BRIEF REPORT

# Brief Report: A Multidisciplinary Initial Workup for Suspected Lung Cancer as Fast-Track Intervention to Histopathologic Diagnosis

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**ABSTRACT**

Guidelines for optimal timing of lung cancer diagnosis and treatment have been implemented in many countries, but the effect of fast-track interventions on the shortening of time interval is still debatable. In this study, the delay from the first specialist visit to the histopathologic diagnosis was compared between two patient cohorts: before (n = 280) and after (n = 247) implementation of a fast-track multidisciplinary diagnosis program. The cumulative incidence function curves were compared, and hazard ratio was adjusted in the Cox model. The implementation allowed a statistically significant increase in the cumulative incidence of the lung cancer histopathologic diagnosis over time. Adjusted hazard ratio for patients accrued in the post-implementation cohort was 1.22 (1.03–1.45) ($p = 0.023$), corresponding to a reduction of this waiting period by 18%. In conclusion, a multidisciplinary approach of the diagnostic process implemented at the initial visit allows a significant reduction of the timeline until the histopathologic diagnosis of lung cancer.



## Introduction

Delays elapsing between the first patient referral and the treatment partly contribute to the poor prognosis of lung cancer.[1] The time separating a suspicious radiologic abnormality to the histopathologic diagnosis is a critical period inasmuch as histopathologic classification hand molecular diagnosis are the milestones between the disease characterization and the multidisciplinary tumor board treatment proposal.[2] Long delays are associated with a putative chance lost due to tumor progression and changes in treatment options.[3] Moreover, waiting time to diagnosis is from the patient's point of view, a period of uncertainty that feeds fears and anxiety.[4,5] Guidelines for optimal timing of lung cancer diagnosis and treatment have been implemented in many countries, but the effect of fast-track interventions in shortening time interval is

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still debatable.[1,6] Among the different timelines, the one elapsing from the first visit to histopathologic diagnosis seems as a limiting step insofar as it is one of the most complex to organize.[4] Therefore, interventions should target this specific delay.

A multidisciplinary organization, chaired by the thoracic imaging department of our institution, was implemented to shorten the time from the first medical visit to the histopathologic diagnosis. In this brief report, the complete facility consisting of an organization and diagnostic algorithms is described. This pre-implementation and post-implementation study aimed at comparing diagnostic timelines in two consecutive cohorts, that is, before-and-after implementation of the multidisciplinary initial workup for suspected lung cancer (thereafter named to as "fast-track multidisciplinary diagnosis").

## Patients and Methods

The study was approved by the institutional review board of the Montpellier University Hospital (IRB-MTP_2020_12_202000641). The organization of the fast-track multidisciplinary diagnosis was based on a formal weekly meeting (with a possible anticipated proposal by virtual permanent meeting) involving interventional radiologists, chest physicians, pathologists, surgeons, and oncologists. In addition, a nurse and an administrative assistant regulated the care pathways in order at coordinating the different exploratory tests decided by the meeting and accompanying the patients throughout the process. This panel proposed a specific strategy patient-by-patient taking into account current diagnostic guidelines[7] and specificities of each case. In an attempt at avoiding biopsy failure (*e.g.,* biopsy of a tumor necrotic area) and to guide the less aggressive way, the strategy was based on imaging by fluorodeoxyglucose-positron emission tomography scan and computed tomography scan. Exclusion criteria were inflammatory or infectious disease, benign diseases, lung metastases of extrathoracic cancer, and history of lung cancer during the 2 previous years.

The end point was the time elapsed from the first medical visit to the date of histopathologic diagnosis in the intention-to-treat population. The cumulative incidence function of histopathologic diagnosis was calculated and compared between the two cohorts. Crude estimates of the cumulative incidence function were constructed using the Kaplan–Meier method. Unadjusted hazard ratio (HR) and 95% confidence interval (95% CI) were calculated with the log-rank test for cohort 2 versus cohort 1 and for covariates (age, sex, histopathologic classification, disease stage, and patient's residency). The HR for time to histopathologic diagnosis in cohort 2 versus cohort 1 was adjusted for covariates by means of the Cox proportional hazard model. The proportional hazard assumption was tested graphically (function LOG [-LOG [S (t)]]). The classical forward selection of variable procedure was used. A $p$ value less than 0.05 was considered significant.

