

Lung Cancer in France



Jean-Louis Pujol, MD, PhD,^{a,b,*} Pascal-Alexandre Thomas, MD, PhD,^c
Philippe Giraud, MD, PhD,^d Marc G. Denis, PharmD, PhD,^e
Brigitte Tretarre, MD,^f Benoît Roch, MD, MSc,^{a,b} Sebastien Bommart, MD, PhD^{g,h}

“It is what we believe we already know that often prevents us from learning”

Claude Bernard (1813-1878)

Introduction

France is a western European country with a population of approximately 67.8 million. Although a very diverse and multicultural country, the French Republic is secular by nature and recognizes no communities, only citizens, in accordance with the inalienable right for equality. This is the reason statistics regarding ethnicity are, up until now, forbidden. France is the third economy in Europe and the sixth worldwide, with a nominal income per capita of US\$ 42,878. Health care is financed through compulsory social insurance covering almost the whole population. In addition, the universal health protection (Protection Universelle Maladie) has been implemented in 2016 as the French social benefit, allowing access to care, reimbursement of care, benefits, and drugs to any person regularly residing in France and who is not already covered by another compulsory health insurance scheme. Health insurance pursues a risk management policy that aims to improve the health of the population by strengthening the efficiency of the health care system and by controlling the trend in health expenditure. In 2016, the share of health spending in France represented around 11% of the gross domestic product.¹

Since May 2005, the French National Cancer Institute, a government expert health agency, has been responsible for coordinating scientific research on cancer, proposing guidelines and rules for a quality organization of patients' care, and for informing the population, particularly with prevention messages.² A point-by-point comparison of the French National Cancer Institute guidelines with other international guidelines, such as from the National Comprehensive Cancer Network, illustrates that evidence-based medicine does not care about frontiers. The French National Cancer Institute organization does not directly employ researchers but is

responsible for funding teams of researchers and labeling academic clinical research groups. The care of patients with lung cancer is assumed by three separate medical systems—the public hospital, the private hospitals, and a network of 20 private nonprofit centers devoted to cancer care (created in 1945 by a Charles de Gaulle's ordinance) called the Regional Anticancer Centers. Whatever the center, the care of patients is equivalent insofar as recommendations and guidelines are regularly updated and accepted.

Epidemiology

In France, there is no national cancer registry but a network—named France Cancer Incidence and Mortality (FRANCIM)—of the existing cancer registries that some French departments have built. These are pathology-based registries.³ FRANCIM collects the incidence data from the administrative French department cancer registries, which cover between 19 and 22 departments

^aThoracic Oncology Unit, University Hospital of Montpellier, Arnaud de Villeneuve Hospital, Montpellier, France, ^bCancerology Research Institute of Montpellier (IRCM), Institut national de la santé et de la recherche médicale (INSERM) unit U1194, Montpellier, France, ^cService de Chirurgie Thoracique, Hôpital Nord, Aix Marseille Univ, APHM, Marseille, France, ^dService d'oncologie radiothérapie, Hôpital Européen Georges-Pompidou, Assistance publique-Hôpitaux de Paris, Université de Paris, Paris, France, ^eDepartment of Biochemistry and INSERM U1232, Nantes University Hospital, Nantes, France, ^fHerault Department Register, French National Network of Cancer Registers, Montpellier, France, ^gDepartment of Medical Imaging, University Hospital of Montpellier, Arnaud de Villeneuve Hospital, Montpellier, France, and ^hPhyMedExp, INSERM U1046, Centre national de la recherche scientifique Unité mixte de recherche 9214, University of Montpellier, Montpellier, France.

Disclosure: Dr. Thomas reports receiving personal fees from Ethicon Endo-Surgery and Medtronic, and nonfinancial support from Europrism outside of the submitted work. The remaining authors declare no conflict of interest.

Address for correspondence: Jean-Louis Pujol, MD, PhD, Thoracic Oncology Unit, University Hospital of Montpellier, Arnaud de Villeneuve Hospital, 371 avenue Doyen Gaston Giraud, 34295 Montpellier, France
E-mail: jl-pujol@chu-montpellier.fr

© 2020 International Association for the Study of Lung Cancer. Published by Elsevier Inc. All rights reserved.

ISSN: 1556-0864

<https://doi.org/10.1016/j.jtho.2020.09.012>

Table 1. World-Standardized Lung Cancer Incidence and Mortality Rates Per 100,000 in Mainland France

Incidence and Mortality	y							Average Change Per y (%)	
	1990	1995	2000	2005	2010	2015	2018	1990-2018	2010-2018
Incidence									
Men	51.8	51.5	50.6	51.9	51.5	50.8	50.5	-0.1 [-0.2, 0.0]	-0.3 [-0.6, 0.0]
Women	5.4	6.7	8.8	12.2	15.7	20.0	23.2	5.3 [5.1, 5.5]	5.0 [4.4, 5.5]
Mortality									
Men	48.2	48.3	45.2	42.8	39.5	36.4	34.7	1.2 [-1.2, -1.1]	-1.6 [-1.8, -1.5]
Women	5.3	6.3	7.5	9.5	11.1	12.7	14.0	3.5 [3.4, 3.6]	3.0 [2.7, 3.2]

depending on the cancer studied, with the origin of collections varying from 1975, for the oldest, to 2008, for the most recent. Every 5 years, FRANCIM estimates the national incidence and its trends from these with the previous update in 2018.

