CLINICAL STUDY PROTOCOL

Lung Cancer Observational Study

This study protocol has been written and will be conducted according to the Helsinki Declaration for Good Clinical Practice and the applicable national regulations.

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1 Background and rationale

Most lung cancer cases correspond to non-small cell lung cancer (NSCLC), while small cell cancer represents the minority of cases. To date, a limited percentage of NSCLC cases are diagnosed in the early stage (in which patients are potential candidates for surgery, possibly followed by chemotherapy to reduce the risk of recurrence) or in the locally advanced stage (in which the treatment is based on the use of chemotherapy, radiotherapy and possibly, upon their completion, immunotherapy). In recent years, the therapeutic strategy in patients with advanced NSCLC has changed profoundly. Until about 10 years ago, chemotherapy was the only option available, however, characterised by limited effectiveness. In recent years, the two crucial therapeutic "revolutions" that we have witnessed in medical oncology (molecularly targeted drugs first and then immunotherapy) have played an essential role in treating these patients. Some molecularly targeted drugs (primarily Epidermal Growth Factor Receptor [EGFR] inhibitors and then drugs directed against other molecular alterations) are superior to chemotherapy as a treatment of the first choice, limited to cases in which the tumour has those specific molecular alterations. Molecular analyses, aimed precisely at identifying these alterations on the tumour tissue, represent a fundamental part of the diagnosis, which necessarily precedes the choice of the best treatment for each patient. In the next few years, we will plausibly see the continuation of the aforementioned therapeutic "revolution", with the availability of new molecularly targeted drugs, which will not only increase the therapeutic possibilities to be used in sequence after the failure of those already available today but which in some cases they will allow a "targeted" treatment in the presence of alterations molecular drugs for which no target drugs were available in clinical practice until now. Immunotherapy first established itself (about five years ago) as an effective treatment in patients who had already failed chemotherapy. Subsequently, it proved to be superior to chemotherapy as a treatment of the first choice, in cases characterised by high expression of the PD-L1 marker. . Finally, in recent years, significant results have been obtained with the combination of chemo and immunotherapy, even in cases characterised by low or absent PD-L1 expression. It is conceivable that in the coming years, based on a series of clinical trials recently conducted or still in progress, innovative drugs (targeted therapies and immunotherapy) will also gain an essential role in the treatment of early stages, used before surgery or after surgery, in order to reduce the risk of disease recurrence and hopefully increase the chances of recovery. The 5-year survival figure (16% in men and 23% in women), which places lung cancer at the bottom of this unfortunate ranking, reminds us that, despite the critical progress made in recent years, the way to go is still very long [AIOM, I numeri del Cancro in Italia 2021].

Globally, there is an increasing trend to use real-world data (RWD) to inform decision making in healthcare and patient registries are regarded as a typical example of RWD. A patient registry can be defined as "an organised system that use observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more predetermined scientific, clinical, or policy purposes [GliklichRE, DreyerNA. Registries for

Evaluating Patient Outcomes: A User's Guide (2nd ed.). Rockville, MD: Agency for Healthcare Research and Quality, 2010.]. Whilst regulatory agencies can require real-world data collection for post-marketing surveillance and risk assessment, payers and reimbursement agencies are consistently considering real-world evidence to make or revise their recommendations. To this end, the information collected in patient registries can extend from appropriate treatment strategies to effectiveness, and cost-effectiveness in real-world clinical practice. Furthermore, achieving and maintaining optimal well-being and health-related quality of life (HRQoL) has become an important objective of current cancer treatment, rehabilitation, and aftercare across the whole cancer continuum. The availability of patient-reported outcomes (PROs) is very important in achieving these goals. Over the past, patient registries have provided clinicians and researchers with a wealth of clinical data (e.g., stage and primary treatment) on cancer patients. However, data on PROs have not been routinely available. PROs were collected using paper-and-pencil questionnaires, with suboptimal response rates, costs and overall efficiency of the process. Online administration of questionnaires has a number of advantages compared to paper-and-pencil questionnaires, including convenience for the participant, potentially large cost savings, efficiency in data collection, and high quality of the data.

Therefore, we propose to develop a web-based registry, for the collection of longitudinal data on clinical, psychosocial and economic impact of lung cancer treatment in Italy.

2 Objectives

ILCAR is a web-based registry developed to facilitate data collection on a number of different outcomes of lung cancer patients diagnosed in the early stage in Italy. The registry can be used simultaneously for multiple studies with different purposes.
The main objectives of ILCAR are to generate data relevant to:

- Performance assessment – through development of national performance benchmarks based on the analysis of (risk-adjusted) outcomes and processes of care indicators (e.g., How does individual center X compare to the national benchmark in terms of length of stay for a certain subgroup of patients?);
- Economic impact assessment of innovative technologies or treatment pathways (e.g., Do different surgical medical devices influence healthcare resource utilisations for a single episode of hospitalisation?)
- Psychosocial impact assessment of innovative technologies or treatment pathways (for example, minimally invasive surgery) (e.g., Do new targeted treatments have a beneficial or adverse impact on PROs?)