## Results

From January 8, 2019, to January 13, 2020, a total of 280 consecutive patients was accrued in the pre-implementation cohort (cohort 1). From February 17, 2021, to January 20, 2022, a total of 247 consecutive patients was accrued in the post-implementation cohort (cohort 2). There were no statistically significant imbalances of covariates between the two cohorts, though a trend toward a slightly higher proportion of women among cohort 2 was observed (34.6% and 40.5% in cohort 1 and 2, respectively, $p = 0.17$). The proportion of SCLC histopathology was less than 6% in both cohorts and 16% of patients in each cohort presented with a metastatic stage at the time of accrual into the fast-track multidisciplinary diagnosis program.

Patients accrued in cohort 2 proved to benefit from a statistically significant shorter time to histopathologic diagnosis insofar as a higher cumulative incidence during the workup time was observed when compared with patients accrued in cohort 1 with an adjusted HR (aHR) and 95% CI of 1.22 (1.03–1.45) ($p = 0.023$) (Fig. 1). The cumulative incidences (95% CI) at 30 days were 71.4% (66.1%–75.6%) and 80.6% (75.4%–85.2%) in cohort 1 and cohort 2, respectively. Median (95% CI) cumulative incidence was 18 (15–21) days and 15 (13–16) days in cohort 1 and cohort 2, respectively. In the Cox model, the fast-track implementation, a metastatic stage (aHR = 1.53; [1.20–1.94]), and a SCLC histology (aHR = 1.49 [1.02–2.19]) were the three statistically significant determinants of a shortened time to histopathologic diagnosis. The prespecified covariate analyses revealed that the shortening of the timeline to histopathologic diagnosis favored cohort 2 versus cohort 1 across all subgroups (Fig. 2). Nevertheless, the implementation mainly benefited patients in the non-metastatic stage, whereas patients with stage IV disease seemed to do not profit from the fast-track multidisciplinary diagnosis program (owing to easier access to extrathoracic sites).

## Discussion

In this report, the implementation of the fast-tract multidisciplinary diagnostic program allowed a statistically significant increase in the cumulative incidence of