In 2018, 46,363 new cases of lung cancers were estimated in mainland France, 67% of were being men. Lung cancer is the second most common cancer in men and the third in women. The world-standardized incidence rates were 50.5 cases per 100,000 person-years in men and 23.2 per 100,000 person-years for women, with a sex ratio of 2.2. Lung cancer is the deadliest cancer for men and the second cause of cancer-related death in women with an estimated number of 33,117 deaths in 2018, 69% of being men. Age-standardized mortality rates (world) were 34.7 and 14.0 for men and women, respectively.

The world-standardized incidence rate of lung cancer in men remains almost stable since 1990. Nevertheless, since 2005, a slightly downward trend was observed with an average annual variation of -0.3% over the recent period from 2010 to 2018 (Table 1 and Fig. 1). The trends by age illustrated a decrease that affected young men only (-2.9% and -1.3% per year respectively for men aged 40 and 50 y over the period 1990-2018) (Table 2 and Fig. 2). In contrast, the state of things for women is worrisome in as much as the incidence has increased sharply since 1990. The standardized incidence rate increased on average by 5.3% per year between 1990 and 2018 (5.4 per 100,000 women in 1990 compared with 23.2 in 2018) and by 5% per year over the recent period from 2010 to 2018 (Table 1 and Fig. 1). Trends by age exhibited an increase in incidence that generally affected all ages, with average annual variations according to age ranging from plus 1.9% to plus 6.3% over the period 1990 to 2018 (Table 2 and Fig. 2).

For men, the mortality rate declined between 1990 and 2018, from 48.2 per 100,000 in the early 1990s to 34.7 in 2018 (on average -1.2% per year over the period 1990-2018 and -1.6% per y over the recent period 2010-2018). Age trends have decreased in parallel with incidence, with a greater decrease in younger

men. In women, mortality follows a fairly overlapping trend with incidence, with an average increase of plus 3.5% per year between 1990 and 2018, and plus 3% per year over the recent period 2010 to 2018. As with incidence, mortality increases for all ages, and most significantly at ages 50 and 60 (Table 1 and Fig. 1). For both sexes, despite many efforts aimed at equal access to health care, there is still an important overmortality in some administrative counties such as the Hauts-de-France (North counties), which is probably related to economic and social deprivation (Fig. 3).

As in any other western country, the distribution of incident lung cancer cases by histologic type has dramatically changed over the past 30 years. This evolution exhibits differences according to sex. In 20 years (periods 1990-1994 and 2010-2015, respectively), the squamous-cell histologic subtype proportion decreased from 51.5% to 26.7% in men and from 27.3% to 12.7% in women. In contrast, adenocarcinoma, which was already the most frequent histologic type in women in the early nineties, now overwhelms all other histologic types, even for men. In 20 years, the proportion of adenocarcinoma increased from 17.2% to 42.1% for men and from 36.7% to 56.6% in women (periods 1990-1994 and 2010-2015, respectively). Within the same period, the proportion of small cell cancers decreased between 1990 and 1995 and 2010 and 2015 in both sexes, from 14.0% to 11.3% in men, and from 15.0% to 11.6% in women.

The National Public Health Agency, Santé Publique France, publishes a yearly health barometer evaluating the effects of regulatory and prevention measures on smoking in the French population.⁴ This barometer uses data harvested by a telephone survey with a random sampling among 10,352 adults aged 18 to 85 years living in mainland France. In 2019, three of 10 French people between 18 and 75 years of age reported smoking (34.6% of men and 26.5% in women), and a quarter are daily smokers (24.0%). The overall smoking rate among men did not significantly vary between 2018 and 2019, and it decreased among women (from 28.9% to 26.5%). Overall, compared with 2014, smoking is down by 3.9

