (+2.1 days per 10 years). In 2013–16, TTT in SCLC was 3.5 days shorter than in the period before and less than half that of NSCLC in the same period, 15 (9–22) versus 33 (22–50) days ($p = 0.001$).
Conclusion: Shorter TTT is seen in higher stage, while longer TTT is a result of increasing complexity of the diagnostic process and treatment decisions of patients with curative intent treatment. Knowledge on delaying factors can shorten TTT and improve clinical practice.

Background

Small-cell lung cancer (SCLC) constitutes 15% of all lung cancers in Norway as in other western countries [1, 2]. SCLC is an aggressive malignancy with high cellular proliferation rate, abundant genetic alterations and a tendency to early metastases [3]. It is typically a rapid growing cancer, with doubling of volume rates reported as low as 38 days [4]. Total time from received referral to treatment (TTT) in lung cancer is often longer than recommended [5, 6]. Recent national guidelines in Norway recommend that systemic therapy should be started within 35 days of received referral [7]. The Norwegian guidelines are fairly in line with other Scandinavian and international recommendations [8, 9, 10, 11].

Rapid progression of cancer coupled with delays in diagnosis may lead to deterioration in patient performance status to such an extent that curative treatment no longer can be offered [12].

In SCLC, TTT becomes especially important since observed tumor doubling times may approximate recommended TTT. Few published articles exist on time intervals and delays in diagnosis and start of treatment in SCLC. The aim of this study is to explore and quantify factors associated with delayed diagnosis and start of treatment in SCLC patients, and additionally, to explore differences in TTT with a

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comparable cohort of non-small cell lung cancer (NSCLC) patients in the latter period, 2013–16.

Material and methods

Data

In the time period from 2007 to 16, all patients at a hospital in southern Norway diagnosed with lung cancer (ICD-10 code C34) were registered in a local quality database. Review of medical records were used to collect data on patients diagnosed from 2007 to 12, while patients diagnosed from 2013 were added prospectively. Registered variables included clinical characteristics, demographic variables, number and type of diagnostic procedures performed and detailed information on time periods from referral to treatment. In Norway, by law, all citizens have equal access to the healthcare system free of charge. All lung cancer patients in the western parts of Agder county are referred to the local hospital serving a population of about 200 000, with no other competing public or private hospitals. This population-based cohort of lung cancer patients from 2007 to 16 is considered virtually complete and unselected.

The regional ethics committee was consulted and determined that the study did not require approval since no interventions was added for study purposes. The Norwegian Center for Research Data approved storage of the de-identified data.

Study population

From the cohort of lung cancer patients diagnosed in 2007–16, all patients with confirmed SCLC were included as well as all patients with NSCLC in the period 2013–16 (Fig. 1). Patients with other neuroendocrine tumors such as large cell neuroendocrine carcinomas and carcinoids ($n = 59$) and cases with no histologic confirmation ($n = 191$) were excluded to get a uniform study population.

An improved diagnostic pathway was implemented at the hospital in 2013 with the intent to reduce delays for patients with suspected lung cancer [13]. Further, national diagnostic cancer pathways were introduced in Norway in 2015, also with the intent of reducing TTT. To adjust for and quantify the possible period effect caused by these two interventions, the cohort of patients with SCLC was divided into two groups based on the period of diagnosis; baseline (2007–12) and With New Pathways (WNP) (2013–16). For comparison of TTT, we chose to include patients also with NSCLC from the WNP period to be able to compare the difference between SCLC after introduction of the diagnostic pathways.