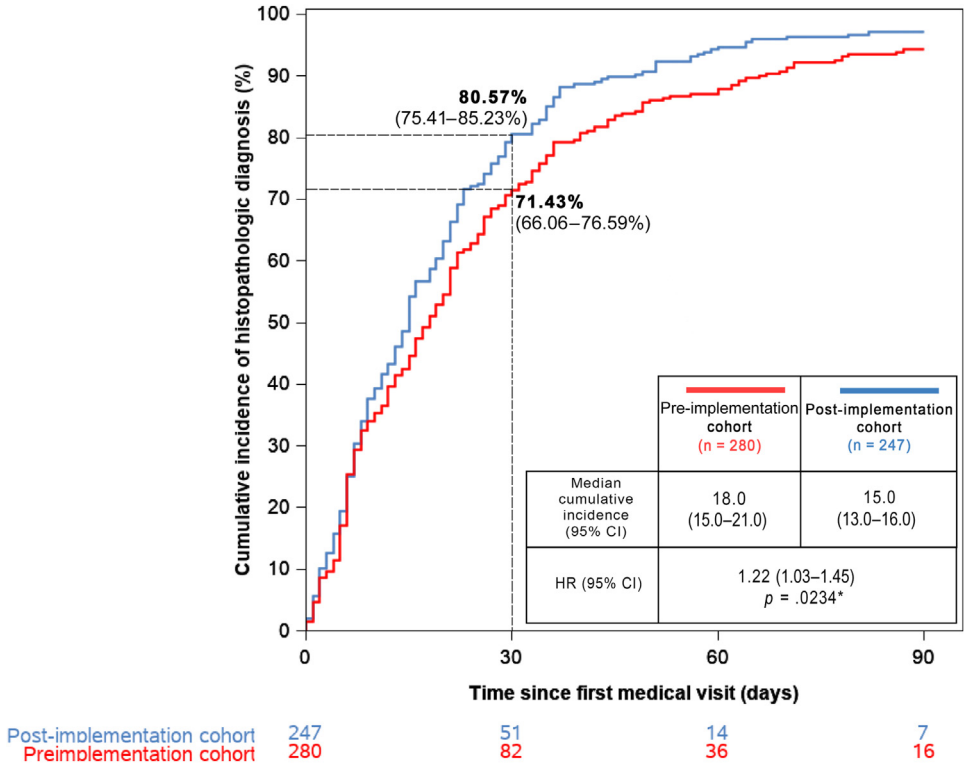


**Figure 1.** Comparison of cumulative incidence function curves for cohort 1 and cohort 2, that is, respectively, pre-implementation and post-implementation of the fast-track multidisciplinary diagnosis program. *HR was adjusted (aHR) for covariates as significant determinants of shorter time to histopathologic diagnosis in the Cox model (disease stage and lung cancer histologic group). aHR, adjusted hazard ratio; CI, confidence interval; HR, hazard ratio.

the lung cancer histopathologic diagnosis over initial workup time. Adjusted HR for patients accrued in the post-implementation cohort was 1.22 (1.03–1.45) ($p$ = 0.023), corresponding to a reduction of this waiting period by 18%. As the biopsy modality choice was systematically based on positron emission tomography scan

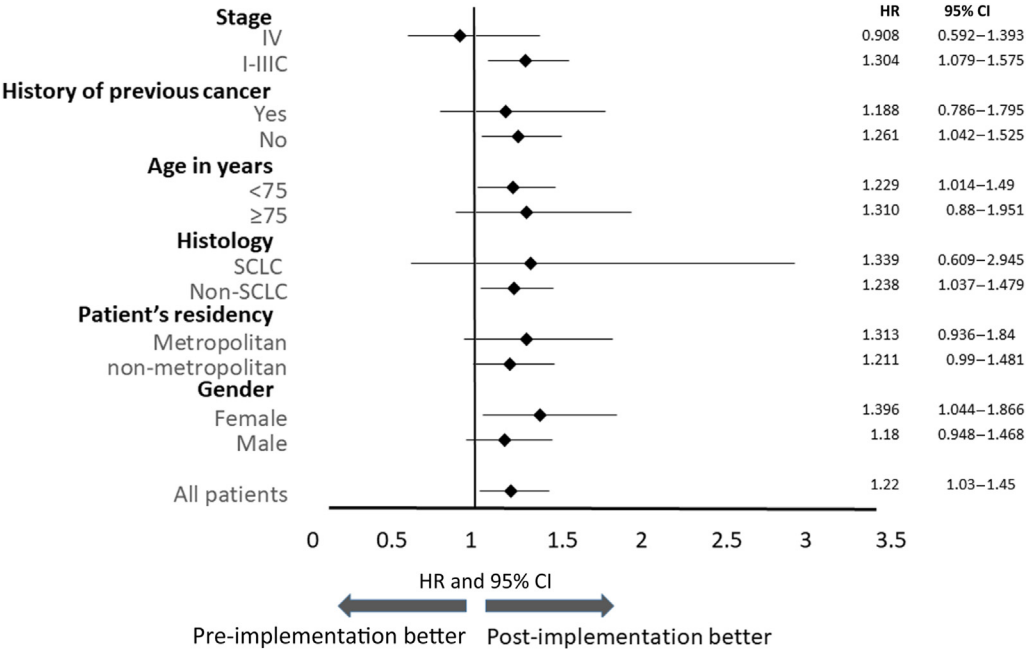


**Figure 2.** Exploration of implementation effect of the fast-track multidisciplinary diagnosis program within levels of clinicopathologic variables of interest. CI, confidence interval; HR, hazard ratio.