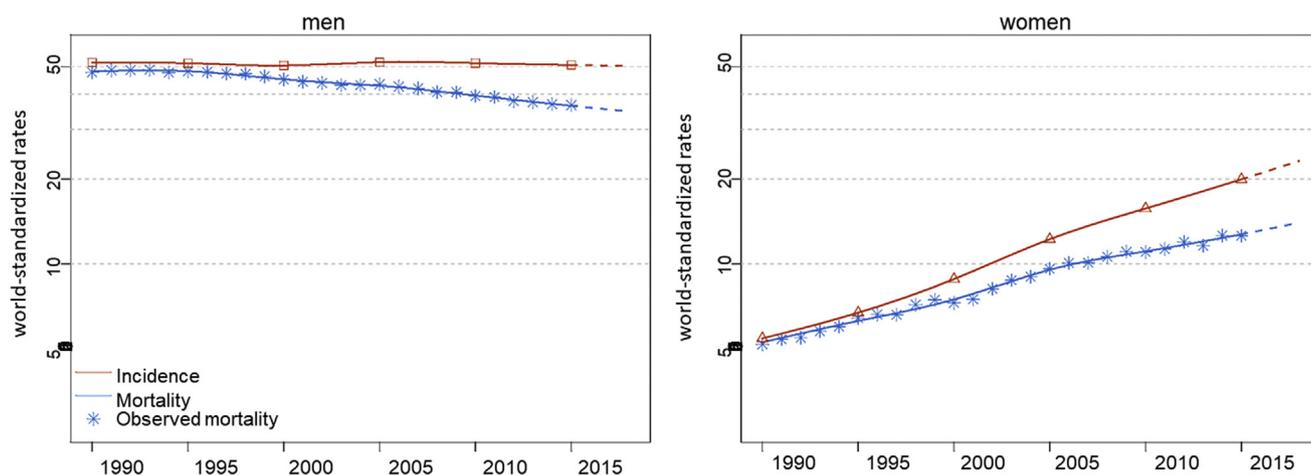


Figure 1. The evolution of world-standardized incidence (per 100,000) and mortality rates of lung cancer in France.

points and by 4.5 points for the daily smoking rate. Social inequalities remain very marked, with a 17-point difference in daily smoking between the unemployed and the employed, and a 12-point difference between the lowest and highest incomes.

Since 2004, France has adopted the MPOWER measures in line with the WHO Framework Convention on Tobacco Control. In its 2019 report, the WHO acknowledged that France had developed a complete policy regarding the monitoring of tobacco consumption and health warnings, and recognized an efficient taxation policy; but, at the same time, WHO considered that smoking cessation programs and advertising bans were still incomplete.⁵ Hitherto, the decrease in smoking incidence in France, as aforementioned, is mainly driven by the progressive increase in the cost of a cigarette pack, which, in 2020, reached the psychological barrier of 10 € (US\$ 12). This policy is efficient in deterring

young people from starting to smoke, but is unfortunately limited by the lack of European harmonization, with a high level of transfrontier tobacco purchase in Belgium, Germany, and Spain, where a pack of cigarettes is sold at almost half the French price.

Screening

There are currently no official lung cancer screening programs in France. The European chest specialists' societies recommend lung cancer screening in the setting of a comprehensive, quality-assured, longitudinal programs within a clinical trial or in routine clinical practice at certified multidisciplinary chest centers. Nevertheless, in May 2016, the French Health Authority, a government agency, gave a decision against implementing screening by low-dose computed tomography (CT) scan in the general population.⁶ Among the different reasons for this rebuttal, this agency considered that too many false-

Table 2. World-Standardized Lung Cancer Incidence and Mortality Rates Per 100,000 According to Age and Year in Mainland France

Incidence and Mortality	Age, y	Men			Women		
		1990	2018	ACY (%)	1990	2018	ACY (%)
Incidence							
	40	19.0	8.3	-2.9 [-3.5, -2.3]	4.2	7.1	1.9 [1.0, 2.7]
	50	89.1	62.7	-1.3 [-1.5, -1.0]	9.6	53.4	6.3 [5.8, 6.9]
	60	226.8	248.2	0.3 [0.1, 0.5]	21.8	115.1	6.1 [5.7, 6.6]
	70	344.8	339.1	-0.1 [-0.3, 0.1]	32.4	111.4	4.5 [4.1, 4.9]
	80	319.7	375.8	0.6 [0.3, 0.8]	29.5	109.9	4.8 [4.3, 5.3]
Mortality							
	40	16.3	5.1	4.0 [-4.4, -3.7]	2.7	3.0	0.4 [0.0, 0.9]
	50	70.3	34.9	2.5 [-2.6, -2.3]	8.0	24.1	4.0 [3.7, 4.3]
	60	202.2	162.2	-0.8 [-0.9, -0.7]	19.3	72.9	4.9 [4.6, 5.1]
	70	319.0	239.2	-1.0 [-1.1, -0.9]	33.6	73.2	2.8 [2.6, 3.0]
	80	411.6	320.6	-0.9 [-1.0, -0.8]	47.7	91.1	2.3 [2.1, 2.5]

ACY, average change per year.

