

1-year mortality in lung cancer in France according to key timepoints of care pathways

Axelle Rivière^{1,2}, Anne Isabelle Lecuyer^{3,4}, Emeline Laurent^{3,4}, Carole Lefebvre⁵, Thierry Lecomte^{2,5,6}, Elodie Olivier⁷, Delphine Carmier¹, Laurent Plantier ¹, and Leslie Grammatico-Guillon ^{2,3}

¹Department of Pulmonology and Pulmonary Function Testing, Teaching Hospital of Tours, Tours, France. ²Medical school, University of Tours, Tours, France. ³Public Health Unit, Epidemiology, Centre-Val de Loire (EpiDclic), Teaching Hospital of Tours, Tours, France. ⁴Research Unit "Education, Ethics and Health", EA 7505, University of Tours, Tours, France. ⁵OncoCentre, Cancer Network of the Centre-Val de Loire Region, Tours, France. ⁶Inserm UMR1069 "Nutrition, Croissance et Cancer", University of Tours, Tours, France. ⁷Cancer Coordination Centre, Teaching Hospital of Tours, Tours, France. ⁸Centre d'Étude des Pathologies Respiratoires (CEPR), Inserm UMR1100, Tours, France.

Corresponding author: Leslie Grammatico-Guillon (leslie.guillon@univ-tours.fr)



Shareable abstract (@ERSpublications)

Care pathways of lung cancer were described with medico-administrative and clinical databases. In unresectable cases, rapid care access was not associated with better survival; the additional time for molecular biology did not impact treatment initiation. https://bit.ly/3qnArf0

Cite this article as: Rivière A, Lecuyer AI, Laurent E, et al. 1-year mortality in lung cancer in France according to key timepoints of care pathways. ERJ Open Res 2022; 8: 00157-2022 [DOI: 10.1183/23120541.00157-2022].

Copyright ©The authors 2022

This version is distributed under the terms of the Creative Commons Attribution Non-Commercial Licence 4.0. For commercial reproduction rights and permissions contact permissions@ersnet.org

Received: 30 March 2022 Accepted: 30 Aug 2022

Abstract

Background It is unclear whether delays in care affect prognosis of patients with lung cancer. The primary objective of this study was to describe the care pathway of patients diagnosed with lung cancer in a French region. Secondary objectives were to identify markers associated with 1) time from imaging to treatment and 2) with 1-year survival.

Methods In a retrospective cohort study, clinical data from multidisciplinary team meetings for all incident lung cancer cases discussed in 2018 in one French region were matched with medico-administrative data from the National Health Insurance Database. Care pathway time intervals were estimated for small cell lung cancer (SCLC), resected nonsmall cell lung cancer (NSCLC) and unresected NSCLC. Factors associated with delay in the care pathway were identified using linear regression; 1-year survival was analysed using Cox modelling.

Results A total of 685 patients were included. Median time between imaging and treatment was 49 days (interquartile range: 33–73), and was lower in cases of metastatic disease, SCLC and private care. At 1 year, 48% had died (resected NSCLC 12%). In unresected NSCLC, time from diagnostic imaging to first treatment <49 days was associated with a higher risk of death. Time intervals were similar in patients with squamous cell carcinoma *versus* adenocarcinoma or undifferentiated carcinoma.

Discussion Time intervals in the care pathways of lung cancer were similar to previous reports, confirming the robustness of retrospective databases. In unresectable NSCLC, rapid care was not associated with better survival.

Introduction

Lung cancer is the leading cause of cancer deaths in Europe. In France, lung cancer is the second most frequent cancer in men and the third most frequent cancer in women with 31 231 and 15 132 new cases in 2018, respectively [1]. Lung cancer includes nonsmall cell lung cancer (NSCLC) and small cell lung cancer (SCLC), which differ in their natural history, prognosis and management [2]. A fraction of patients with limited NSCLC benefit from surgical resection. In recent years, prognosis of unresectable NSCLC has been improved by the introduction of targeted therapies and immune checkpoint inhibitors in addition to chemotherapy and radiotherapy [3]. According to current guidelines on NSCLC care [4], patients with unresectable adenocarcinoma or undifferentiated carcinoma require molecular biological analysis for optimal treatment, as do the rare nonsmokers with squamous cell carcinoma. Prognosis of SCLC, mainly treated by chemotherapy and radiotherapy, is poor [5, 6].