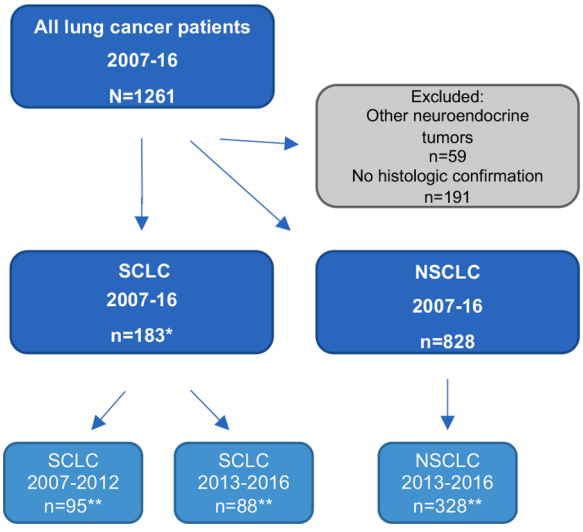

Fig. 1. Diagram showing selection of patients. SCLC: small-cell lung cancer, NSCLC: non-small cell lung cancer. * Small-cell lung cancer population included in regression analysis of TTT. ** Small-cell lung cancer and non-small cell cancer populations included in comparison of TTT.

Diagnostics

In the period 2007–16, SHK had the equipment, skills and personnel for a complete diagnostic work-up except for positron emission tomography - computed tomography (PET/CT). Patients requiring PET/CT were referred to the PET/CT-center at Oslo University Hospital (OUH).

All patients with lung cancer were discussed in a local multidisciplinary team (MDT) meeting. Treatments were administered at SHK except surgery and stereotactic body radiation therapy (SBRT) which were performed at OUH. For the latter group of patients, a second MDT-meeting at OUH was required before patients could be transferred for treatment.

Patients were designated as outpatients when referred to and diagnosed at the outpatient clinic. Inpatients were patients acutely admitted to hospital and who started the diagnostic process while hospitalized. The number of diagnostic procedures needed for a proper lung cancer diagnosis and staging was registered in order to give a measure of the complexity of the diagnostic process. Diagnostic procedures were either imaging (initial chest/abdominal computed tomography (CT), brain magnetic resonance imaging (MRI) and PET/CT-scanning) or tissue retrieving procedures (bronchoscopy, endobronchial ultrasound-guided fine needle aspiration cytology (EBUS-FNAC), esophageal ultrasound-guided fine needle aspiration (EUS-FNAC), CT and ultrasound-guided percutaneous biopsies, surgical excision biopsies or pleural effusion cytology). Staging of cases were according to TNM-7 [14].

Time intervals

TTT was defined as time from received referral from the primary physician or the date of acute admission to the pulmonary unit (whichever came first) to start of treatment. First consultation in hospital and the final multidisciplinary team meeting concluding on treatment allocations were used to divide TTT into three separate time periods, referral, diagnostic and treatment intervals respectively (Fig. 2). In patients directly admitted to hospital, referral interval was not registered and TTT was estimated from day of admittance to hospital to day of first treatment (either surgery, radiation, chemotherapy or no tumor-directed therapy). The date of treatment decision was used to calculate TTT in patients not receiving any treatment beyond best supportive care.

The national recommended maximum time for TTT in lung cancer in Norway is 35 or 42 days depending on first given treatment. For the three sub-intervals the recommendations are seven days for referral, 21 days for diagnostic and seven (chemotherapy) or 14 days (surgery or radiotherapy) for the treatment intervals, respectively.

Statistics

Patient characteristics were presented as descriptive statistics with mean and standard deviation for normally distributed continuous data and frequencies and percentages for categorical data. Non-normally distributed time intervals were reported with median as a measure of central tendency and with inter-quartile range (IQR) as a measure of dispersion. Descriptive statistics were compared using Student's *t*-test, Chi-square test, Mann-Whitney U or Kruskal-Wallis test, where appropriate.