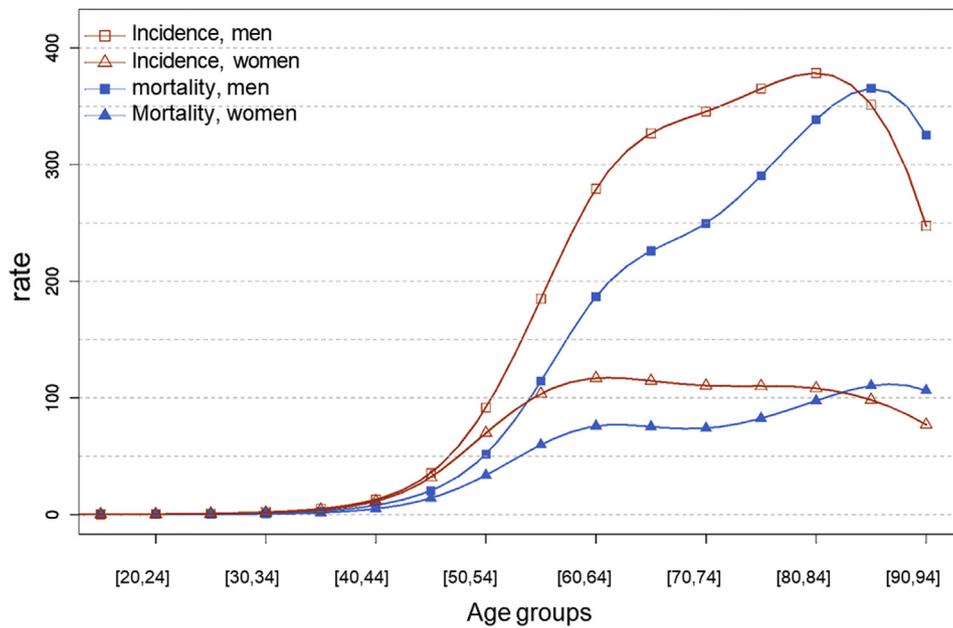


Figure 2. Incidence and mortality rate by age group in France in 2018.

positive results expose screened people to adverse events induced by the characterization procedure of noncancerous nodules. At the time of this decision, the main results came from the National Lung Screening Trial study. As the NELSON (Dutch-Belgian Randomized Lung Cancer Screening Trial) study design has reduced the false-positive rate, a change in the French Health Authority statement is expected. Meanwhile, many chest physicians and oncologists recommend individual screening to their high-risk patients (chronic obstructive pulmonary disease, lung cancer history), regularly performed with low-dose CT scan. Unfortunately, this wild screening has neither a formal framework nor standardized interscreening intervals.

Diagnosis

The staging procedures follow current international guidelines. Access to brain magnetic resonance imaging and fluorodeoxyglucose-positron emission tomography (PET) might be the most limiting steps in terms of delay from suspicious abnormalities to treatment. There is still too much delay from the suspicious abnormality to the final diagnosis and tumor staging that is mainly because of the incomplete coordination of multiple specialists. This is a concern that many institutions try to improve by integrating all steps of the diagnosis process into a unique journey. Regarding mediastinal staging, a shift was observed during the past two decades from mediastinoscopy to endobronchial ultrasound (EBUS)

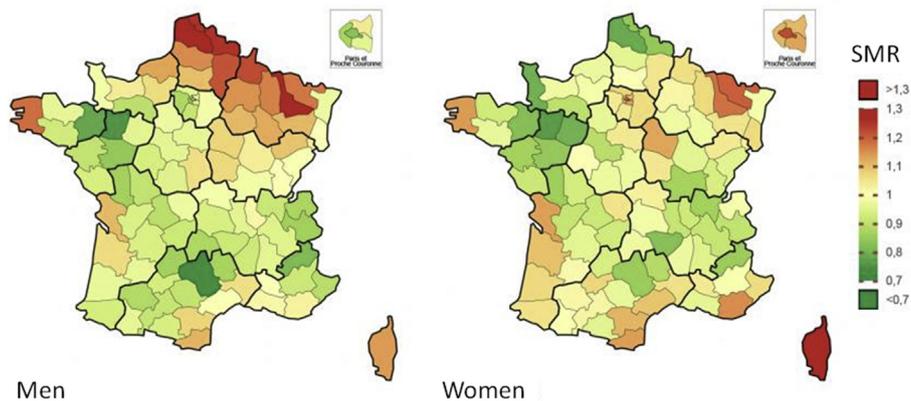


Figure 3. Lung cancer mortality by French administrative counties during the period 2007 to 2014. SMR (the numbers are the ratio of a given county SMRs to the overall French SMR) Source: France Public Health (<https://www.santepubliquefrance.fr/>). SMR, standardized mortality rates.

with the latter technique being more widespread. In most of the institutions, nodal status assessment using EBUS is no longer systematic but fluorodeoxyglucose-PET-guided.

The pathologic diagnosis of lung cancer in France benefits from a large network of interventional chest physicians and radiologists. Central tumors with evidence of bronchus signs on chest CT scan are usually assessed on biopsies harvested through standard fiberoptic bronchoscopy or cytopuncture performed through EBUS, when appropriate. The diagnostic approach of peripheral lesions may be multimodal, and thus, vary depending on its accessibility. It is mainly assessed on CT-guided needle biopsies and less frequently through bronchoscopy guidance tools. With the widespread training, most interventional radiologists are able to perform CT-guided needle biopsies for nodules as small as 1 cm.

Workup is standardized, particularly regarding tumor imaging. Moreover, the decision of the best pathway to the diagnostic procedure is decided by a multidisciplinary approach, in which thoracic surgeons, pulmonologists, anesthesiologists, and interventional radiologists are involved. To do so, the interventional radiologists and pulmonologists act into medicosurgical structures part of corridors of access to specialized oncology care. The goal is to obtain the most efficient tumor sampling in terms of pathologic diagnosis and molecular profiling in the safest conditions. That needs efficient interaction with each specialist.