Rapid diagnosis and treatment are considered indicators of quality of care in lung cancer, although evidence is lacking to support this concept in patients with unresectable lung cancer [7]. While large population-based studies have reported an association between swift surgery and longer survival in patients with resectable NSCLC [8, 9], it is unclear whether care pathway delays impact on outcomes in patients with unresectable lung cancer [10]. In fact, currently available data indicate either inverse associations between care delays and survival (*i.e.* longer survival in patients with longer care delays) [11–13] or the absence of any link [14–19]. Only one study reported an association between short time to management and increased survival in unresectable NSCLC [8]. These data are in opposition to current guidelines of lung cancer care, which set clear objectives in terms of care time intervals for unresectable lung cancer [20–23]. Specific to unresectable NSCLC, concern may be raised that the recent need for lengthy molecular analyses, which are required for access to targeted therapies, may lead to increased time intervals between diagnosis and treatment [24].

To better inform public policy into lung cancer care, we aimed to further explore the hypothesis that delays in the care pathway are associated with poor prognosis of lung cancer. The primary goal of the study was to measure time intervals between the major steps of medical care of patients newly diagnosed with lung cancer in a French region. The secondary objectives were to assess factors associated with 1) time intervals from imaging to treatment and 2) with 1-year survival. We then explored whether patients with adenocarcinoma or undifferentiated carcinoma, in whom molecular biology analyses are required, had longer time to treatment in comparison with patients with squamous cell carcinoma.

Methods

Study design and data sources

A multicentre retrospective observational study was conducted in the Centre-Val de Loire region of France by merging two existing databases, the Shared Medical reports in Oncology (Dossier Communicant en Cancérologie (DCC)) and the French Health Insurance Database (Système National des Données de Santé (SNDS)). The Centre-Val de Loire region includes six administrative departments that were anonymised (A to F). Patients were identified from DCC data. DCC is a French regional register which gathers data on diagnosis and treatment of all cancer patients. These data were collected during multidisciplinary team meetings (MTMs) in 35 Centre-Val de Loire centres. By law, MTMs are mandatory for all cancer patients in France. Inclusion criteria were 1) age over 18 years old and 2) first thoracic oncology MTM in 2018. Diagnoses of lung cancer were checked by reviewing all medical records.

As DCC does not include follow-up data, matching with SNDS was performed to describe the entire care pathway for each patient. SNDS includes all care reimbursement data such as type and date of any diagnostic procedure or treatment, and date of death. Since the two databases have no common patient identification number, matching of DCC and SNDS databases was probabilistic, based on sex, month and year of birth, date of diagnosis and residence postal code. Patients were excluded if 1) they had lung cancer in the previous 5 years, 2) they had pre-existing extrapulmonary cancer or synchronous extrapulmonary cancer, 3) review of medical records ruled out lung cancer or 4) variables required for matching were missing.

Definition of care pathway key points, time intervals and secondary outcomes

The dates of diagnostic imaging, pathological diagnosis, MTM and first treatment were used to calculate pathway-specific time intervals. Date of diagnostic imaging (computed tomography (CT) or positron emission tomography (PET) or chest radiograph), date of cancer pathology diagnosis, date of treatment (surgical resection, targeted therapy, immunotherapy, chemotherapy, radiotherapy or palliative care) and date of death were obtained from SNDS. Medical procedures were identified using the French medical procedures thesaurus (Classification Commune des Actes Médicaux - French Classification of procedure terminology (CPT)). Date of MTM and lung cancer type (NSCLC including adenocarcinoma, undifferentiated carcinoma and squamous cell carcinoma, or SCLC) were obtained from DCC. The date of pathological diagnosis was the date of the initial pathology report which included the immunohistochemical study (ALK, ROS1, PD-L1), or the sampling date if the pathology report was not available. The date of the final report including molecular biology analyses was not available. Drugs were identified according to the Anatomical Therapeutic Chemical Classification system. Driving times to the first healthcare facility were estimated with the METRIC software from the French Institute of Statistics and Economical Studies (Institut National de la Statistique et des Etudes Economiques (INSEE)). Patients were allocated to three care pathway groups according to tumour type and treatment: "unresected NSCLC", "SCLC" and "surgically resected NSCLC". In patients with SCLC and unresectable NSCLC, time intervals from imaging to cancer pathological diagnosis, from pathological diagnosis to MTM, from MTM to treatment initiation and from imaging to treatment were calculated. When the time intervals were

negative numbers, these outcomes were excluded from the analyses (for instance when the first treatment occurred before MTM).

In patients with resected NSCLC, only the time intervals from diagnostic imaging to pathological diagnosis and from diagnostic imaging to surgical resection were calculated; MTM was often conducted after surgery, resulting in a negative MTM to treatment interval. The following secondary outcomes were calculated: 1) time from diagnostic imaging to first treatment and 2) death at 1 year, defined as the frequency of patients deceased 1 year after diagnostic imaging.

