Variation in the time to treatment for stage III and IV non-small cell lung cancer patients for hospitals in the Netherlands

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ABSTRACT

Objectives: Increased emphasis on molecular diagnostics can lead to increased variation in time to treatment (TTT) for patients with stage III and IV non-small cell lung cancer. This article presents the variation in TTT for advanced NSCLC patients observed in Dutch hospitals before the widespread use of immunotherapy. The aim of this article was to explore the variation in TTT between patients, as well as between hospitals.
Material and methods: Based on the Netherlands Cancer Registry, we used patient-level data (n = 4096) from all 78 hospitals that diagnosed stage III or IV NSCLC in the Netherlands in 2016. To investigate how patient characteristics and hospital-level effects are associated with TTT (from diagnosis until start treatment), we interpreted regression model results for five common patient profiles to analyze the influence of age, gender, tumor stage, performance status, histology, and referral status as well as hospital-level characteristics on the TTT.
Results and conclusions: TTT varies substantially between and within hospitals. The median TTT was 28 days with an inter-quartile range of 22 days. The hospital-level median TTT ranges from 17 to 68 days. TTT correlates significantly with tumor stage, performance status, and histology. The hospital-level effect, unrelated to hospital volume and type, affected TTT by several weeks at most. For most patients, TTT is within range as recommended in current guidelines. Variation in TTT seems higher for patients receiving either radiotherapy or targeted therapy, or for patients referred to another hospital and we hypothesize this is related to the complexity of the diagnostic pathway. With further advances in molecular diagnostics and precision oncology we expect variation in TTT to increase and this needs to be considered in designing optimal cancer care delivery.

1. Introduction

Non-small cell lung cancer (NSCLC) is a heterogeneous group of tumors that make up approximately 73% of lung cancers in the Netherlands [1]. 75% of patients with NSCLC are diagnosed with a tumor already at an advanced stage (stage IIIA, IIIB or IV) [2]. These patients typically have a poor prognosis. For example, median survival times are approximately 2 and 9 months, for untreated patients with stage IV NSCLC and systemically treated patients with stage IV NSCLC, respectively [3]. In order to improve their survival, increased emphasis is put on targeted therapy and immunotherapy in NSCLC [4,5]. Use of either treatment modalities requires detailed molecular testing for mutation analysis. Some of these molecular diagnostics can have a long turnaround time and thus potentially impose an increased time to treatment (TTT) [6]. While the association between TTT and mortality remains unclear in lung cancer [7], more evidence begins to indicate that a longer TTT is associated with poorer outcomes [8].

Previous research on TTT for lung cancer patients in the Netherlands has focused on a subset of patients [9], which makes a national, comprehensive analysis impossible. In addition, previous research on hospital variation in the Dutch setting in diagnostics or treatments for NSCLC patients has mostly looked at the utilization of care in the years 2001 until 2012 [10,11], or with only a relatively small sample of Dutch hospitals, probably reducing representativeness [12,13]. Previous studies conducted in other countries that analyzed the TTT for lung cancer patients nationally or regionally showed large variability. For example, a median TTT of 20 days and very large institutional variation was observed in Belgium [14]. A median TTT of

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40 days and large regional variation was found in Canada [15], and 90% of first treatments started within 115 days. For 22 hospitals in Spain, the median TTT for lung cancer was 39 days [16].

TTT depends on several factors. The TTT consists of a diagnostic delay and a treatment delay [17]. Important components of the time to treatment is the turnaround time of diagnostic tests, hospital capacity for conducting diagnostic tests and initiating treatment. Moreover, referrals for treatment can also impact the time to treatment. It is possible that hospitals have designed their diagnostics pathway such that they will diagnose most of their patients within an acceptable interval. In addition, hospitals have different diagnostic pathways based on differences in case-mix. The diversity of available diagnostic techniques and platforms is substantial [18], and they have varying turnaround times [19]. We expect that the TTT varies among hospitals and that, unless diagnostic procedures are planned carefully, further adoption of molecular diagnostics will increase the variation in the TTT. Increased variation in TTT can ultimately lead to increased variation in outcomes.

The individual and tailored diagnostic pathways partly explain variation in TTT as does the first-line treatment provided. There are several treatment options for patients with stage III and IV NSCLC. The Dutch Clinical Practice Guidelines (CPG) [20], which were last updated in 2015, indicate targeted therapy with tyrosine-kinase inhibitors for patients with metastatic disease with a tumor harboring an anaplastic lymphoma kinase (ALK) rearrangement or epidermal growth factor receptor (EGFR) mutation positive. Furthermore, a specific recommendation was issued in 2018 to use chemotherapy in combination with pembrolizumab [21] as a first-line treatment. Because this recommendation does not require testing for programmed death-ligand 1 (PD-L1) expression in the tumor and thus these patients potentially have a shorter diagnostic pathway and potentially a shorter TTT. Other, leading CPG [22–24] were updated after the study period of this research. According to those CPG, targeted therapy is also indicated for patients with a tumor that harbors a BRAF V600E mutation or ROS1 rearrangement. Patients who have a tumor harboring a high PD-L1 expression or patients who have a high tumor mutation burden (TMB) should receive immunotherapy in the first line.