**Table 1.** Patients Demography and Disease Characteristics by Cohort and Overall

| Characteristics | Cohort 1 (n = 280) | Cohort 2 (n = 247) | All Patients (N = 527) | *p* Values[a] |
|---|---|---|---|---|
| Age, y, n (%) | | | | |
| <75 | 218 (77.8) | 204 (82.6) | 422 (80.1) | 0.17 |
| ≥75 | 62 (22.1) | 43 (17.4) | 105 (19.9) | |
| Sex, n (%) | | | | |
| Female | 97 (34.6) | 100 (40.5) | 197 (37.4) | 0.17 |
| Male | 183 (65.4) | 147 (59.5) | 330 (62.6) | |
| Histologic group, n (%) | | | | |
| Non-SCLC | 267 (95.3) | 232 (93.9) | 499 (94.7) | 0.47 |
| SCLC | 13 (4.6) | 15 (6.1) | 28 (5.3) | |
| Patient residence, n (%) | | | | |
| Out of metropolitan area | 204 (72.9) | 182 (73.7) | 386 (73.2) | 0.83 |
| Metropolitan area | 76 (27.1) | 65 (26.3) | 141 (26.8) | |
| History of cancer, n (%) | | | | |
| No | 232 (82.86) | 202 (81.78) | 434 (82.35) | 0.75 |
| Yes | 48 (17.14) | 45 (18.22) | 93 (17.65) | |
| Stage | | | | |
| I-IIIC | 233 (83.21) | 207 (83.81) | 440 (83.49) | 0.86 |
| IV | 47 (16.79) | 40 (16.19) | 87 (16.51) | |

[a]Comparisons of variable distributions using Fisher's exact test or chi-square test.

imaging, the histopathologic diagnosis time is the final step of the exhaustive initial workup of lung cancer in this study.

Indirect comparison with other fast-track experiments is always subject to cautions. Nevertheless, the last National Lung Cancer Audit annual report (published online by the Royal College of Physicians [RCP] on January 2022[8]) recommended, by means of the National Optimal Lung Cancer Pathway, a delay not exceeding 49 days from presentation to treatment. The same audit reported the interval from diagnosis to treatment for the audit period (2019–2020). The benchmark according to standard cancer waiting times for this interval is 31 days and shortened to 21 days in the National Optimal Lung Cancer Pathway. Nevertheless, there might be some bias in this timeline shortening from diagnosis to treatment insofar as, In the United Kingdom, coronavirus disease 2019 (COVID-19) pandemic measures from March 16, 2020, to 2021, have resulted in the suspension of cancer screening and deferral of routine diagnostic investigations, with emergency remaining as the only access for symptomatic patients, that is, advanced disease stage.[9] Therefore, it is not paradoxical to observe a reduction in time to treatment as reported by the RCP audit and a model estimating an increase in U.K. lung cancer mortality as reported by Maringe et al.[9] in the *Lancet Oncology* (lockdown allowed only symptomatic patients, those with the worst prognosis, to access the diagnostic facilities).

Our study has some limitations.

1. This study belongs to a before-and-after study design.[10] The post-implementation cohort was the prospective part of the study as it followed a protocol designed to reach a shortened timeline to diagnosis. For ethical reasons, we chose the pre- and post-implementation comparison rather than a controlled randomized study comparing a standard process with the fast-track multidisciplinary organization. The latter would have been more methodologic convincing but would have been unethical inasmuch as a slow-down diagnostic process clearly exposed to a loss of chance for treatment at curative intent. Therefore, the pre–post-implementation method adopted here exposed the study to the classical confounders. In Table 1, the reader will see that minor differences appeared between the two cohorts regarding patients' demography and disease characteristics. That allowed to run the analysis; the Cox proportional hazard model reveals that the multidisciplinary approach is an independent determinant of a shorter time to diagnosis.
2. Although statistically significant, the benefit remains modest inasmuch as the median time to diagnosis was 18 and 15 days in the pre-implementation and post-implementation cohorts, respectively, and the difference in cumulative incidence of histopathologic diagnosis at the end of the first month was 9%. In the recent literature, the delays from first visit to diagnosis and treatment are reported to vary in a wide range, and the median time to diagnosis frequently exceeds 2 months[1,6,11,12] and was shorter than the one reported by the RCP.[8] In our study, the pre-implementation cohort encompassed patients admitted in our institution during the 1-year period starting in January 2019 and closing in January 2020. This period was chosen to avoid a putative bias

