FONDAZIONE
POLICLINICO UNIVERSITARIO
CAMPUS BIO-MEDICO

March 08, 2023

PROTOCOL **FAHIC – Lung**

OBSERVATIONAL PROSPECTIVE ACADEMIC TRIAL

Observational, prospective, multicentre study to investigate the family history of cancer in patients with non-small cell lung cancer (FAHIC – Lung).

Short Title
Family history of cancer in NSCLC
Title acronyms or Protocol Code: FAHIC – Lung
Version and Date: V 1.0 08th March 2023

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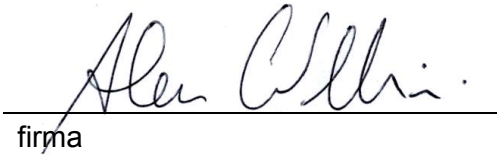
PAGINA DELLE FIRME DEL PROTOCOLLO

DICHIARAZIONE DELLO SPERIMENTATORE:

Codice del protocollo: FAHIC – Lung

Dichiaro di aver letto il protocollo ed acconsento a condurre questo studio clinico in accordo a tutti i requisiti del protocollo e secondo le Linee Guida di Buona Pratica Clinica ed i principi della Dichiarazione di Helsinki.



29/08/2023

(Sperimentatore) firma data
Dott. Alessio Cortellini

1 Background and rationale

Familial aggregation and inherited predisposition have been increasingly investigated in multiple cancer types. In breast, ovarian, prostate and colorectal malignancies, genetic counselling is recommended in patients showing risk criteria for syndromes of inherited susceptibility to cancer, as aggregations with other malignancies have been widely described within families of these patient populations [1–3].

With a predicted number of death of about 160 000 cases in 2023 in Europe and 127 070 in US [4,5], Non-Small Cell Lung Cancer (NSCLC) still remains a leading cause of cancer death worldwide. A positive smoking history represents the main cause related to NSCLC (90% of cases)[6], while environmental factors such as exposure to radon, asbestosis and air pollution have been linked to lung cancer among never smokers [7–9]. However, few studies have investigated the impact of a positive family history of cancer (FHC) in patients with NSCLC, describing types of other malignancies that can co-occur within relatives of patients with NSCLC. In previous reports, the relative risk (RR) of developing lung cancer directly correlated with the number of lung cancer cases in fist-degree relatives y (RR= 2.57 for first-degree relative >= 1 to RR= 4.24 for first-degree relative affected ≥3), and a similar trend has been observed when taking into account second and third degrees [10]. Furthermore, RR of developing lung cancer has been estimated to be up to 1.89 among those having a first-degree relative with lung cancer as second primary malignancy [11]. However, all these studies were conducted using local national registry, with no additional info on potential within-families clustering of other risk factors, including tobacco smoking exposure and other geographical/epidemiological factors. In addition, retrospective approaches to this topic are heavily impacted by recall bias and misclassification [12-13].

More recently, a “high burden” of family history of cancer in patients with advanced stage NSCLC, has emerged as potential predictive factor for systemic treatment with PD-1/PD-L1 checkpoint inhibitors, but without showing enrichment of somatic DNA damage and repair (DDR) gene alterations in tumour samples [14]. In terms of germline genetic alterations, lung cancer risk has been associated with rare genetic syndromes such as the Li-Fraumeni syndrome [15]. Furthermore, in multiple genome-wide associations studies three main susceptibility loci have been associated with increased risk of developing NSCLC including 15q25, 5p15 and 6p21 regions, corresponding to *CHRNA3*, *CHRNA5*, and *CHRNB4, TERT, CLPTM1L, APOM, BAG6* genes [7].

To underline the importance and the potential clinical implications of investigating FHC in patients with NSCLC, a recent retrospective study conducted in a cohort of 7,7888 patients with NSCLC, undergoing to commercially available genetic germline testing, but with no information about their FHC, pathogenic germline variants (PGV) or likely PGV were found in 14.9% of cases and an additional 2.9% of cases carried a single PGV in a gene associated with autosomal recessive inheritance. Among these 14.9% PGV positive, 61.3% of them had a PGV in DDR/HRR genes and 95.1% of them harboured a PGV in clinically actionable genes, with BRCA2 (2.8%),

CHEK2 (2.1%), ATM (1.9%), TP53 (1.3%), BRCA1 (1.2%), and EGFR (1.0%) being the most commonly reported PGVs [16].
Despite this few evidence, genetic causes of lung cancer still remain largely unknown, and FHC/potential within-family clustering of other risk factors need to be prospectively assessed.
With the aim of individuating and describing FHC and potential within-family clustering of other risk factors in patients with NSCLC the FAHIC – Lung study will represent the firsts prospective observational study in this area.

2 Study Objectives

2.1 Primary Objectives:

The primary objectives of this study will be:

- description of the FHC and potential within-family clusters of other risk factors among patients with NSCLC
- identification of potential FHC patterns and within-family clusters of other risk factors to address patient with NSCLC to systematic genetic counselling.