Molecular profiling of NSCLC has been considered as a priority by the French national institute. The first period of the implementation of routine molecular profiling was led by the National Cancer Institute in 2007.⁷ A total of 28 hospital molecular genetics centers for cancer were labeled to carry out molecular profiling (at least one genetic center in each administrative region). Different analytical approaches were used, including Sanger sequencing and more sensitive approaches, such as pyrosequencing or allele-specific polymerase chain reaction. In 2016, the first experience of routine molecular testing in the setting of nonsquamous NSCLC was reported by the French Cooperative Thoracic Intergroup under the auspices of the institute, and encompassed 18,679 molecular analyses of 17,664 patients with NSCLC over a 1-year period (2012–2013). A total of five genes (*EGFR*, *KRAS*, *BRAF*, *HER2*, *PIK3CA*) with the aforementioned techniques (plus fluorescence in situ hybridization for *ALK*) were identified. The turnaround times in obtaining analysis results were considered as acceptable (median 11 d with interquartile range: 7–16). Since that time, molecular profiling was boosted by the technical progress and by the consolidated organization of molecular platforms.

The increasing number of clinical trials assessing targeted therapies has led the National Cancer Institute to strongly promote the development of next-generation sequencing technology within the 28 genetic centers. In the meantime, a new financial regulation for innovative testing has been established for the acts out of nomenclature, allowing all private and public laboratories in France to access funding for molecular biology testing in oncology. The objective is to organize a sufficient territorial network so that tumor samples arriving from routine pathology departments may benefit from a rapid analysis of high technical standards, regardless of the hospital where the patient will receive therapy. The most recent national report of the routine molecular testing by gene mutations and the evolution of tests are illustrated in Figure 4. During the past 5 years, all platforms have shifted their routine molecular profiling from gene-specific, polymerase chain reaction-based assays to next-generation sequencing. The genes encompassed in the panel fluctuate greatly from one platform to the other, but always integrate druggable mutations plus *KRAS*. In patients for whom research of mutations remains negative at that state, RNA sequencing is also being implemented by many platforms to detect rare but druggable gene fusions such as *NTRK*, *RET*, and *NRG-1*.

Organization of Decision Making in Oncology

The cancer plan promoted during President Chirac's mandate allowed progresses in the organization of treatment decisions and patient care. In 2005, an ordinance gave an excellent framework to the organization of oncology care in health structure.⁸ Although many institutions had a lifelong experience of multidisciplinary tumor boards (MTB), this was not uniformly performed. The MTB is now a milestone step in the decision-making for treatment of patients as no oncologic treatment could be delivered without formal MTB written conclusions (except, of course, in cases of emergency). Moreover, this ordinance has greatly modified the patient-physician relationship by promoting diagnostic announcement procedures. The plan was also an opportunity for new medical tasks to emerge, such as clinical nurses with specific training and competence in oncology.

Surgery

The practice of thoracic surgery is defined within a strict legal framework. Since 2009, the National Professional Council in Thoracic and Cardiovascular Surgery is the sole representative of the specialty in France for the trustee authorities. It is responsible for implementing continuous professional development, accreditation criteria of units, certification and recertification of