Statistical analyses

Qualitative data were presented as numbers and percentages. Continuous data were presented as median and interquartile range (IQR). Factors associated with time from diagnostic imaging to first treatment were identified by a multiple linear regression model. The type of tumour was used as an adjustment variable. A sensitivity analysis was performed on the subgroup of NSCLC patients. For each care pathway, factors associated with 1-year survival were identified by a Cox regression model giving hazard ratios (HRs) along with their 95% confidence intervals (95% CIs). Variables with p<0.2 in bivariate analysis were included in the initial multivariate models. A descending stepwise process was then used to select the final models, including all the statistically significant variables at the threshold p<0.05. Analyses were performed with SAS Enterprise Guide 71 64-bit (SAS Institute Inc., Cary, NC, USA).

The study was authorised by the French data protection board (Commission Nationale de l'Informatique et des Libertés (CNIL)), allowing access to SNDS data, decision DR-2019–371. Moreover, the study was granted a waiver of the individual information requirement by the French data protection board, as most patients were deceased at the time of the retrospective study and their personal details were not known. As an alternative measure, collective information about the study was made available and required by the protection board on the websites of the regional epidemiology unit and of the regional oncology centre, mentioning the rights of access, rectification and opposition, in accordance with the provisions of article R. 1461–9 of the Code de la Santé Publique (CSP), as well as the following rights and information, in accordance with the European Data Protection Regulation.

Results

Study population

Screening of the DCC database yielded 962 adult patients. Of these, 102 were excluded due to a previous history of lung cancer (n=55), no lung cancer or synchronous extrapulmonary cancer or pre-existing extrapulmonary tumours (n=33), or missing data (n=14). Matching failure between DCC and SNDS data led to 175 additional exclusions (figure 1). Thus, the final sample included 685 patients, corresponding to a 79.7% matching rate.

Median age was 66 years (59–73) (table 1). Most patients were male (72%). Performance status (PS) was \leq 1 in 82% of patients. 113 (16%) patients had SCLC, 106 (15.5%) had resected NSCLC and 466 (68%)

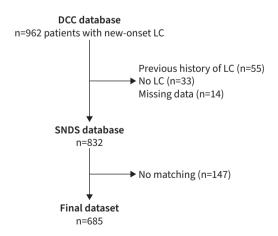


FIGURE 1 Flow chart of patient selection. DCC: Dossier Communicant en Cancérologie; SNDS: Système National des Données de Santé; LC: lung cancer.

	Total	Death at 1 year	SCLC	Resected NSCLC	Unresected NSCLO
Subjects n	685	331	113	106	466
General characteristics					
Male	496 (72.4)	254 (51.2)	88 (77.9)	72 (67.9)	336 (72.1)
Age years, median (interquartile range)	66.0 (59-73)		65.0 (60-74)	66.0 (60-72)	67.0 (58–74)
Performance status score					
0–1	565 (82.5)	233 (41.2)	90 (79.6)	104 (98.1)	371 (79.6)
2	85 (12.4)	65 (76.5)	18 (15.9)	2 (1.9)	65 (13.9)
3–4	35 (5.1)	33 (94.3)	5 (4.5)		30 (6.5)
Histology, n=662					
Adenocarcinoma	311 (47.6)	138 (44.4)		54 (56.2)	257 (57.9)
Undifferentiated carcinoma	62 (9.5)	38 (61.3)		9 (9.4)	53 (11.9)
Squamous cell carcinoma	149 (22.8)	70 (47.0)		30 (31.2)	119 (26.8)
Others	50 (7.3)	10 (55.5)		13 (12.2)	37 (7.9)
SCLC	113 (17.3)	67 (59.3)	113 (100)		
Disease stage, n=531					
Ι	29 (5.4)	2 (6.9)	1 (1.2)	26 (38.8)	2 (0.5)
II	27 (5.1)	3 (11.1)	2 (2.4)	21 (31.3)	4 (1.0)
III	72 (13.5)	23 (31.9)	5 (6)	13 (19.5)	54 (14.2)
IV	403 (75.9)	253 (62.8)	75 (90.4)	7 (10.4)	321 (84.3)
First healthcare facility					
Administrative department					
A	49 (7.2)	27 (55.1)	5 (4.4)	6 (5.7)	38 (8.2)
В	87 (12.7)	58 (66.7)	23 (20.4)	9 (8.5)	55 (11.8)
С	38 (5.5)	21 (55.3)	9 (8)	5 (4.7)	24 (5.2)
D	265 (38.7)	111 (41.9)	36 (31.9)	45 (42.5)	184 (39.5)
E	40 (5.8)	20 (50.0)	6 (5.3)	7 (6.6)	27 (5.8)
F	174 (25.4)	81 (46.5)	28 (24.8)	25 (23.6)	121 (26)
Outside of CVL region	32 (4.7)	13 (40.6)	6 (5.3)	9 (8.5)	17 (3.6)
Nature					
Teaching hospital	203 (29.6)	96 (47.3)	29 (25.7)	31 (29.2)	143 (30.7)
Public hospital	223 (32.6)	135 (60.5)	49 (43.4)	24 (22.6)	150 (32.2)
Private Hospital	259 (37.8)	100 (38.6)	35 (31.0)	51 (48.1)	173 (37.1)
Driving time min					
00-14	187 (27.4)	101 (54.0)	36 (31.9)	21 (19.8)	130 (28.0)
15-25	153 (22.5)	74 (48.4)	29 (25.7)	23 (21.7)	101 (21.8)
25–45	153 (22.5)	71 (46.4)	22 (19.5)	24 (22.6)	107 (23.1)
≽ 45	188 (27.6)	84 (44.7)	25 (22.1)	37 (34.9)	126 (27.1)
First treatment					
Therapeutic abstention	136 (19.9)	123 (90.4)	23 (20.3)		113 (24.2)
Resection	99 (14.5)	12 (12.1)	3 (2.7)	96 (90.6)	
Targeted therapy	27 (3.9)	10 (37.0)			27 (5.8)
Immunotherapy	60 (8.8)	26 (43.3)		1 (0.9)	59 (12.7)
Chemotherapy	329 (48.0)	148 (45.0)	83 (73.5)	9 (8.5)	237 (50.9)
Radiotherapy	30 (4.4)	11 (36.7)	3 (2.7)		27 (5.8)
Radio-chemotherapy	4 (0.6)	1 (25)	1 (0.9)		3 (0.6)
Case-fatality					
Death at 1 year	331 (48.3)		67 (59.3)	13 (12.3)	251 (53.9)