introduced by the coronavirus disease 2019 pandemic that slowed down the cancer diagnostic process, worldwide.[9] The time to diagnosis observed in the preimplementation cohort was in the shorter range reported in the literature, where the standard procedure frequently exceeds 2 months before reaching a complete histopathologic molecular and TNM workup. Therefore, the impact of the multidisciplinary initial workup might have been minimized by the performance of the standard procedure as previously used in our institution. Moreover, the forest plot in Figure 2 reveals that there is a benefit in terms of reducing timeliness across all subgroups except for analysis by disease staging: herein, there is no benefit for stage IV (i.e., concerning only 16% of each cohort), whereas, for early to locally advanced stages, the HR (95% CI) was 1.30 (1.08–1.58). Therefore, the benefit of the multidisciplinary approach stands in localized disease (i.e., the more complex access to histopathologic diagnosis) for which a 24% reduction in delay was reached. Finally, even modestly, the reduction of time to diagnosis from the patient's point of view also reduces the difficult period of uncertainty.

3. The metastatic stage and the SCLC histopathology were both covariates that statistically significantly reduced the delay analyzed herein. The 16% proportion of patients with metastatic lung cancer does not reflect the whole accrual of the Montpellier University Hospital Thoracic oncology department where stage IV represents most of our patients' disease characteristics. As the Montpellier University Hospital is a tertiary hospital providing all treatment facilities including phase 1 trials, many patients with stage IV NSCLC and SCLC are referred directly to the oncologists by chest physicians and other providers working in primary and secondary care hospitals where a complete histopathologic diagnosis has been performed. Patients having early or locally advanced disease are referred to Montpellier University Hospital outside an emergency context and for diagnostic and therapeutic purposes. The accessibility of some distant metastases such as peripheral lymph nodes or skin metastases may explain their important timeliness effects and the low impact of the fast-track program in those specific cases. Nevertheless, in the Cox model, the implementation of the fast-track intervention remains a significant determinant of a shorter time to diagnosis. The low percentage of SCLC among both cohorts does not reflect the percentage of patients entering therapy in our institution; as an academic institution, most of our patients with SCLC were referred by chest physicians outside our institution with a previously obtained histopathologic diagnosis. The same can be said for the low percentage of patients affected by a stage IV disease. Finally, the end point of this study was time to histopathologic diagnosis; this time did not take into account two subsequent periods, that is, the delay toward molecular diagnosis for metastatic NSCLC and the delay to treatment. These additional timelines are taken in charge by the weekly meeting of the multidisciplinary tumor board.

In conclusion, a multidisciplinary approach of the diagnostic process implemented at the initial visit allows a reduction of the timeline until the histopathologic diagnosis of lung cancer. The translation of the timeliness of histopathologic diagnosis in terms of curability for localized disease stages or improvement of survival rates for the whole cohort will be our next step. This goal will need a more extensive cohort with homogeneously treated subgroups.

## CRediT Authorship Contribution Statement

**Jean-Louis Pujol, Sébastien Bommart:** Conceptualization, Methodology, Investigation, Validation, Writing—reviewing and editing.

**Maria Vasile**: Software, Data curation, Statistics.

**Grégoire Mercier**: Methodology, Statistics, Validation.

**Isabelle Serre and Hélène Vernhet-Kovacsik**, Investigation, Validation, Reviewing.

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