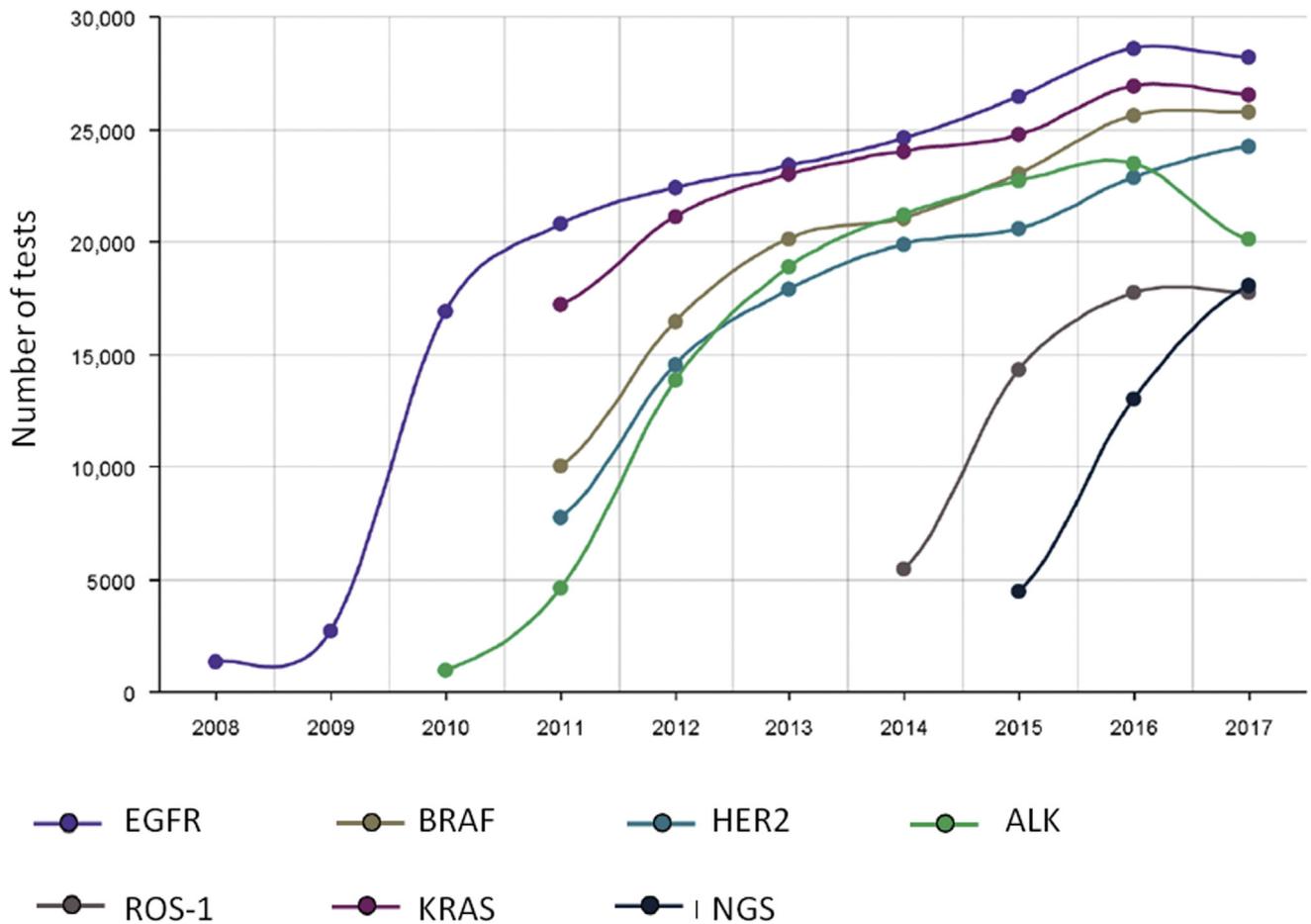


Figure 4. Progression of molecular profiling for French patients with NSCLC. The values for each tested genes represent the number of tests done either by specific polymerase chain reactions or sequencing. NGS, next-generation sequencing.

surgeons, assessment, and analysis of professional practices with the objectives of improving the management processes, the quality and safety of care, and the competencies of physicians. In 2020, 343 board-certified surgeons were practicing thoracic surgery in 147 authorized centers in France, including overseas territories and departments. About 8000 lung cancer resections are performed annually for primary lung cancer according to the national administrative database.

A national general thoracic surgery database, named EPITHOR, was created in 2003 by the French Society of Thoracic and Cardiovascular Surgery with the main objective to allow the evaluation of surgical practices at surgeon-, center-, and national-levels. For this purpose, the software includes functions that allow participating surgeons to benchmark their own activity against national averages.⁹ The French Health Authority has labeled this database. Since 2016, a total of 112 contributing centers have captured 83% of the overall national volume of surgical activity. Contributing to EPITHOR remains voluntary in nature but is already mandatory in the processes of continuous professional

development, certification, and recertification of surgeons. In 2020, a key step forward has been done with the linkage of EPITHOR to the National Institute of Statistics and Economic Studies database, providing exhaustive survival information.

From January 1, 2016 to June 30, 2020, a total of 31,381 patients with primary lung cancer were registered in EPITHOR. Lobectomy was the main type of lung resection performed ($n = 22,530$; 72%), followed by infralobar resections ($n = 5388$; 17%), with more anatomical segmentectomies ($n = 3424$) than wedge resections ($n = 1964$). Pneumonectomy was seldom performed ($n = 1938$; 6%), as was bilobectomy ($n = 1065$; 3%). Purely diagnostic surgery was achieved in 512 patients (1.6%). The rate of “open and close” surgeries was 1.3% ($n = 405$). Thoracotomy was the most performed approach ($n = 18,734$; 60%). Minimally invasive techniques were used in 12,647 patients (40%), namely: (1) video-assisted thoracoscopy (VATS) in 10,352 (33%), and (2) robot-assisted thoracoscopy in 2295 (7%). When compared with the 2010 to 2015 period, these features illustrate obvious changes in

surgical practices with very few active VATS (3.7% patients operated on by VATS) and robot-assisted thoracoscopy programs (2.5%) at that time.

The volume of surgical activity grew annually: 6149 patients in 2016, 6843 in 2017 (+11.3%), 7592 in 2018 (+10.9%), and 7626 in 2019 (+0.4%). The first semester of 2020 was affected by the coronavirus disease 2019 pandemic, especially during the containment period between March 17 and May 11, and was characterized by a decline of surgical activity of 12.4%, overall.

During the same period (2016–2020), postoperative complications occurred at a mean rate of 0.3 per patient. Major complications (grade 3 and higher, according to the Clavien-Dindo classification) represented 26% of them. The mean hospitalization stay was 7 days. The mean 30-day mortality was 1%–0.6% after wedge resection, 0.4% after segmentectomy, 0.8% after lobectomy, 1.7% after bilobectomy, and 2.9% after pneumonectomy.