The associations between co-variates and TTT were studied through a multivariable median regression analysis. Age at diagnosis (years), sex (male or female), stage (I-III or IV), evaluation setting (inpatient or outpatient), diagnostic period (baseline 2007–12 or WNP 2013–2016) and number of diagnostic procedures were included as co-variates in the

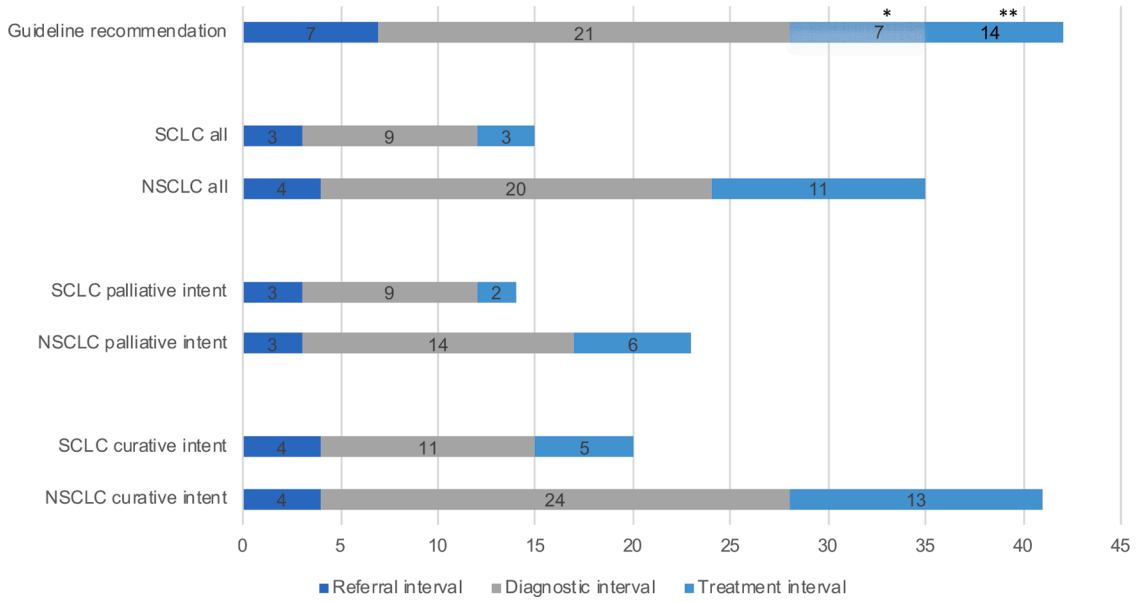

Fig. 2. Median days in referral, diagnostic and treatment intervals (2013–2016). Stratified by histology (small-cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC)) and treatment intent. Guideline recommendations according to Norwegian National diagnostic pathways. Referral interval: date of receiving referral letter to first consultation in pulmonary department. Diagnostic interval: date of first consultation in pulmonary department to date of multidisciplinary team meeting with final treatment decision. Treatment interval: date of multidisciplinary team meeting with final treatment decision to first day of treatment. *Recommended treatment interval is 7 days for chemotherapy. ** Recommended treatment interval is 14 days for surgery and radiation therapy.

regression model. Treatment (curative intent, palliative intent, or no treatment) was not included in the regression model because of multicollinearity with stage. Results were presented as median values with 95% confidence intervals (CI).

The significance level was set to 5%. Analysis was performed by Stata statistical software, version 15 (StatCorp Lp, College Station, TX, USA).

Table 1
Patient and cancer characteristics in a cohort of small-cell lung cancer (2007–12 and 2013–16) and non-small cell lung cancer (2013–16) patients.