This study examines hospital variation in TTT by using patient-level data from the population-based Netherlands Cancer Registry (NCR) from all stage III or IV NSCLC diagnosing hospitals in the Netherlands to analyze the TTT for each hospital. In addition, we investigated how patient characteristics are correlated with the TTT, as more complex cases may require a more elaborate diagnostic pathway, and how TTT was associated with hospital-specific aspects, such as hospital-side planning, capacity, and testing platforms.

2. Material and methods

2.1. Data

We retrieved the data from the Netherlands Cancer Registry (NCR). The Netherlands Comprehensive Cancer Organisation (IKNL) manages the NCR and routinely registers all new cancer incidences in the Netherlands. The data include patient and tumor characteristics, diagnostics, and treatments prescribed in the first line. The NCR is notified of all newly diagnosed malignancies by the automated pathology archive (PALGA). Additional sources are the national registry of hospital discharge, hematology departments, and radiotherapy institutes. The data allow us to identify at which hospital the patient was clinically diagnosed, at which hospital the patient received his or her first-line treatment, as well as the type of hospital (academic, teaching, general). All 8 academic hospitals, 27 teaching, and 43 general hospitals are included. Finally, patient-level data from 78 hospitals (100%) in the Netherlands that have diagnosed patients with stage III or stage IV NSCLC in 2016 were included. In total, the dataset contains 7550 unique patients. Considering that this study is retrospective, it does not require approval from an accredited medical research ethics committee (MREC) or the Central Committee on Research involving Human Subjects (CCMO). However, the study has been reviewed and approved by the

Privacy Review Board of the NCR.

2.2. Patient selection

Patients with stage IIIA, IIIB, or IV non-small cell lung cancer have been included in the analysis. We assigned patients to the hospital in which they were clinically diagnosed. Patients who did not receive a first-line treatment or patients who underwent active surveillance in the first line did not have a registered time of starting first-line treatment and thus were excluded from the analysis (n = 2782; 37%). Patients who only received treatment that was aimed at only treating the metastases, for example with a metastasectomy, instead of the primary tumor, were also excluded (n = 592; 8%). Finally, patients with a registered time of starting first-line treatment but with an unknown performance status were excluded (n = 80; 1%). In total, we used 4096 patients (54%) in the analysis, which is 99% of all stage III and IV NSCLC patients who have received a first-line treatment in the Netherlands in 2016.

2.3. Statistical analysis

Statistical analysis was conducted in Stata 14 [25] and consisted of descriptive statistics, data visualization, and regression analysis.

2.3.1. Variables

For the descriptive statistics and regression analysis, we used several patient-level and hospital-level variables. First, we discuss the patient-level variables. TTT is determined by calculating the time in days between the date of diagnosis and the start of the first-line treatment. The date of diagnosis is one of the following moments, with descending priority: the date of the first histological or cytological confirmation of a tumor, the date of first hospital admission related to the tumor, or the date of the first visit to outpatient clinic related to the tumor. Regarding the date of the first histological or cytological confirmation of a tumor, the following moments with descending priority are used: the date on which the sample was obtained, the date on which the sample was received, or the date on which the result was recorded. The NCR uses these criteria to determine the date of diagnosis.

The well-being of the patient is indicated by the Eastern Cooperative Oncology Group Performance Status (ECOG PS), which is bound between 0, indicating asymptomatic disease, and 5, indicating death. To improve statistical power, we have grouped the ECOG PS in 0-1, 2+, and unknown. For 5.6% of all patients, performance status was denoted on the Karnofsky scale (10–100) whereas scores for all others were reported on the WHO ECOG scale (0–5). The former was converted to the latter, using Buccheri et al. [26]. The performance status was registered prior to starting treatment.

Tumor staging is according to the seventh edition of the TNM classification. The histology of the tumor is grouped by type according to the WHO classification of lung tumors [27]. Histology groups were squamous cell carcinomas (ICD-O 8050-8078, 8083-8084), adenocarcinomas (ICD-O codes 8140, 8211, 8230-8231, 8250-8260, 8323, 8480-8490, 8550-8552, 8570-8574, 8576), large cell carcinomas (ICD-O codes 8010-8012, 8014-8031, 8035, 8310), unspecified malignant neoplasms (ICD-O codes 8000-8005), other specified carcinomas (remaining ICD-O codes between 8010-8576), and other (ICD-O codes 8972, 8980). The referral status of the patient was established by examining whether a patient was referred from hospital of clinical diagnosis to hospital of first-line treatment, as we expect that this will influence the TTT [28]. The first-line treatments were determined by, for each patient, cross-referencing the treatment indications and the time of treatment initiation. In cases where patients have received chemoradiotherapy, it means that a patient has received both chemotherapy that was not neoadjuvant or adjuvant to surgery, and radiotherapy within 12 weeks of each other. Due to the large variability in treatment combinations in the first-line, we decided to explore only the four most prescribed treatments.