Interventional Radiology and Pulmonology

During the past decade, the interventional radiology in oncology grew rapidly in terms of both diversity of procedures and volume of activity. EPIFRI (Registre EPIdémiologique de la Fédération de Radiologie Interventionnelle), the official registry recording image-guided therapy procedures, indicates that 9000 thermoablations were performed in 2018. Radiologists are active participants in MTB. The French Radiology Society considers three levels of expertise, with the interventional radiology in oncology considered at the highest level. These interventions consist of thermoablation, chemoembolization, radioembolization, implantation of prosthetic devices, management of complications such as hemostasis embolization, and analgesic cementoplasty. The training of radiologists in thoracic oncology integrates expertise in diagnosis and interventions. Consequently, most radiologists involved in lung cancer are specialized as chest radiologists. A similar organization exists for interventional chest physicians with specific training for various interventions such as endobronchial hemostasis and bronchial prosthetic device insertion.

Radiotherapy

Lung cancer ranks among the most difficult malignancies to be irradiated, combining ballistic complications owing to respiratory movements, the number and low tolerance of surrounding healthy organs, and dosimetric difficulties caused by heterogeneity in circumambient tissues. Today, the emergence of thoracic radiotherapy—integrating novel techniques in the

treatment procedure besides the latest technological developments in medical imaging, dosimetry, and treatment devices—raise new hopes for the treatment of thoracic malignancies. Three techniques seem particularly promising: (1) intensity-modulated conformal radiotherapy (IMRT); (2) stereotactic body radiotherapy (SBRT); and (3) irradiation with respiratory gating. These various innovations are designed to achieve high-precision radiotherapy to better focus the irradiation fields on the tumor while protecting critical organs (e.g., lung, heart).

Approximately 14,500 patients with lung cancer are treated with irradiation each year in France. At the end of 2018, a total of 169 centers were authorized for radiotherapy activity. About half of them are distributed between liberal centers and public hospitals. French centers were equipped with 457 treatment devices: 435 modern linear accelerators, 93 dedicated units (Cyberknife, Novalis, TomoTherapy), four Gammaknife, 11 orthovoltage devices, 13 intraoperative radiotherapy devices, and four cyclotrons. About 800 radiotherapist oncologists and 700 medical physicists work in these 169 centers.

IMRT and SBRT activities increased by approximately 22% between 2017 and 2018. This significant development implies that more than 75% of patients with lung cancer were treated with IMRT, and more than 51% were treated with SBRT in 2018. SBRT was carried out in 2018 in 71 French centers and amounted to around 9900 first preparations. For radiotherapy plan preparation, 70% of centers have a four-dimensional scanner, and 80% use data fused from PET imaging.

With regard to these high-precision techniques, a very important effort has been made these past few years in terms of equipment and training. At the present time, most of the treatment (around 84%) is, therefore, carried out using conformational techniques with intensity modulation (around 95%), and about 50% of the centers have radiotherapy equipment for intra- or extracranial stereotactic treatments. These techniques are now available nationwide, although disparities between regions remain.

Systemic Therapy

The European Medicines Agency issues guidelines regarding cancer treatment marketing authorization that members must follow. Each country has its own regulations, and they vary. In France, patients benefit from an efficient system of access to innovative drugs by means of the Temporary Use Authorization (TUA). This program is similar to the U.S. expanded access program; both programs were implemented at the same period (1986–1987) and started through the

same circumstances to accelerate the development of therapy against human immunodeficiency virus-acquired immunodeficiency syndrome. As a matter of fact, the French drug authorization is a multistep process: after marketing authorization by the European Medicines Agency, the new drug has to go through a complete process under the auspices of the French Health Authority. The transparency committee,¹⁰ an agency of the Health Authority, is in charge of guiding the French Ministry of Health by giving advice on the degree of effectiveness of a new treatment compared with existing drugs. This system allows health insurance to set the reimbursement rate and negotiate the price with the pharmaceutical companies. Since March 2019, the physician's request for a given patient has been made through a computerized system, called e-Saturne, which considerably simplifies the process. TUA allows patients to receive innovative therapy while a given drug is undergoing this long-lasting process. Recently extended, a new TUA, named extended cohort-TUA, has been set to allow patients with lung cancer receiving drugs that have already complete marketing authorization for other malignancies (e.g., dabrafenib-trametinib).

As in any country, the complete development of targeted therapies is a major goal of medical oncology because of the dramatic survival benefit of these treatments in patients with druggable genes alterations, and also because immunotherapy results are frequently poor in these subpopulations. The first-line treatment of patients with NSCLC harboring *EGFR*-sensitizing mutations has shifted from first- or second-line tyrosine kinase inhibitors (TKIs) toward osimertinib. For those with *ALK*-positive tumors, most oncologists prescribe upfront alectinib. Brigatinib is approved in the second line. Lorlatinib is also approved but is conditioned to the failure of a first-line therapy consisting either of alectinib or ceritinib and a second line, whatever the TKI. For *ROS-1* translocations, the only approved TKI is crizotinib, and its prescription is restricted to second-line treatment. The prescription of dabrafenib plus trametinib was approved in January 2017 for patients with advanced NSCLC with *BRAF V600E* mutation. This approval is restricted to second-line treatment and more, after the failure of chemotherapy, immunotherapy, or combination of both. As for any cancers that have shared common *NTRK* fusion, larotrectinib and entrectinib have been approved for patients with *NTRK*-altered NSCLC who failed standard systemic therapy. Patients with *RET* fusion could benefit from selpercatinib in the setting of TUA. Recently, in a TUA framework, patients with NSCLC with *c-MET* exon 14 skipping mutations could receive capmatinib after the failure of a first-line consisting of

immunotherapy, chemotherapy, or a combination of both.