2.2 Secondary Objectives:

Secondary objectives include:

- description of clinic-pathological and oncological characteristics of patients with NSCLC of according to FHC patterns and within-family clusters of other risk factors.

3 Study design

3.1 General Design

This is a prospective, observational, multi-centre study. Our study population will be represented by consecutive patients with histologically diagnosed NSCLC, regardless of their age, TNM stage, smoking status, and other clinic-pathologic characteristics.
Patients' history will be carefully collected by investigators through a dedicated self-reported study questionnaire, which has been developed for the purpose of this study (provided as **Appendix 1**)
The ad-hoc study questionnaire has been validated by the genetic expert of the steering committee who will train each investigator to translate the returned questionnaire into standardized family trees. Study questionnaire will focus on:

- Family history of cancer;
- Type of tumours/primary tumour site among relatives with history of cancer;
- Age at diagnosis among relatives with history of cancer;
- Biological sex of relatives with history of cancer;

- Exposure to tobacco smoking and smoking habits among relatives with history of cancer;
- Geographical origin of participants and relatives with history of cancer;
- Personal history of multiple malignancies;
- Potential professional and environmental exposure to carcinogens of participants and relatives with history of cancer;
- Ethnicity of both participants and relatives with history of cancer.

To minimize risks of recalling bias, each patient will be given a minimum time of 4 weeks to gather family history information. The study-questionnaire will be then collected at the following clinical consultation as already planned per clinical practice, with no additional study-specific procedures.

During the first study visit all patient's clinic-pathologic will be collected and study participants will be given the ad-hoc questionnaire, which will be returned to the study personnel at the follow-up study visit.
The following clinic-pathologic characteristics will be collected:

- Smoking status (active/passive, package/year, total years of smoking)
- Eastern Cooperative Oncology Group Performance Status (ECOG-PS)
- Age at diagnosis;
- Tumour histology;
- Tumour stage at diagnosis according to the 8th edition of TNM staging system;
- Ethnicity;
- Professional and environmental exposure to carcinogens;
- Programmed death ligand-1 tumour proportion score (PD – L1 TPS)
- Any available oncogenic drivers including epidermal growth factor receptor (EGFR), Kirsten rat sarcoma virus (KRAS), BRAF, c-MET, mutations and Anaplastic lymphoma kinase (ALK), ROS-1, RET, neurotrophic tyrosine receptor kinase NTRK translocation/gene fusions.
  Personal history of other synchronous/metachronous primary malignancies.

Study data will be collected through dedicated electronic case report form (e-CRF). A full list of information that will be collected through the dedicated eCRF (provided as **appendix 2**).
Even though no established FHC criteria exists to refer patients with NSCLC to a genetic counselling for germ-line testing, investigators will assess participant questionnaire at the follow-up study visit and refer patients to genetic counselling when clinically indicated as per local routine practice.
Following collection of participants' questionnaires, we will be able to reconstruct patients' family three with additional information on how other potential risk factors, such as history of

smoking, exposure to professional/environmental carcinogens, segregate within the relatives with history of cancer.

We will be able to describe whether recurrent family clusters of malignancies/risk factors are specifically associated with risk of lung cancer in order to individuate patients to specifically address to systematic genetic counselling, to assess eligibility for germ-line testing in clinical practice. Secondly, we will also investigate distribution of participants clinic-pathologic characteristics to assess whether any patients and/or tumour-related feature is associated with patterns of FHC and within-family clustering of other risk factors.

3.2 Participants Selection

Inclusion Criteria

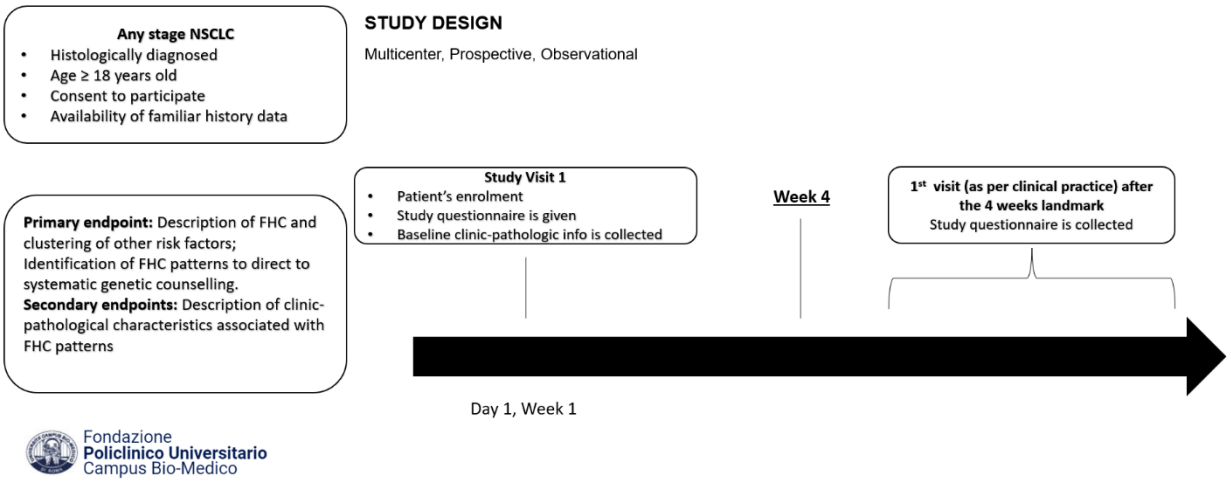
- Histopathological diagnosis of Non-Small Cell Lung Cancer (all stages)
- Age ≥ 18 years old
- Signed informed consent
- Availability of familiar and/or personal anamnestic data of cancer