Second, the hospital-level variables consist of hospital type and volume.

Table 1
Characteristics of the patient population.

Characteristics	Treated patients N (% or 95% CI)	Untreated patients N (% or 95% CI)	p-value
Patients	4,176 (55.1%)	3374 (44.9%)	N.A.
Median TTT (in days)	28 (IQR: 22)	–	N.A.
Mean age (in years)	65.4 (65.1, 65.7)	72.4 (72.1, 72.8)	0.000
Gender			
Male	56.0% (54.4%, 57.5%)	61.7% (60.1%, 63.3%)	0.000
Female	44.0% (42.5%, 45.5%)	38.3% (36.7%, 40.0%)	0.000
ECOG PS			
0-1	62.4% (61.0%, 63.9%)	23.2% (21.8%, 24.6%)	0.000
2+	8.0% (7.1%, 8.8%)	23.3% (21.9%, 24.7%)	0.000
Unknown	27.7% (26.3%, 29.1%)	52.7% (51.0%, 54.4%)	0.000
Missing	1.9% (1.5%, 2.3%)	0.9% (0.6%, 1.2%)	0.000
Tumor stage			
IIIA	23.6% (22.3%, 24.9%)	9.9% (8.9%, 10.9%)	0.000
IIIB	15.5% (14.4%, 16.6%)	7.9% (7.0%, 8.9%)	0.000
IV	60.9% (59.4%, 62.4%)	82.1% (80.8%, 83.4%)	0.000
Histology			
Squamous cell carcinoma	24.0% (22.7%, 25.3%)	16.2% (15.0%, 17.5%)	0.000
Adenocarcinoma	58.0% (56.5%, 59.5%)	42.3% (40.6%, 43.9%)	0.000
Large cell carcinoma	3.9% (3.3%, 4.5%)	5.6% (4.8%, 6.4%)	0.000
Other specified carcinoma	12.2% (11.1%, 13.2%)	12.2% (11.1%, 13.3%)	0.920
Unspecified malignant neoplasm	1.8% (1.4%, 2.3%)	23.6% (22.1%, 25.0%)	0.000
Other	0.1% (0.0%, 0.1%)	0.1% (0.0%, 0.1%)	0.831
Referral			
No	70.0% (68.6%, 71.4%)	82.2% (80.9%, 83.5%)	0.000
Yes	30.0% (28.6%, 31.4%)	17.8% (16.5%, 19.1%)	0.000
Basis for diagnosis			
Clinical diagnostic examinations, explorative surgery, or obduction[a]	1.8% (1.4%, 2.2%)	22.7% (21.2%, 24.1%)	0.000
Biochemical or immunological laboratory tests	0.0% (0.0%, 0.0%)	0.0% (0.0%, 0.0%)	0.124
Hematological or cytological confirmation on primary tumor	31.7% (30.3%, 33.2%)	29.5% (28.0%, 31.0%)	0.036
Histological confirmation exclusively on metastasis	22.0% (20.8%, 23.3%)	22.6% (21.2%, 23.9%)	0.598
Histological confirmation on primary tumor or metastasis, or obduction[b]	44.4% (42.9%, 46.0%)	25.2% (23.8%, 26.7%)	0.000
First-line treatments			
Only chemotherapy	1,712 (41.8%)	–	N.A.
Only chemoradiotherapy	956 (23.3%)	–	N.A.
Only radiotherapy	464 (11.3%)	–	N.A.
Only targeted therapy	302 (7.4%)	–	N.A.
Only surgery	133 (3.3%)	–	N.A.
Only immunotherapy	11 (0.3%)	–	N.A.
Other	518 (12.6%)	–	N.A.

Note: P-values are based on t-tests. [a]Obduction without microscopically confirmation. [b]Obduction with histological confirmation.

Hospital type makes a distinction between academic, teaching, and general hospitals. Hospital volume is the number of patients that were diagnosed with stage III or IV NSCLC in that hospital in 2016.

2.3.2. Regression model

To investigate how patient characteristics and hospital-level effects are associated with TTT, we created a regression model. To increase the understanding of the results of the regression model, we predicted the TTT for five different patient profiles. These patient profiles are constructed such that statistically significant variables vary among the profiles, while also making sure that these profiles reflect a substantial percentage of patients. The prediction of TTT for the patient profiles also include the hospital-level effects.