	SCLC 2007–12			SCLC 2013–16			NSCLC 2013–16	p-value (All) SCLC 2007–12 vs SCLC 2013–16	p-value (All) SCLC 2013–16 vs NSCLC 2013–16
	All	Pal./No treat****	Cur.	All	Pal./No treat****	Cur.	All		
n	95	80	15	88	70	18	328		
Age in years, mean (SD)	66.5 (8.9)	65.4	66.6	69.5 (10.1)	69.6	69.4	68.9 (9.5)	0.03	0.56
Sex (%)								0.69	0.22
Male	48.5	51.9	33.3	45.5	55.7	50.0	52.7		
Female	51.5	48.1	66.7	54.5	44.3	50.0	47.3		
Stage (%)								0.65	< 0.001
I	3.2	1.2	13.3	1.1	0	5.6	22.0		
II	0	0	6.7	2.3	1.4	5.6	13.7		
III	24.7	13.6	80	28.4	12.9	88.8	21.6		
IV	72.1	85.2	0	68.2	85.7	0	42.7		
In- or outpatient evaluation (%)								0.81	0.01
Outpatient	50.5	49.4	53.3	53.5	50	66.7	67.4		
Inpatient	49.5	50.6	46.7	46.6	50	33.3	32.6		
Treatment (%)								0.70	< 0.001
Palliative*	73.7			70.5			39.3		
Cur. intent treatment**	15.8			20.4			48.2		
No treatment***	10.5			9.1			12.5		
Number of procedures, mean (SD)	2.42 (0.6)	2.38	2.67	2.90 (1.1)	2.67	3.78	3.44(1.2)	< 0.001	< 0.001
PET-CT (%)	4.2	1.2	20.0	29.5	18.6	72.2	60.4	< 0.001	< 0.001
Magnetic resonance imaging (%)	9.5	9.9	6.7	40.9	30.0	83.3	35.1	< 0.001	0.31

SCLC: small cell lung cancer, NSCLC: non-small cell lung cancer, PET-CT: Positron emission tomography – computed tomography, SD: standard deviation, Pal.: palliative, Cur.: curative.
*Chemotherapy, palliative radiotherapy or palliative chemoradiation.
**Curative intent treatment: surgery, stereotactic body radiation therapy or curative intent chemoradiation therapy.
*** No tumor directed therapy.
**** Chemotherapy, palliative radiotherapy or palliative chemoradiation and patients not receiving tumor directed therapy ($n = 10$ in 2007–12 and $n = 8$ in 2013–16).

Results

Characteristics of cohort

A total of 183 patients were diagnosed with SCLC during the study period (Table 1). This represent 17% of all patients with histologically confirmed lung cancer (Fig. 1). Stage distribution showed 70% stage IV, 26% stage III and 4% stage $I + II$.

Mean age at diagnosis increased with three years from baseline to the WNP period, 66.5 to 69.5 years ($p = 0.03$) (Table 1). At the same time the number of procedures performed in the diagnostic workup increased from a mean of 2.4 to 2.9 ($p < 0.001$). This growth was for the most part caused by more frequent use of PET-CT and brain MRI among patients receiving treatment with curative intent; PET-CT utilization increasing from 20% to 72.2% and MRI from 40.9% to 83.3% of the patients (Table 1). Diagnosis and staging in the entire cohort required more procedures in stages I-III (mean 3.0) than in stage IV (mean 2.5).

Comparing patients with SCLC and NSCLC diagnosed in the WNP period, show half of the SCLC cohort were diagnosed as inpatients compared to one third in NSCLC (Table 1). Significantly fewer diagnostic procedures were needed in the SCLC group compared to the NSCLC group, 2.9 vs. 3.4, respectively. Further, more patients with SCLC were in stage IV compared with NSCLC (68 vs 42%, respectively), while stage I or II were rarer (3% vs 36%, respectively).

Time intervals in SCLC

In univariate analyses the median TTT was three days shorter in the WNP than the baseline period (15 vs 18). Intervals were evaluated in the complete ten-year period.

Referral interval was short in patients seen at the outpatient clinic, i.e. four calendar days (median) from receiving referral to first consultation with specialist (Table 2). Most patients (88%) had their first consultation within the recommended seven days.

The median diagnostic interval of the SCLC cohort was nine days. In univariate analyses the largest difference in diagnostic interval was found in patients with $\leq$ two diagnostic procedures (seven days) compared to $\geq$ four diagnostic procedures (15 days). Outpatient diagnostic interval was two days longer than in inpatients. The diagnostic interval was in both the baseline and WNP period concluded within 21 days in 87% of cases.