had unresected NSCLC. Among NSCLC cases, the most frequent cancer pathology was adenocarcinoma. The stage of the disease was available for 531 (77%) patients; 403 patients had metastatic disease.

Of the 106 patients undergoing resection, surgery was the first treatment in 99 patients. Among patients with unresected NSCLC, the first treatment was chemotherapy in 329 (48%) patients, immunotherapy in 60 (9%) patients, targeted therapy in 27 (4%) patients, and palliative care or abstention in 136 (23%) patients.

A total of 243 (35%) patients were cared for in teaching hospitals, 195 (28%) in secondary public hospital and 220 (32%) patients in private healthcare facilities. 188 (28%) patients lived over a 45-min drive from the healthcare facility.

1 year after diagnostic imaging, 331 (48%) patients died, ranging from 12.3% for resected NSCLC to 59.3% for SCLC.

Care pathway key points and time intervals

The diagnostic imaging procedure was CT for 571 (83.3%) patients, chest radiograph for 64 (9.4%) patients and PET for 18 (2.6%) patients, whereas no imaging was reported in 32 (4.7%) cases. The date of pathological diagnosis was that of the pathology report in 515 (75.2%) patients and the date of sampling in 154 (22.5%) patients; no date was found in 16 (2.3%) patients. Eventually, 18% of the time intervals were excluded from the analyses.

In the whole study population, time from diagnostic imaging to pathological diagnosis, from pathological diagnosis to MTM and from MTM to first treatment were 12 days (6–30), 14 days (8–22) and 16 days (9–28) respectively. Time from diagnostic imaging to first treatment was 49 days (33–76) (figure 2a). It was shorter for patients with SCLC (figure 2b). Among patients with unresected NSCLC, this time interval was no different in patients with adenocarcinoma or undifferentiated carcinoma *versus* squamous cell carcinoma (figure 2c). In patients with resected NSCLC, 41% had surgery before MTM. Time from diagnostic imaging to surgery was 59 days (41–91) (figure 2d).