The data have a hierarchical structure: patients are nested within hospitals, that is, patients who are treated at the same hospital are likely to be more similar than patients treated at a different hospital. When present, ignoring this non-independence of the data leads to biased results. Therefore, in order to estimate the effect of patient and hospital characteristics on TTT, we used a mixed model. A mixed model allows estimation of TTT caused by not only the patient-level variables, the so-called fixed effects, but also due to hospital-level variables, the so-called random effects. The magnitude of the random effects or hospital-level effect may differ between hospitals. The size of the hospital-level effect is identical for all patients treated at the same hospital. The random effects reflect the unobserved heterogeneity at the hospital level. Because the components of the heterogeneity between hospitals

are unobserved, we cannot know for sure what it entails. However, if the goodness of fit of the model does not improve after including additional random effects, it is unlikely that the unobserved heterogeneity relates to the additional random effects. In other words, the hospital-level effects are reflective of the comparative performance of hospitals with respect to TTT, as the differences in case-mix caused this part of the variation in the TTT.

We have included patient-level variables that are often used to correct for differences in case-mix so that the unobserved heterogeneity among hospitals is not a reflection of differences in case-mix. We selected variables to include in the regression analysis by reviewing the literature on hospital variation in outcomes. We used the following patient-level or fixed-effects variables in the model: age, gender, ECOG PS, and tumor stage. These case-mix variables were similar to what was previously used [29,30], but we lack other lung cancer-specific data, such as data on the presence of symptoms such as chest pain and hemoptysis. Additionally, we included the referral status of a patient. With respect to the random effects, we included a random intercept for each hospital to reflect unobserved heterogeneity between hospitals. The goodness of fit was assessed with the Akaike Information Criterion (AIC), residual diagnostics, and likelihood ratio tests.

We used a negative binomial mixed model (NBMM) with a log link function [31]. In this type of models, the dependent variable, in this case TTT, is expected to follow a negative binomial distribution. A negative binomial model is preferred over a linear model because we found that the residuals in a linear model to be not normally

distributed, which violates an important assumption. Moreover, TTT contains only nonnegative integers, which makes it suitable for a negative binomial model [32].

3. Results

3.1. Patient population

Table 1 provides the patient characteristics for both treated and untreated patients with stage III or IV NSCLC. In addition, it includes the treatment history of patients with a known TTT.

3.2. Time to treatment

The population level median TTT was 28 days with a range of 0 to 395 days, while the hospital-level median TTT ranges from 17 to 68 days. Of all first-line treatments, 90% was initiated within 58 days of clinical diagnosis. Fig. 1 displays the distribution of the TTT for each hospital. Note that hospital volume ranged from 3 to 144. The median, inter-quartile range (IQR), and mean patient volume was 68, 64, and 71, respectively. The figure shows that there is substantial variation in TTT between hospitals, and there is large within-hospital variation as indicated by the lengths of the boxes and whiskers. No pattern can be deduced with respect to variation across hospital types.

3.2.1. Relationship with treatment

Treatments correlate with TTT, as different treatments require different diagnostics to be conducted prior to starting first-line treatment. Table 2 shows summary statistics for the TTT for the four most frequently given first-line treatments, as well as the utilization of these treatments. To be clear, we only explore the relationship that TTT has with the four most prescribed treatments. On a population-level, most patients only receive chemotherapy in the first line, followed by chemoradiotherapy, radiotherapy, and targeted therapy.

The left-hand panel in Fig. 2 shows for each hospital the median TTT for the four most frequently given first-line treatments. Each horizontal line and bar represents the respective metrics for one hospital. Note that we used a logarithmic scale for the horizontal axis of the left-hand panel. The right-hand panel shows the percentage of patients for whom that was their first-line treatment. No distinction is made

Table 2
Summary statistics on time to treatment per first-line treatment.

First-line therapy	Time to treatment					Utilization
	Median	Mean	Std. Dev.	Min.	Max.	
Only chemotherapy	29	34.7	23.0	0	286	41.8%
Only radiotherapy	32	38.3	31.9	0	288	11.3%
Only chemoradiotherapy	23	27.5	16.6	0	146	23.3%
Only targeted therapy	27	33.6	31.0	0	395	7.4%

between hospital types in Fig. 2 because Fig. 1 indicates that there is no such pattern deducible in the variation of TTT. Fig. 2 indicates that the between-hospital variation in TTT is smallest with chemotherapy, which is, in most hospitals, the treatment that most patients received in the first line. Between-hospital variation in TTT is larger for radiotherapy and targeted therapy. However, the right-side panel indicates their utilization is relatively low in most hospitals, which may indicate that the variation in TTT may be just a feature of a small sample.

3.2.2. Relationship with patient characteristics and a hospital-level effect

Using the regression model, we have determined the association between TTT and patient characteristics, as well as predict the hospital-level effect on TTT for each hospital. These hospital-level effects are displayed in Fig. 3, where each dot represents the predicted hospital-level effect for one hospital. Including hospital type and hospital volume as additional random effects did not improve the goodness of fit, so the hospital-level effects is also not related to hospital type or the number of patients with stage III or IV NSCLC in each hospital. In Fig. 3, a negative value means that the hospital-level effect has led to a lower average TTT for that hospital, while a positive value means that the hospital-level effect has led to a higher average TTT for that hospital.