The treatment interval was short with 87% receiving treatment within seven days. The shortest treatment interval was two days median in the inpatient group compared to four days in the outpatient group.

Median TTT in patients with SCLC was 16 days. The shortest TTT was seen among inpatients where 50% were diagnosed within twelve days. The longest TTT interval was seen in patients undergoing four or more diagnostic procedures where 50% were diagnosed within 22 days. Overall, 92% received treatment within the recommended 35 days in the Norwegian national cancer pathway guidelines.

Risk factors of delay

In the regression analyses a longer TTT in SCLC was significantly associated with outpatient diagnostic evaluation, number of diagnostic procedures, stage I-III and increasing age (Table 3).

The co-variate with the largest impact on TTT was outpatient compared to inpatient evaluation with +8.4 days ($p < 0.001$). Each additional procedure prolonged the median TTT by 4.3 days ($p < 0.001$) when adjusted for other variables. Patients in stage I-III disease, thus considered for curative intent treatment, received treatment 3.6 days ($p = 0.05$) later than stage IV patients. While increasing age was associated with delayed diagnosis and treatment (+2.1 days pr. 10 years), no significant difference was found for sex. TTT was significantly reduced in the WNP (-3.5 days, 2013–16) compared to the baseline period (2007–12).

Table 2
Total time to treatment and time intervals for all small-cell lung cancer patients 2007–16 in median days (inter quartile range) stratified by risk factor.

	N	Referral interval	Diagnostic interval	Treatment interval	TTT
All	183	4(1–6)	9(6–16)	3(1–6)	16 (10–23)
Sex					
Female	97	3(1–6)	10(6–17)	3(1–6)	15 (10–22)
Male	86	4(1–7)	9(6–15)	3(1–6)	18 (10–23)
Stage					
Stage I-III	54	4(2–6)	10(8–12)	4(1–6)	21 (14–29)
Stage IV	127	3(1–6)	8 (5–13)	2(1–5)	14 (8–21)
Level of diagnostic work up					
Inpatient	89	NA	8(5–16)	2(0–4)	12 (6–18)
Outpatient	94	4(2–6)	10(7–15)	4(2–6)	21 (14–28)
Diagnostic period					
2007–12	95	4(1–7)	10(6–15)	3(1–6)	18 (10–24)
2013–16	88	3(1–6)	9(6–16)	3(1–5)	15 (10–22)
Treatment					
Palliative*	132	4(1–6)	9(6–15)	3(1–6)	15 (10–22)
Curative intent chemoradiation	33	4(2–7)	12(8–16)	4(1–6)	20 (14–27)
No treatment**	18	6(2–10)	11(6–17)	NA	16 (6–23)
Number of diagnostic procedures					
≤ 2	104	4(1–6)	7(5–13)	3(1–6)	15 (8–21)
3	52	4(1–6)	11(7–19)	3(1–5)	16 (12–28)
4+	27	2(1–3)	15(9–25)	5(3–6)	22 (15–34)

TTT: total time to treatment, NA: not available.
*chemotherapy, palliative radiotherapy or palliative chemoradiation.
** no tumor directed therapy.

Table 3
Univariable and multivariable median regression of total time (days) to treatment in small-cell lung cancer patients, 2007–2016 (N = 183).

	Unadjusted difference	Adjusted difference	p-value*
Age per 10-years	+2.9	+2.1(0.43,3.8)	0.01
Sex			
Female	-3	-0.71(-4.4,2.1)	0.48
Male	Ref.	Ref.	
Stage			
Stage I-III	+7	+3.6(0.01,7.1)	0.049
Stage IV	Ref.	Ref.	
Level of care for evaluation			
Inpatient	Ref.	Ref.	
Outpatient	+9	+8.4(5.2,11.6)	<0.001
Diagnostic period			
2007–12	Ref.	Ref.	
2013–16	-3	-3.5(-6.8,-0.2)	0.04
Number of diagnostic procedures	+5.0	+4.3(2.4,6.1)	<0.001

*multivariable analysis.