Factors associated with time from diagnostic imaging to first treatment

Multivariate analysis showed that time from diagnostic imaging to first treatment increased in patients with NSCLC (± 10.4 days; p<0.001) compared to patients with SCLC (table 2) along with care given in the

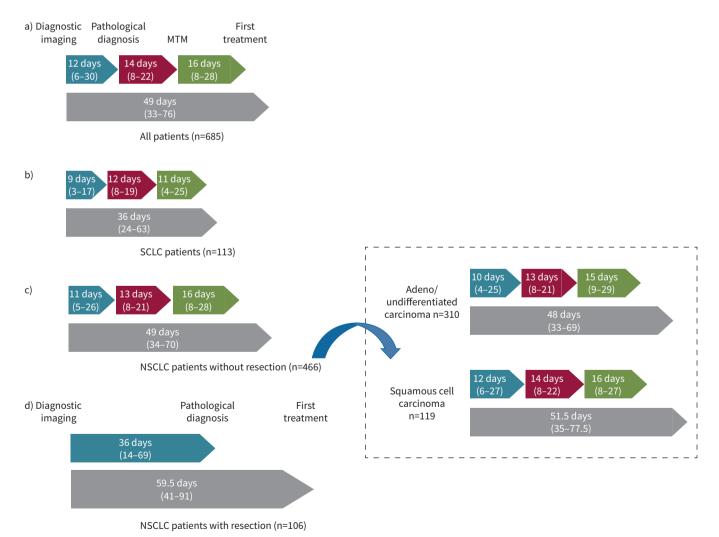


FIGURE 2 Care pathway key points and time intervals for a) all patients, b) small cell lung cancer (SCLC) patients, c) nonsmall cell lung cancer (NSCLC) patients and d) NSCLC patients with resection. MTM: multidisciplinary team meeting.

Variation of time interval between diagnostic imaging to first treatment – multivariate analysis	irst treatment – All patients [#]			Patients with unresected NSCLC ^{4],+}	
	Days (n)	95% confidence interval	Days (n)	95% confidence interval	
Origin time	50.7		48.2	(37.9–58.6)	
Male	-0.8	(-5.6-4.1)	1.1	(-5.12-7.3)	
Age ≽65 years	0.9	(-3.4-5.3)	1.4	(-4.2-7.1)	
Metastatic disease	-15.8	(-20.4 - 11.2)	-14	(-20.8 - 7.3)	
NSCLC (as compared to SCLC)	10.4	(4.2–16.5)			
Adeno/undifferentiated carcinoma (versus squamous cell carcinoma)			2.5	(-4.1-9.1)	
Nature of the first healthcare facility					
Teaching hospital	ref.				
Public hospital	-0.7	(-7.8-6.4)			
Private hospital	-7.1	(-12.51.7)			
Administrative department of the first healthcare facility					
A	8.7	(-1.2-18.6)	9.6	(-2.1-21.3)	
В	2.7	(-5.7-11.1)	-3.6	(-14.1-7)	
C	14.5	(3.4–25.7)	20.3	(4.4–36.3)	
D	ref		ref.		
E	7.6	(-1.8-17.0)	4.2	(-8.4-16.8)	
F	10.0	(4.5–15.5)	17.5	(10.6-24.4)	
Outside CVL region	-5.1	(-15.0-4.8)	0.4	(-15.8-16.6)	
Nature of the first treatment facility [§]					
Teaching hospital			ref.		
Public hospital			10.2	(2.2-18.2)	
Private hospital			4.3	(-2.9-11.5)	

administrative department C (+14 days; p=0.01) or F (+10 days; p<0.001) compared to D (table 2). Conversely, time from diagnostic imaging to first treatment decreased in patients with metastatic cancer (-16 days, p<0.0001) or in a private healthcare facility (-7 days, p=0.01). No association was found between time from diagnostic imaging to first treatment, along with driving time to first healthcare facility and either sex or age.

Focusing on patients with unresectable NSCLC, no significant difference was found between cancer requiring molecular biology tests as standard (adenocarcinoma or undifferentiated carcinoma) or not (non-squamous cell carcinoma) (table 2).

Factors associated with death at 1 year

In patients with unresected NSCLC, factors associated with increased risk of death (table 3) were PS >1, squamous cell carcinoma or undifferentiated carcinoma (*versus* adenocarcinoma), metastatic disease, care in the administrative department B or in a public hospital, absence of targeted therapies, radiotherapy or immunotherapy, and time from imaging to treatment under 49 days.

Of the 96 patients with SCLC, 59% died within the year following diagnostic imaging. No association was found between death and the time interval from imaging to first treatment, driving time to the care facility and type of healthcare facility (supplementary table S1). No variable was significantly associated with risk of death in patients with resected NSCLC (supplementary table S2).

Discussion

"others", n=37; §: can be different from first healthcare facility.