Exclusion Criteria

- Unavailability of familiar and/or personal anamnestic data of cancer
- Patient's refusal

3.3

3.4 Study flow-chart



3.5 Study duration

The esteemed study duration is 24 months. Enrolment will start after protocol approval and will last for 12 months. Data analysis will last 12 months from the closure of data collection.

4 Statistical Plan and Sample Size

Given the descriptive nature of the study, and the lack of available data on the relationship between family history of cancer and NSCLC, the minimum sample size for the study has been established on the only study available to date which investigated distribution of FHC among unselected patients with stage IV NSCLC, which described a high familiar burden of cancer (i.e. especially enriched FHC with cases of cancer in both the collateral and lineal family lines) in up to the 6.8% of patients [14]. On the basis of this data, we hypothesized a prevalence of 10% of participants with an especially enriched family history of cancer in our study population; assuming a confidence level of 95% with a total width for the confidence interval of 0.1 (precision of +/- 5%) and considering a 10% drop out, the minimum number of study questionnaire to collect to properly describe the group of interest following a binomial "exact" calculation of the sample size is 175.

Descriptive statistics will be used as appropriate to report FHC data, distribution of within-family other risk factors and baseline clinic-pathologic characteristics. The Fisher exact test and the $\chi 2$ test will be used as appropriate to compare categorical variables (e.g. distribution of baseline characteristics according to the personal/familial positive or negative history). Analyses were performed using the R-studio software, R Core Team (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, and the MedCalc® Statistical Software version 20 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2021).

5 Data Management and confidentiality

Data will be collected and retained in accordance with the European General Data Protection Regulation (GDPR) L119, 4 May 2016 and in compliance with other international data protection regulations, such as the title 21 CFR Part 11 of the Code of Federal Regulations, the Health Insurance Portability and Accountability Act of 1996 (HIPAA), and the United Kingdom GDPR.

Data will be collected by investigators at each participating site through a dedicated electronic case report form (eCRF) designed by the study staff with the Research Electronic Data Capture software (REDCap, Vanderbilt University, Nashville, TN, USA) using a GDPR-compliant secure server at the coordinating center (Fondazione Policlinico Universitario Campus Bio-Medico, Rome, Italy) and will be kept for 5 years after the study completion.

Access to the database will be given to authorized personnel only at each site, log of access will be kept in the study file by the Principal Investigator with a secure two factor authentication system for each investigator.
A unique reference number will be assigned to each institution and a second-level unique and sequential ID number will be assigned to each participant.
Each participating institution will ensure that all anamnestic, clinical and follow-up information will be collected after a complete anonymization process. Investigators at the coordinating center (Fondazione Policlinico Universitario Campus Bio-Medico, Rome, Italy) will not be able to match participants' ID with potentially identifiable information, which will be accessible to local investigators only at each participating site.
Principal Investigator will ensure that the patient's privacy is maintained at all times. On the Case Report Form (CRF) or other documents, patients will be identified by a study ID number only.
Technical and organizational measures to ensure data protection will include: anonymization and encryption, confidentiality, integrity, availability and resilience of processes and services on a permanent basis, procedures for regularly testing, verifying and evaluating the effectiveness of technical and organizational measures in order to guarantee the security of the processing.
The investigator shall permit direct access to study source document for the purposes of monitoring, auditing, or inspection by the Sponsor, authorized representatives of the Sponsor and Regulatory Authorities.

6 Ethical consideration

The study will be conducted in accordance with the principles of Good Medical Practice and the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.
A written informed consent to participate to the study and to personal data processing will be ask at each participating institution by local investigators to all patients. Study-related medical risks are the same as for clinical practice.
The Investigators declares no direct conflicting interest for the proposed study.

7 Fundings

This is an academic study, which did not receive any direct funding.

8 Publication policy

A whole or part of the study results will be communicated, orally presented, and/or published in appropriate scientific journals. Full anonymity of subject's details will be maintained throughout. Subjects wanting to see the results of the trial can request a copy of the article from the investigators once it has been published.

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