The first-line treatment of *ALK* and *EGFR* wildtype metastatic NSCLC has quickly evolved in the past few years. Pembrolizumab single-drug regimen was approved by the French national agency in August 2018 (for those with tumor programmed death-ligand 1 [PD-L1] score $\geq 50\%$), and a combination of chemotherapy and pembrolizumab was approved in 2020 (March for nonsquamous and May for squamous NSCLC, whatever the tumor PD-L1 score). Atezolizumab plus chemotherapy combination is also approved by our national agency for nonsquamous NSCLC since March 2020. However, this combination is quadruplet, as the adjunction of bevacizumab is compulsory (to be congruent with the publication). The prescription of this combo in France is therefore limited. This latter shift of paradigm has consequences in the subsequent line choice. Before the approval of this combo, most patients received second-line immune checkpoint inhibitors (ICPI), namely nivolumab, pembrolizumab (for those with tumor PD-L1 score $\geq 1\%$), or atezolizumab. Since the advent of immunotherapy or immunotherapy plus chemotherapy in the first-line setting, many patients now receive standard second-line treatment such as docetaxel. Rechallenge or restart of an ICPI is not approved. For locally advanced NSCLC, radiotherapy-chemotherapy concurrent combination is the standard of care. A followed consolidation treatment with durvalumab is approved, pending a tumor PD-L1 score greater than or equal to 1%.

As in many countries, the treatment of extensive-disease SCLC has dramatically changed recently. Combining chemotherapy with ICPI is rapidly becoming the standard of care for first-line treatment of extensive-disease SCLC. For over two decades, therapy of limited-stage SCLC consists of concurrent platinum and etoposide chemotherapy-radiotherapy combination. Once-daily radiotherapy is more frequently applied than the twice-daily scheme despite the results of the CONVERT study (Concurrent once-daily versus twice-daily chemoradiotherapy),¹¹ which did not invalidate the landmark Intergroup 0096 study. Most patients who achieve a response then receive prophylactic cranial irradiation.

Conclusions

The relatively efficient public health organization in France allows a fairly rapid implementation of therapeutic advances in the care of patients with lung cancer. Unfortunately, despite efforts to provide fair and equal access to care, some shadows persist. The academic research is very active, with several collaborative groups able to address new concepts. These structures allow

many oncologists and chest physicians to participate in international efforts to change lung cancer prognosis.

References

1. Sécurité sociale. Direction de la Sécurité sociale: les chiffres clés de la Sécurité sociale 2017. Edition 2018. <https://www.securite-sociale.fr/files/live/sites/SSFR/files/medias/DSS/2017/CHIFFRES%20CLE%202017.pdf>. Accessed September 9, 2020.
2. Institut National Du Cancer. The French National Cancer Institute. <https://en.e-cancer.fr/>. Accessed September 9, 2020.
3. Uhry Z, Chatignoux E, Dantony E, et al. Multidimensional penalized splines for incidence and mortality-trend analyses and validation of national cancer-incidence estimates. *Int J Epidemiol*. 2020;49:1294-1306.
4. Pasquereau A, Andler R, Arwidson P, Guignard R, Nguyen-Thanh V. Tobacco use among adults: review five years of the national tobacco control program, 2014-2019. *Bull Epidemiol Hebd*. 2020;14:273-281.
5. WHO. WHO report on the global tobacco epidemic, 2019. Country profile:France. https://www.who.int/tobacco/surveillance/policy/country_profile/fra.pdf?ua=1. Accessed September 9, 2020.
6. Haute Autorité de Santé. Lung cancer: conditions not met for screening in smokers. https://www.has-sante.fr/jcms/c_2632491/fr/. Accessed September 9, 2020.
7. Hofman P, Rouleau E, Sabourin JC, et al. Predictive molecular pathology in non-small cell lung cancer in France: the past, the present and the perspectives. *Cancer Cytopathol*. 2020;128:601-610.
8. Ordinance DHOS/SDO no 2005-101 of February 22, 2005 relating to the organization of cancer care. <https://solidarites-sante.gouv.fr/fichiers/bo/2005/05-03/a0030034.htm>. Accessed September 9, 2020.
9. Bernard A, Falcoz PE, Thomas PA, et al. Comparison of Epithor clinical national database and medico-administrative database to identify the influence of case-mix on the estimation of hospital outliers. *PLoS One*. 2019;14:e0219672.
10. Law n. 2004 About National Health Insurance. *Off J French Repub N 0190* du 17 August 2004. 2004-;810 du 13 August:14598.
11. Faivre-Finn C, Snee M, Ashcroft L, et al. Concurrent once-daily versus twice-daily chemoradiotherapy in patients with limited-stage small-cell lung cancer (CONVERT): an open-label, phase 3, randomised, superiority trial. *Lancet Oncol*. 2017;18:1116-1125.