This study is the first to provide a comprehensive description of care pathways of patients diagnosed with lung cancer in France. Key time intervals of the care pathway were similar to those reported in other European regions, confirming the robustness of retrospective databases, reinforced by a new combined approach. Indeed, completeness and analysis strength were enhanced by matching an exhaustive medico-administrative database with MTM medical records. The exhaustiveness of clinical databases is the key factor for optimising studies with such a design.

otential risk factors of death at 1 year – patients with unresected NSCLC (n=360)	Hazard ratio	95% confidence interval
General characteristics		
Age ≥65 years	1.2	(0.8–1.6)
Male	1.0	(0.7–1.5)
PS >1	2.1	(1.5–3.0)
Histology		, ,
Adenocarcinoma	ref	
Squamous cell carcinoma	1.6	(1.1-2.4)
Undifferentiated carcinoma	2.0	(1.3-3.1)
Others	1.4	(0.6-2.9)
Metastatic stage	2.4	(1.6-3.8)
ealthcare pathway		
No immunotherapy	1.8	(1.3-2.7)
No targeted therapy	2.5	(1.3-4.9)
No radiotherapy	2.8	(1.7-4.7)
Administrative department of the first healthcare facility		
A	1.1	(0.5–2.3)
В	1.9	(1.1–3.3)
C	0.8	(0.4–2.0)
D	ref	
E	1.3	(0.6–2.5)
F	0.8	(0.6–1.3)
Outside of the CVL region	1.7	(0.7–3.8)
Nature of the first healthcare facility		
Teaching hospital	ref	
Public hospital	0.8	(0.5–1.3)
Private hospital	0.5	(0.4–0.8)
Time interval between diagnostic imaging and first treatment <49 days [#]	1.5	(1.1-2.1)

NSCLC: nonsmall cell lung cancer; PS: performance status; CVL: Centre-Val de Loire. $^{\#}$: 49 days corresponded to the median time interval between diagnostic imaging and first treatment.

An accurate description of lung cancer care pathways in real-life conditions of patients with new-onset lung cancer was performed in a large French region with >2.5 million inhabitants. We could observe that access to treatment initiation reversely impacted 1-year survival in patients with unresected NSCLC, strengthening the notion that rapid care may not translate into better outcomes in patients with unresectable lung cancer. Furthermore, this study suggests that molecular biology analyses such as next-generation sequencing for unresectable NSCLC did not result in extending time to treatment initiation. It may be speculated that the lack of a difference in the time from imaging to treatment may be related to the fact that, when targeted treatment is prescribed, treatment delivery is quite rapid compared to chemotherapy or immunotherapy.

Although the Centre-Val de Loire region combines multiple factors associated with increased time intervals in care such as low population density, low personal income and educational level, and scarce health resources [25–27], care time intervals were similar to the literature. Hence, although there was a possible selection bias due to possible mismatches between the two databases, the convergence of results with other European studies confirmed the robustness of the design. The median time from diagnostic imaging to treatment initiation was 49 days. The time interval between symptom onset and diagnostic imaging would have been interesting to study; however available databases did not provide information on symptoms. In recent studies, median time from symptom onset to treatment was 130 days in Finland [18] and 123 days in Spain [13]. It may be hypothesised that in Centre-Val de Loire, time from symptom onset to diagnosis may be longer due to the low density of general practitioners in that region [25].

Importantly, care intervals in the present study mostly complied with current RAND corporation [22], Ontario Cancer Plan [23], British NHS [21] and BTS [20] guidelines for lung cancer care. At the European level, median time from pathological diagnosis to treatment was 28 days in the Netherlands [28] and 35 days in England [29]. In the present study, time from pathological diagnosis to MTM and from

MTM to treatment were 14 days and 16 days, respectively. Thus, time from pathological diagnosis to first treatment of lung cancer may actually be rather similar among different Western European countries. Altogether, these data suggest that key time intervals in the lung cancer care pathway are relatively homogeneous across Western European countries, supporting the fact that the present study's results may be useful to other countries with similar healthcare systems.

Shorter time between diagnostic imaging and first treatment was associated with poorer survival in patients with unresected NSCLC, independent of PS and disease stage, as reported in previous studies [11–13], although one previous study reported an inverse association [8]. The mechanisms driving the association between shorter care time intervals and worse prognosis are not fully understood. It is questionable whether aiming to reduce unresected NSCLC care time intervals beyond what is currently recommended by RAND corporation [22], Ontario Cancer Plan [23], British NHS [21] and BTS [20] guidelines is of interest in a public health and care quality perspective. The key time intervals were shorter in patients with metastatic disease and SCLC, in accordance with earlier studies [30, 31].

This study presents an evaluation bias, particularly with regard to the definition of the date of pathological diagnosis (absence of date of anatomopathological examination for 24.8% of patients), which led to underestimation of the time from diagnostic imaging to pathological diagnosis and overestimation of time from pathological diagnosis to treatment. Missing data are common in studies of this type. In a previous French national study, the date of pathology report was not available in 19.1% of cases and the time to diagnosis could not be calculated in 37.5% of cases [32].