Time intervals in the WNP period, a comparison between SCLC and NSCLC

The median TTT in SCLC was 15 (10–22) compared to 33 (22–50) days in NSCLC ($p = 0.001$). Recommended limits for the referral, diagnostic and treatment intervals were met in more than 90% and TTT in 93% of all patients with SCLC. This is in contrast to only 63% of the NSCLC patients in the WNP period meeting the TTT recommendation of 35 days in case of chemotherapy and 42 days in surgery or radiotherapy. Adherence to recommendations was lower in NSCLC compared to SCLC mainly due to longer median diagnostic (20 vs 9 days) and treatment intervals (11 vs 3 days) (Fig. 2). Differences in TTT persisted in similar groups of patients, for instance SCLC and NSCLC patients with palliative treatment (14 vs 23 days).

Discussion

In this study focusing on waiting time for patients with SCLC, characteristics associated with time to treatment were identified and quantified. Waiting times were shorter with more advanced stages and shorter for SCLC compared to NSCLC. As we have formerly demonstrated in patients with NSCLC, reduced waiting time was also demonstrated for SCLC when local and national efforts were introduced to improve these measures.

Factors associated with delay in SCLC

Evaluations at the outpatient clinic were associated with an eight day longer TTT compared to inpatient investigations. In our cohort, patients diagnosed while admitted to ward accounted for 50% indicating a symptomatic disease and high disease burden in a large percentage of patients. A faster diagnosis in admitted patients could be explained by quicker and easier access to diagnostic biopsy due to more widespread disease. As reflected in a higher percentage of stage IV among the admitted patients (78% vs 62%). Biopsy is often performed within 24–48 h in inpatients while outpatient requested biopsies often takes longer. Immediate start of treatment while admitted in the ward as opposed to outpatient initiation of treatment within a few days contribute to shorter TTT. Inpatient diagnosis and treatment could reduce time to treatment in patients with less symptoms and need for admission to ward, but the cost of doing so is hardly cost-effective. Improvements should therefore be aimed at optimizing outpatient diagnosis and treatment. More important, however, the median TTT experienced among our outpatients may be regarded as within acceptable limits and thus support current practice as acceptable and sound.

In our study each additional diagnostic procedure leads to 4.3 days longer TTT. In a study by Ezer [15], non-conclusive diagnostic procedures were correlated to prolonged TTT. In an article on predicting delays in lung cancer by Leiro-Fernández, number of diagnostic tests was one of the variables that increased delays [16]. Given that the number of procedures is such an important factor for TTT, proper planning of the entire diagnostic process is important to reduce delays. In SCLC where a high fraction of patients presents with stage IV disease, selecting the most easily accessible tumor site for primary biopsy is essential. This will both confirm staging and give necessary histologic confirmation. In our cohort of SCLC patients, a single CT scanning and one selected biopsy were the only procedures that were necessary to start treatment in more than half of the patients.

Number of diagnostic procedures are higher in early stage than in late stage due to the increased need for staging imaging procedures. Stage I-III experience a delay of close to four days even after correcting for the covariates number of diagnostic procedures and inpatient diagnosis. In early stage, the MDT meeting decision to treat with curative intent with chemoradiation or palliative intent is based on comorbidity, weight loss and performance status. Immediate start of chemotherapy is practiced after confirmation of SCLC in some patients with stage IV admitted with symptomatic disease. The decision process in advanced stage SCLC is fairly straight forward. Knowing early in the diagnostic process that palliative chemotherapy will be the primary treatment may facilitate early treatment by arranging treatment or reserving slots even before tests and imaging have finished. This difference in the treatment decision process may explain the delay seen in stage I-III compared to stage IV.