Table 3 presents the relation between TTT and patient characteristics for five patient profiles defined using the regression model. The regression model indicated that the ECOG PS, tumor stage, histology, and referral status are associated with TTT, so these characteristics are varied among the patient profiles. Approximately 77% of the patients had one of the profiles listed in Table 3. In addition, the regression model also allows us to estimate the hospital-level effect on TTT. As Fig. 3 indicates, that effect differs among hospitals, so Table 3 does not
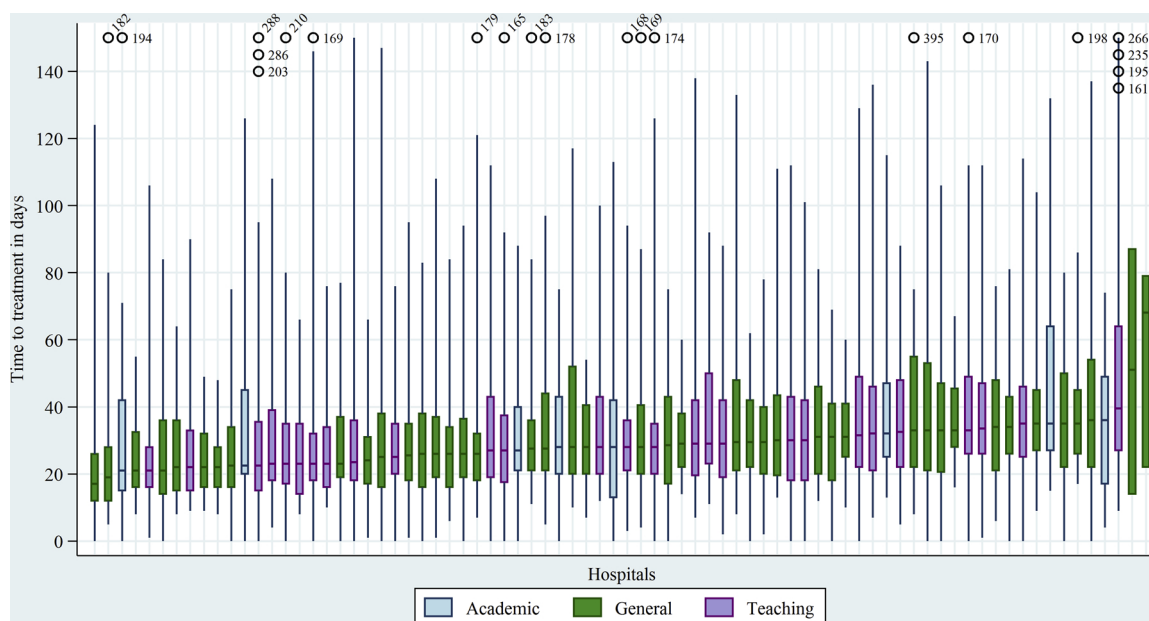