It is possible that in patients with unresected NSCLC, missing data may have precluded precise estimation of disease severity. In particular, nutritional status, the location of metastases and full documentation of somatic mutations may have been of interest. It is possible that disease severity determines survival to a much larger extent than treatment-related aspects such as achieving reduction in care intervals. Another limitation is that 41% of patients with resectable lung cancer were operated on before MTM, which precluded analysis of the MTM to surgery delay in many patients.

In conclusion, these new results confirm the high interest of retrospective real-life databases and the power of approaches combining medico-administrative and clinical databases, in order to assess healthcare pathways in a cost- and time-saving process, giving trends to help enhance public health policies. Exhaustiveness of clinical databases is a key factor to optimise retrospective studies. It seems useful for each country to develop good databases to analyse the key points to improve in order to offer lung cancer patients the best treatment. Key time intervals in the lung cancer care pathway in this large French population-based study were similar to those reported in other European regions. A shorter time from diagnostic imaging to first treatment was associated with increased 1-year mortality in patients with unresectable NSCLC, strengthening the notion that accelerating care beyond what is already achieved may not translate into better outcomes for those patients. Moreover, this study suggests that the introduction of molecular biology analyses did not lead to an increase in management intervals.

Acknowledgement: The authors would like to thank all the 3C team members of Centre-Val de Loire region who contributed to the completion of the study.

Provenance: Submitted article, peer reviewed.

Ethical statement: The study was authorised by the French data protection board (Commission Nationale de l'Informatique et des Libertés), decision DR-2019–371.

Availability of data and materials: If you require more details concerning data and materials, please contact us by sending an email to leslie.guillon@univ-tours.fr.

Authors contributions: A. Rivière, A.I. Lecuyer, E. Laurent, C. Lefebvre, T. Lecomte, E. Olivier, D. Carmier, L. Plantier and L. Grammatico-Guillon conceived the study and drafted the study protocol. C. Lefebvre, E. Olivier and A. Rivière provided and reviewed clinical data. A.I. Lecuyer analysed the data. A. Rivière, D. Carmier and L. Plantier helped to interpret the data. A. Rivière, A.I. Lecuyer, E. Laurent and L. Grammatico-Guillon drafted the manuscript. The final manuscript was read and approved by all authors.

Conflict of interest: The authors declare that there is no conflict of interest.