3 Study design - Data to be collected

ILCAR Registry is a national collection and storage of clinical and surgical data for patients suffering from lung cancer candidates for minimally invasive manual, robot-assisted or traditional open pathology surgeries.

The Database is maintained by the ILCAR clinical guidelines ad hoc committee. ILCAR guidelines are accessible by using the following address:

The clinical and surgical data collected in a standardised ILCAR endorsed Dataset can be downloaded at the local level and used for internal quality analyses or institutional research purposes.

3.1 Prospective study

The prospective collection of clinical and surgical data for lung cancer patients, candidates for minimally invasive manual, robot-assisted or traditional open surgery, will begin in June 2022.

3.3 Inclusion criteria

Subject enrolled must meet the following criteria:

- Age > 18 years.
- Patients suffering from lung cancer candidates to surgical intervention
- Signature of informed consent

3.4 Exclusion criteria

The subject who meets the following criteria are excluded:

Age < 18 years

4. Forms and procedures for collecting data and data managing

The methodology of collecting data will be done using a website platform that will agree with international standards and rules for data privacy protection. Notably, data is anonymously reported, independently accessed, and encrypted to other users. It is possible to access the Database from the ILCAR website.

To join the Database, each institution login account is supplied by downloading and completing an application form from the ILCAR homepage by directly sending an email to one of the members of the Database Committee.

5. Ethical considerations

5.1. Patient protection

The responsible investigator will ensure that this registry is conducted in agreement with either the Declaration of Helsinki (Tokyo, Venice, Hong Kong, and Somerset West amendments) or the laws and regulations of the country, whichever provides the most outstanding protection of the patient.
The protocol and its annexes are subject to review and approval by the competent Independent Ethics Committee(s) ("IEC").

5.2. Subject identification – Personal Data protection

All records identifying the subject must be kept confidential and, to the extent permitted by the applicable laws and/or regulations, not be made publicly available. The patient's name will not be asked for nor recorded at the Data Center. A sequential identification number will be automatically attributed to each patient registered in the study. This number will identify the patient and be included in all case report forms. In order to avoid identification errors, patient initials and date of birth will also be reported on the case report forms. All patient information or documentation about a clinical trial, to the extent permitting, through a "key" kept anywhere, regardless of whether such key is supplied along with the information or documentation or not, must be considered as containing sensitive personal data of the patient and is therefore subjected to the provisions of applicable data protection ("privacy") regulations. Breach of such regulations may result in administrative or even criminal sanctions. Mainly, an information sheet prepared according to such regulations and a form to evidence patients' consent to process such data must accompany the informed consent administered to the patient (see paragraph 4.3 below). Such information must (i) identify the roles of the holder ("titolare") and processor ("responsabile", appointed by the holder) of the patient personal data (also if not directly identifying the patient), as well as the purposes of the personal data collection and processing (medical treatment and related/unrelated scientific research), (ii) adequately describe the flows of communication involving them, particularly if third parties should become involved, and (iii) seek the patient's prior and specific consent to such processing. Patient information or documentation may be considered "anonymous", and as such, not subject to privacy regulations, only when no key whatsoever, permitting the patient's identification, is no longer available. Therefore, particular attention should be paid (and information/consent materials adapted accordingly) whenever patient data are supplied to third parties and may be autonomously processed.

5.3. Informed consent

All patients will be informed of the aims of the study, the possible adverse events, the procedures, and the possible hazards to which he/she will be exposed. They will be informed about the strict confidentiality of their patient data but that their medical records may be reviewed for study purposes by authorised individuals other than their treating physician. It will be emphasised that the participation is voluntary and that the patient can

refuse further participation in the registry whenever he/she wants. This will not prejudice the patient's subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered at the Data Center. This must be done under the national and local regulatory requirements. For European Union member states, the informed consent procedure must conform to the OSR guidelines on Good Clinical Practice. This implies that "the written informed consent form should be signed and personally dated by the patient or by the patient's legally acceptable representative."

6. Conflict of Interest

Any investigator and/or research staff member who has a conflict of interest with this study (patent ownership, royalties, or financial gain more remarkable than the minimum allowable by their institution) must fully disclose the nature of the conflict of interest.

7. Publication Policy

7.1 Statistic Analysis

The project aims to create a data collection. The studies will be defined based on data collected. It is impossible to predict a statistical analysis as this will change according to the outcomes defined for every single project. When a project is proposed, it should be submitted to the ILCAR Database Committee for peer review, and, if accepted, the requested and anonymised data will be provided to the proponent of the project. ILCAR thorough SDA Bocconi will be responsible for the final analysis and interpretation of results.

References

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