Fig. 1. Distribution of time to treatment across and within hospitals. The whiskers encompass the minimum and maximum TTT for each hospital, whereas the box depicts the 25th and 75th percentile, and the median. Values for time to treatment larger than 150 days are shown individually.
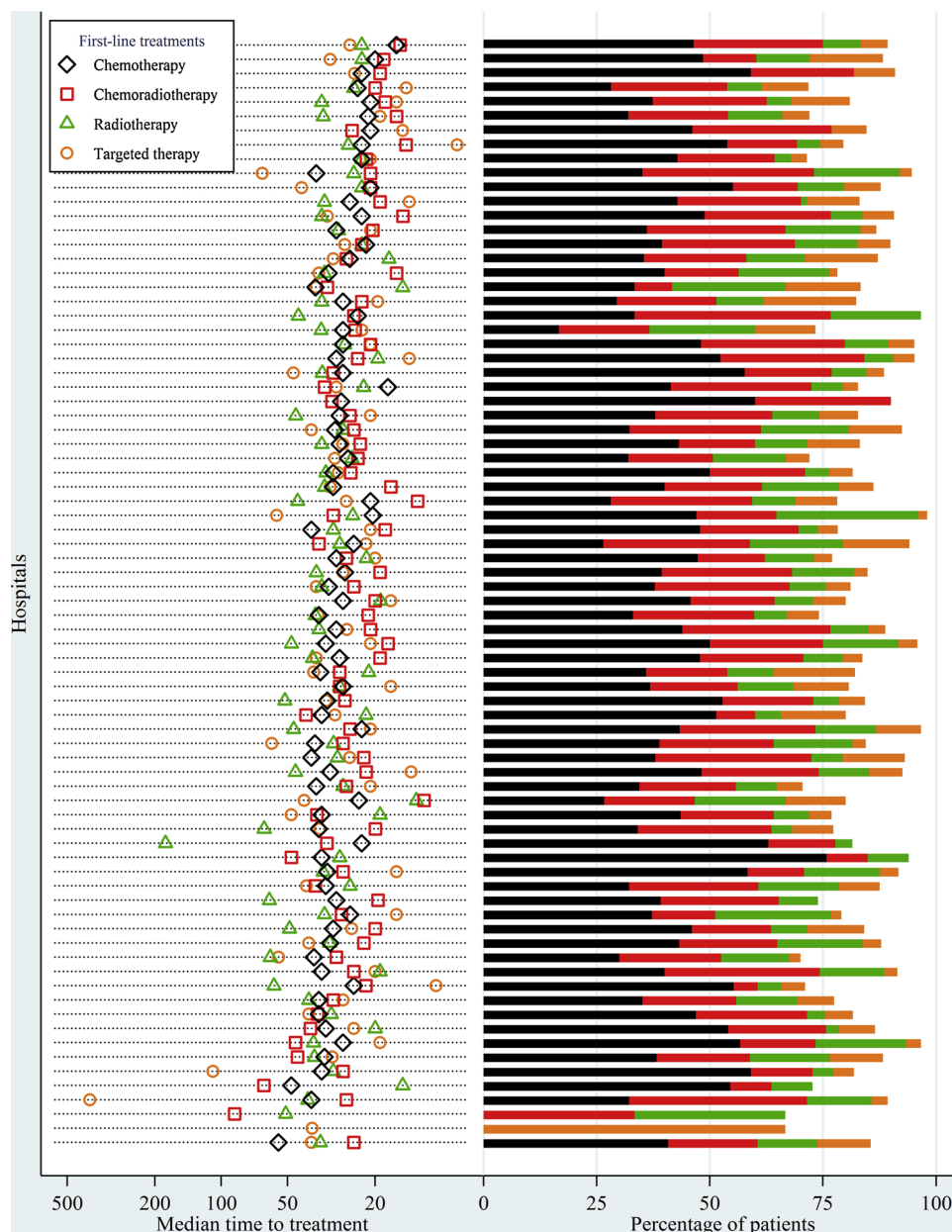
Fig. 2. Hospital median time to treatment and the percentage of patients per first-line treatment. Only the four most prescribed treatments are shown.

only report the estimated TTT for a hospital with an average hospital-level effect, it also shows the estimated TTT for the hospitals with the largest positive and largest negative hospital-level effect, denoted by low and high in Table 3 respectively. The largest change in TTT is related to the referral status of the patient. Patients who are referred to a different hospital for treatment are predicted to have an increase in TTT of at least a week.

4. Discussion

In this study, we quantified the variation in TTT for advanced NSCLC patients in the Netherlands. We found a median TTT of 28 days, and considerable variation in TTT between and within hospitals. The median TTT found in this article is in the range of what previous studies reported that have analyzed the TTT for lung cancer patients nationally or regionally. However, a study from 2013 on a Canadian region reported that 90% of first treatments started within 115 days [15], which is almost twice the 58 days in the current article. By calculating the

estimated TTT for five patient profiles, we showed how patient characteristics correlate with the TTT. We have also shown how a hospital-level effect affects the predicted TTT for these patient profiles. The TTT for the patient profiles ranged from approximately 19 days to 68 days.

There is no legally binding maximum TTT for cancer patients in the Netherlands. However, several institutions have created guidelines. The Dutch Cancer Society (KWF) deems a maximum TTT of 30 days acceptable [33], while SONCOS recommends a maximum of 6 weeks, but in case of referrals, an extra 3 weeks is granted [34]. Finally, the so-called "Treeknormen" [35], which were created by healthcare providers and health insurers, find a maximum TTT of 7 weeks to be acceptable. The hospital-level median TTT, which incorporates all values for TTT of patients treated at each hospital, ranges from 17 to 68 days. We can conclude that the median TTT reported in this study is less than the maximum acceptable TTT. It means that at least 50% of the patients receive a first-line treatment within an acceptable time interval. However, for a small number of patients the maximum acceptable TTT is exceeded as only 50% of treatments is initiated within 28 days, and
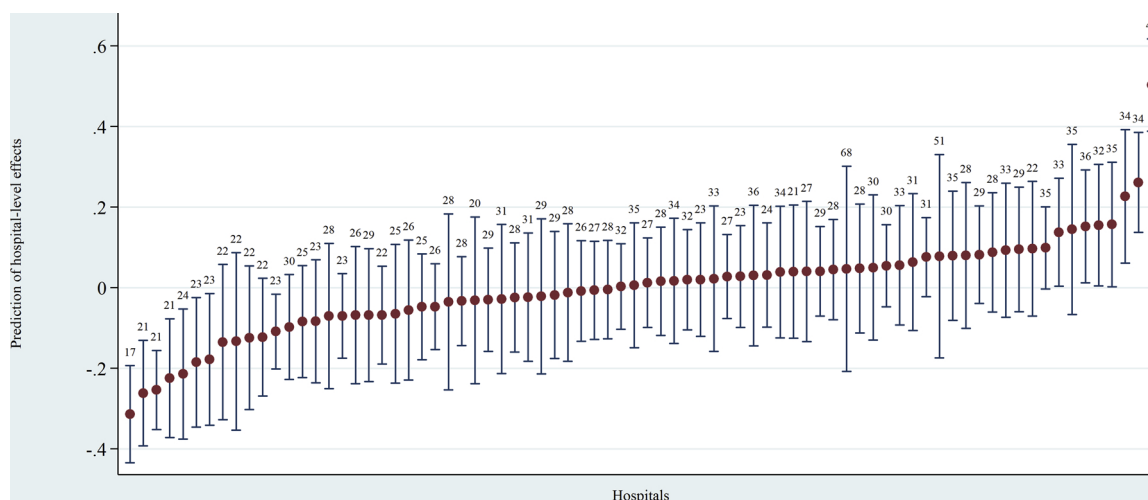
Fig. 3. Hospital-level effects or i.e. Empirical Bayes predictions of the random effects. The 95% confidence intervals of the predicted hospital-level effects are indicated by the error bars. The number above the error bars is the hospital-level median time to treatment.