SCLC and NSCLC and differences in TTT

The factors that are associated with delay in SCLC can to some extent explain why TTT is shorter in SCLC than in NSCLC. First, in the WNP period (2013–16) somewhat less procedures are required in SCLC than in NSCLC patients (2.90 vs. 3.44). Second, inpatient diagnosis and treatment rates are higher (52% vs. 33%). Third, stage IV is more common (68% vs. 43%). These variates separately add 3 to 8 days in the regression analysis when other confounding factors are corrected for.

When similar groups were compared, for instance SCLC and NSCLC patients receiving palliative tumor-directed treatment, a quite large difference in TTT of 12 days was evident (16 days vs 28 days). This appears despite comparable staging, admission rates and number of diagnostic procedures.

Thus, this difference in TTT could be explained by other factors. First, the preliminary pathologic diagnosis of SCLC can sometimes be given without immunohistochemical diagnosis and allow the clinician to start planning treatment. Second, treatment options are sparse in SCLC, with no need to consider or wait for further pathology diagnostics considering specific mutations or PDL-1 status before initiation. Third, surgery is very rarely an option in SCLC. Fourth, treatment can be planned ahead of scheduled MDT meeting since first line treatment is more standardized. Fifth, the aggressiveness and bulky nature of the disease could also lead to prioritizing these patients in starting treatment.

SCLC and recommended TTT

International guidelines address maximum acceptable waiting times for both the diagnostic process and the waiting time for treatment. Published data reveal that most often criteria of timely care are not met [5, 17]. New Norwegian guidelines was implemented January 2015. These are in line with other guidelines from the Scandinavian countries. Few others have investigated TTT in SCLC patients. In a smaller cohort of 45 patients from a single institution, median time from abnormal radiograph to tissue diagnosis was 10 days and from abnormal radiograph to initiation of treatment 35 days [18]. In a study based on the Kentucky Cancer Registry, patients commenced treatment at a median of 18 days after diagnosis with 80% receiving treatment within 4 weeks [19]. Diagnosis to treatment was median thirteen days in a Greek study [20]. A median time from referral to treatment of 16 days in our cohort must be considered to be very short. Even in the more complex patients with four or more diagnostic procedures, the median TTT was 22 days, far from 35 days that is the recommended maximum TTT in the Norwegian guidelines. The referral to treatment recommendation of 35 days was met in 92% of the entire cohort.

This study has some limitations. It was a single hospital study which could limit the generalizability of the results. Patients prior to 2013 were included based on ICD code lists and the data were retrospectively collected from the electronic medical records. A mix of retrospective and prospective data can introduce registration bias. Patients were included in a 10-year period in which diagnostic recommendations changed and both PET-CT and brain MRI were introduced in the diagnostic work-up of lung cancer, especially in patients receiving treatment with curative intent. This resulted in imbalance between the baseline and WNP period. However, this imbalance should be accounted for in the regression analysis by including procedure number as a covariate.

The main strength of this study is the completeness of the cohort of

SCLC patients from our area, and the detailed characteristics of the patients. It represents real life data that includes all patients also those with poor performance status and short survival.

Conclusion

This study demonstrates that outpatient evaluation, number of diagnostic procedures, limited disease (stage I-III) and age are independent factors associated with delay in SCLC TTT. More than 90% of the SCLC populations meet the recommended time limits (35 days) of the national cancer pathways. TTT in SCLC is shorter than in NSCLC and this can partly be explained by more frequent inpatient evaluation, lower number of diagnostic procedures and a higher fraction with stage IV in the SCLC population.

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CRediT authorship contribution statement

Dan Laerum: Conceptualization, Methodology, Formal analysis, Writing – original draft, Visualization. **Odd Terje Brustugun:** Writing – review & editing, Conceptualization. **Frode Gallefoss:** Writing – review & editing, Conceptualization. **Ragnhild Falk:** Writing – review & editing, Validation. **Trond-Eirik Strand:** Writing – review & editing, Validation. **Lars Fjellbirkeland:** Writing – original draft, Writing – review & editing, Conceptualization, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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