References

- Brosseau S, Pluvy J, Soussi G, et al. [Epidemiology of lung cancer in France and in the world]. Rev Prat 2020; 70: 844–848.
- 2 Johnson DH, Schiller JH, Bunn PA. Recent clinical advances in lung cancer management. J Clin Oncol 2014; 32: 973–982.
- 3 Cheng Y, Zhang T, Xu Q. Therapeutic advances in non-small cell lung cancer: focus on clinical development of targeted therapy and immunotherapy. MedComm 2021; 2: 692–729.
- 4 Mosele F, Remon J, Mateo J, et al. Recommendations for the use of next-generation sequencing (NGS) for patients with metastatic cancers: a report from the ESMO Precision Medicine Working Group. Ann Oncol Off J Eur Soc Med Oncol 2020; 31: 1491–1505.
- 5 Oze I, Hotta K, Kiura K, et al. Twenty-seven years of phase III trials for patients with extensive disease small-cell lung cancer: disappointing results. PLoS One 2009; 4: e7835.
- 6 Berghmans T, Lievens Y, Aapro M, et al. European cancer organisation essential requirements for quality cancer care (ERQCC): lung cancer. Lung Cancer Amst Neth 2020; 150: 221–239.
- 7 Hanna TP, King WD, Thibodeau S, et al. Mortality due to cancer treatment delay: systematic review and meta-analysis. BMJ 2020; 371: m4087.
- 8 Gomez DR, Liao KP, Swisher SG, et al. Time to treatment as a quality metric in lung cancer: staging studies, time to treatment, and patient survival. Radiother Oncol 2015; 115: 257–263.
- 9 Samson P, Patel A, Garrett T, et al. Effects of delayed surgical resection on short-term and long-term outcomes in clinical stage I non-small cell lung cancer. Ann Thorac Surg 2015; 99: 1906–1912, discussion 1913.
- Jacobsen MM, Silverstein SC, Quinn M, et al. Timeliness of access to lung cancer diagnosis and treatment: a scoping literature review. Lung Cancer Amst Neth 2017; 112: 156–164.
- Diaconescu R, Lafond C, Whittom R. Treatment delays in non-small cell lung cancer and their prognostic implications. J Thorac Oncol 2011; 6: 1254–1259.
- 12 Redaniel MT, Martin RM, Ridd MJ, *et al.* Diagnostic intervals and its association with breast, prostate, lung and colorectal cancer survival in England: historical cohort study using the Clinical Practice Research Datalink. *PloS One* 2015; 10: e0126608.
- 13 González-Barcala FJ, García-Prim JM, Alvarez-Dobaño JM, et al. Effect of delays on survival in patients with lung cancer. Clin Transl Oncol 2010; 12: 836–842.
- 14 Radzikowska E, Roszkowski-Sliz K, Chabowski M, et al. Influence of delays in diagnosis and treatment on survival in small cell lung cancer patients. Adv Exp Med Biol 2013; 788: 355–362.
- Shin DW, Cho J, Kim SY, et al. Delay to curative surgery greater than 12 weeks is associated with increased mortality in patients with colorectal and breast cancer but not lung or thyroid cancer. Ann Surg Oncol 2013; 20: 2468–2476.
- 16 Gould MK, Ghaus SJ, Olsson JK, et al. Timeliness of care in veterans with non-small cell lung cancer. Chest 2008; 133: 1167–1173.
- 17 Vinod SK, Chandra A, Berthelsen A, et al. Does timeliness of care in non-small cell lung cancer impact on survival? Lung Cancer Amst Neth 2017; 112: 16–24.
- 18 Alanen V, Koivunen JP. Association of diagnostic delays to survival in lung cancer: single center experience. Acta Oncol 2019; 58: 1056–1061.
- 19 Živković D. Effect of delays on survival in patients with lung carcinoma in Montenegro. Acta Clin Croat 2014; 53: 390–398.
- 20 BTS recommendations to respiratory physicians for organising the care of patients with lung cancer. The Lung Cancer Working Party of the British Thoracic Society Standards of Care Committee. *Thorax* 1998;53: Suppl. 1, S1–S8.
- 21 Department of Health and Social Care. GOV.UK. Available from: www.gov.uk/government/organisations/ department-of-health-and-social-care Date last accessed: 2 March 2022.
- 22 Asch SM, Kerr EA, Hamilton EG, et al. Quality of Care for Oncologic Conditions and HIV [online]. 2000. Available from: www.rand.org/pubs/monograph_reports/MR1281.html Date last accessed: 12 August 2019.
- 23 Cancer Care Ontario. Cancer Care Ontario. Available from: www.cancercareontario.ca/en Date last accessed: 2 March 2022
- 24 Barlesi F, Mazieres J, Merlio JP, et al. Routine molecular profiling of patients with advanced non-small-cell lung cancer: results of a 1-year nationwide programme of the French Cooperative Thoracic Intergroup (IFCT). Lancet Lond Engl 2016; 387: 1415–1426.
- 25 INSEE. Professionnels de santé au 1^{er} janvier 2018 [Internet]. Available from: www.insee.fr/fr/statistiques/ 2012677 Date last accessed: 23 February 2022.
- INSEE. La France et ses territoires [Internet]. 3.1 Poids économique des regions. Available from: www.insee.fr/ fr/statistiques/5039891?sommaire=5040030 Date last accessed: 23 February 2022.

- 27 INSEE. Statistiques locales Indicateurs : cartes, données et graphiques [Internet]. Available from: https://statistiques-locales.insee.fr/#c=indicator&i=rp.dipl_pluseleve_nscol15p&s=2018&view=map3 Date last accessed: 23 February 2022.
- van de Ven M, Retèl VP, Koffijberg H, *et al.* Variation in the time to treatment for stage III and IV non-small cell lung cancer patients for hospitals in the Netherlands. *Lung Cancer Amst Neth* 2019; 134: 34–41.
- 29 Forrest LF, Adams J, White M, *et al.* Factors associated with timeliness of post-primary care referral, diagnosis and treatment for lung cancer: population-based, data-linkage study. *Br J Cancer* 2014; 111: 1843–1851.
- 30 Kourlaba G, Gkiozos I, Kokkotou E, *et al.* Lung cancer patients' journey from first symptom to treatment: results from a Greek registry. *Cancer Epidemiol* 2019; 60: 193–200.
- 31 Yurdakul AS, Kocatürk C, Bayiz H, et al. Patient and physician delay in the diagnosis and treatment of non-small cell lung cancer in Turkey. Cancer Epidemiol 2015; 39: 216–221.
- 32 Pourcel G, Ledesert B, Bousquet PJ, et al. [Waiting times for cancer care in four most frequent cancers in several French regions in 2011 and 2012]. Bull Cancer (Paris) 2013; 100: 1237–1250.