Table 3
Predictions of time to treatment for patient profiles.

Characteristics	Patient profiles				
	(1)	(2)	(3)	(4)	(5)
N (%)	1353 (33.0%)	603 (14.7%)	99 (2.4%)	829 (20.2%)	261 (6.4%)
ECOG PS	0-1 or unknown	0-1 or unknown	2 +	0-1 or unknown	0-1 or unknown
Tumor stage	IIIA or IV	IIIA or IV	IIIA or IV	IIIA or IV	IIIB
Histology	Adenocarcinoma	Adenocarcinoma	Adenocarcinoma	SCC[a], LCC[b], other specified carcinomas, or other histology	SCC[a], LCC[b], other specified carcinomas, or other histology
Referral	No	Yes	No	No	No
TTT (Average)[c]	30.5	41.0	25.2	28.4	25.2
TTT (Low)[c]	22.5	30.3	18.6	21.0	18.6
TTT (High)[c]	50.8	68.3	41.9	47.3	41.9

Note: [a]Squamous cell carcinoma. [b]Large cell carcinoma. [c]Predictions of TTT in days for hospitals with an average, largest negative (low), and largest positive (high) hospital-level effect. The TTT is predicted for five different patient profiles in which statistically significant variables vary among the profiles, while also representing a substantial percentage of patients. The prediction of TTT for the patient profiles also include the hospital-level effects. The hospital-level effect is identical across patient profiles.

90% of treatments have initiated within 58 days, while the guidelines recommend a maximum of 30 days [33], 7 weeks [35], and 9 weeks [34]. This conclusion is in line with previous research [36]. Additionally, the median TTT in 53 hospitals (68%) was below 30 days, which means it is below the strictest guideline. The median TTT in only one hospital exceeded the SONCOS guidelines of 9 weeks, which is the least strict. This supports the claim that hospitals have designed their diagnostic pathways in a way that they will diagnose most of their patients within an acceptable interval. In countries where there is a legally binding maximum TTT such as England, patients should receive first-line treatment within 31 days after diagnosis [37]. If we apply these maxima to our results, only approximately 57% of all patients would have received treatment in a timely manner.

Table 2 shows that the TTT varies for the different treatments and that the largest variation in TTT was found in patients who have received either radiotherapy or targeted therapy. For patients with stage IV disease, radiotherapy has often a palliative intent and is often only started once the patient experiences symptoms. Moreover, radiotherapy requires an appointment with the radiology department. This can be an explanation for the variation in TTT for radiotherapy. The variation in TTT for targeted therapy could be caused by the time required by molecular diagnostics, and the various test strategies hospitals employ, given the lack of a molecular diagnostic best practice [18]. The result that TTT tends to be longer for patients with adenocarcinomas (Table 3), for whom molecular diagnostics are indicated, compared to patients with other histologies, supports this claim. Although the median TTT in most hospitals is below the recommended maxima, hospitals should be aware that, without careful planning, conducting diagnostics with long turnaround times could extend the TTTs beyond the recommended maxima. Finally, the role of immunotherapy has increased substantially since the study period. However, as the remaining parts of the treatment landscape, such as treatment with TKIs or chemotherapy, have remained similar, our study represents the key aspects of the current care pathway.

Table 3 shows that the predicted TTT is much longer if the patient is referred to a different hospital for treatment. Patient profile 1 and 2 indicate that the increase in predicted TTT resulting from the patient's referral status ranges from one week to several weeks, depending on which hospital the patient would visit. Considering that 30% of the treated patients were referred, there is potential for significant improvement in the TTT if the planning of appointments of referred patients and cooperation between hospitals would become more efficient.

Fig. 2 shows that at both extremes, the hospital-level effect on TTT is substantial. However, the hospital-level effect is modest or insignificant for most hospitals. In other words, a few hospitals perform either substantially better or substantially worse than expected considering their case-mix with respect to TTT, while most hospitals perform as expected considering their case-mix. The hospital-level effect is independent of hospital type and hospital volume. Both hospital type and hospital volume do not influence the TTT, which is not typically found in studies on the relationship between quality and volume [12,38–40]. An explanation for our findings could be that TTT is not necessarily a

metric in which experience and thus volume are involved, but it is rather a consequence of the design and efficiency of the diagnostic care pathway.

We chose to include also patients that had other additional primary tumors. Excluding these patients (n = 705) did not influence the overall TTT. On the population level, it resulted in the same median TTT, as well as the same minimum and maximum TTT. Moreover, the hospital-level median TTT remained in a similar range compared to when these patients are included. The validity of extreme values for TTT, i.e. values of zero and larger than 200 days, was confirmed by the NCR. In cases where TTT of zero days was registered, either a tumor was confirmed in the operating room or chemotherapy started on the same day as the diagnosis was registered. TTT larger than 200 days was mostly caused by extensive diagnostic pathways or observed in patients who were first treated for tuberculosis. Table 1 indicates that untreated patients typically have a worse performance score, a higher age, and a more advanced tumor stage, and that their diagnosis is more often non-microscopically confirmed. The combination of these factors makes a strong case that untreated patients are correctly classified in our study. Previous research shows that the number of patients with stage IV NSCLC that did not receive anticancer treatment ranges from approximately 25% to 50% [41–43]. In our data, this percentage was within that range, at approximately 37%. Thus, it is likely that an appropriate subset of patients was selected in our study.

One of the major strengths of this article is the national coverage of first-line NSCLC care that allows us to draw conclusions based on the entire population and to make comparisons between hospitals. The data used in this study allow for some degree of hospital benchmarking, but increased transparency for example through linking hospitals to regions would facilitate benchmarking even better. This study also has limitations. For instance, having direct evidence on what happened during the TTT, e.g. the types of diagnostics and the dates at which they were conducted, would put us in a better position to explain the variation in the TTT. For example, in cases where patients have started with chemotherapy whilst still waiting on the results from molecular diagnostics, knowing the types of diagnostics conducted would allow us to explain better their TTT. In addition, having extra information on, for example, comorbidities and other prognostic factors might have improved our case-mix adjustment. While socio-economic status is associated with variation in outcomes [44], this does not seem to be the case with time to treatment [45]. However, the presence of a hospital-level effect indicates that the differences in case-mix did not solely cause the variation in TTT. In addition, we assigned patients to the hospital in which they were clinically diagnosed. Our underlying assumption is that in the hospital of diagnosis certain decisions are made that could affect the TTT, for example, what diagnostics should be conducted and possibly deciding on the type of first-line treatment. In fact, we do not know how early in the care pathway a patient was referred to a different hospital, so the influence of the hospital of diagnosis on the TTT will vary case-by-case. A different source of potential bias is the heterogeneity in which moment was used to determine the date of diagnosis. While our data do not provide direct evidence on this matter, Table 1 indicates that the diagnosis of approximately 98% of the patients who have received treatment was microscopically confirmed. The date of first histological or cytological confirmation of the tumor has the highest priority when determining the date of diagnosis, it is likely that the date of first histological or cytological confirmation was used as the date of diagnosis for most patients. Hence, we believe that the heterogeneity in the date of diagnosis is relatively limited.

Currently, the TTT for similar patients that are treated at different hospitals is considerably different. This variation is undesirable and should be eliminated by trying to optimize diagnostic procedures in hospitals. Consequently, determining an optimal TTT for lung cancer is thus an interesting topic for future research. Additionally, finding the causes of variation between hospitals in TTT as well as possible approaches to reduce this type of variation would be of significant value.

Even so, TTT warrants its own study, as timeliness of care is an important aspect of the accessibility and quality of healthcare.

5. Conclusion

This article described the TTT for stage III and stage IV NSCLC patients, by using patient-level data from the NCR from all NSCLC diagnosing hospitals in the Netherlands in 2016. We found a median TTT of 28 days and considerable variation in TTT between and within hospitals, however, for most patients, TTT is within the acceptable norms. Variation in TTT seems higher for patients receiving either radiotherapy or targeted therapy. We hypothesize this is related to the complexity of the diagnostic pathway. Also patient referral to another hospital seems to increase TTT. With further advances in molecular diagnostics and precision oncology, we expect variation in TTT to increase and needs to be considered in designing optimal cancer care delivery. By estimating the TTT for five patient profiles, we showed how ECOG PS, tumor stage, histology, and referral status correlate with the TTT. We have shown the extent to which TTT may vary for these patients through estimating the best (lowest) and worst (highest) TTT across all hospitals.

Conflict of interest statement

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2019.05.023.

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