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STUDY PROTOCOL

Novel prospective umbrella-type lung cancer registry study for clarifying clinical practice patterns: CS-Lung-003 study protocol

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Keywords
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Trial registration: This study was registered on March 25, 2017 with UMIN-CTR Clinical Trial as UMIN000026696.

Abstract

Introduction: Conventional cancer registries are suitable for simple surveillance of cancer patients, including disease frequency and distribution, demographics, and prognosis; however, the collected data are inadequate to clarify comprehensively diverse clinical questions in daily practice.

Methods: We constructed an umbrella-type lung cancer patient registry (CS-Lung-003) integrating multiple related prospective observational studies (linked studies) that reflect clinical questions about lung cancer treatment. The primary endpoint of this registry is to clarify daily clinical practice patterns in lung cancer treatment; a key inclusion criterion is pathologically diagnosed lung cancer. Under this registry, indispensable clinical items are detected in advance across all active linked studies and gathered prospectively and systematically to avoid excessive or insufficient data collection. Researchers are to input information mutually, irrespective of the relevance to each researcher's own study. Linked studies under the umbrella of the CS-Lung-003 registry will be updated annually with newly raised clinical questions;

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some linked studies will be newly created, while others will be deleted after the completion of the analysis. Enrollment began in July 2017.

Discussion: We successfully launched the umbrella-type CS-Lung-003 registry. Under this single registry, researchers collaborate on patient registration and data provision for their own and other studies. Thus, the registry will produce results for multiple domains of study, providing answers to questions about lung cancer treatment raised by other researchers. Through such analysis of each linked study, this registry will contribute to the comprehensive elucidation of actual daily practice patterns in lung cancer treatment.

Key points

- CS-Lung-003 registry directly integrates multiple linked studies created under the umbrella of this cancer registry to solve various clinical questions regarding daily practice patterns of lung cancer treatment.

Introduction

The results of many pivotal lung cancer clinical trials can be used to update treatment guidelines leading to improved daily practice. However, many real-world clinical questions remain. To clarify these questions, it is indispensable to collect relevant information on clinical practices and analyze these data comprehensively; this real-world data analysis of practice patterns will provide clues to current clinical questions and also lead to the creation of new meaningful clinical questions further improving daily treatment.

In recent years, large-scale cancer registries for patient surveillance have been constructed worldwide.[1] We also created a registry of 1000 patients with lung cancer in one and a half years to clarify the characteristics of a subpopulation with HER2-positive tumors.[2–4] In most situations, existing cancer registry data are best used for relevant observational studies that researchers newly plan and conduct with the primary purpose of answering their own clinical questions; thus, almost all these observational studies are retrospective. These studies are valuable as they clarify clinical practice patterns for cancer treatment, actual safety data and quantification of potential risks, and the effectiveness of therapeutics involving a broader patient population within a community-based setting compared to randomized clinical trials.

However, the patient information contained in conventional cancer registries is monotonous, repetitive, static, and limited. In contrast, clinical questions raised by clinicians in their daily practice are complicated, dynamic, and subject to change. Thus, conventional cancer registries are inadequate for data analysis to address such clinical questions appropriately and timeously.[5] Specifically, the biggest disadvantage of conventional cancer registries is that data on many clinical items are usually collected in an unfocused manner, without any insight beforehand as to what kind of clinical information is truly needed for relevant observational studies. Therefore, conventional cancer registries may be lacking in specific items for some researchers or may collect unnecessary or excessive items for others.[6,7] Ultimately, conventional cancer registries are suitable for simple surveillance of cancer patients; however, these registries lack efficient processes for data collection to clarify multiple researchers' clinical questions as they are not specifically designed and constructed to address such questions (Fig 1).

In this article, we introduce a unique, umbrella-type lung cancer patient registry equipped with multiple related prospective observational studies created in accordance with assorted concrete clinical questions; this novel registry will solve the above-mentioned problems with existing registry studies.

Methods

The CS-Lung-003 is a new prospective lung cancer patient registry compiled by 29 hospitals that provide lung cancer treatment in Chugoku and Shikoku regions in western Japan. This study was registered on 25 March 2017 with UMIN-CTR Clinical Trial as UMIN000026696. As a unique feature of this registry, it integrates multiple studies from related fields (Table 1; Fig 1, 2). We use the term "linked study" which means one that falls in a related field of this CS-Lung-003 cancer registry study. These linked studies must fulfill all the following conditions: (i) Each are to be conducted as a prospective observational study; (ii) their common target population is to be pathologically diagnosed lung cancer patients; and (iii) their study objective is determined according to each study, with a minimum shared commonality regarding the clarification of some patterns of daily clinical practices. The latter two conditions have also been set as the eligibility criteria and the

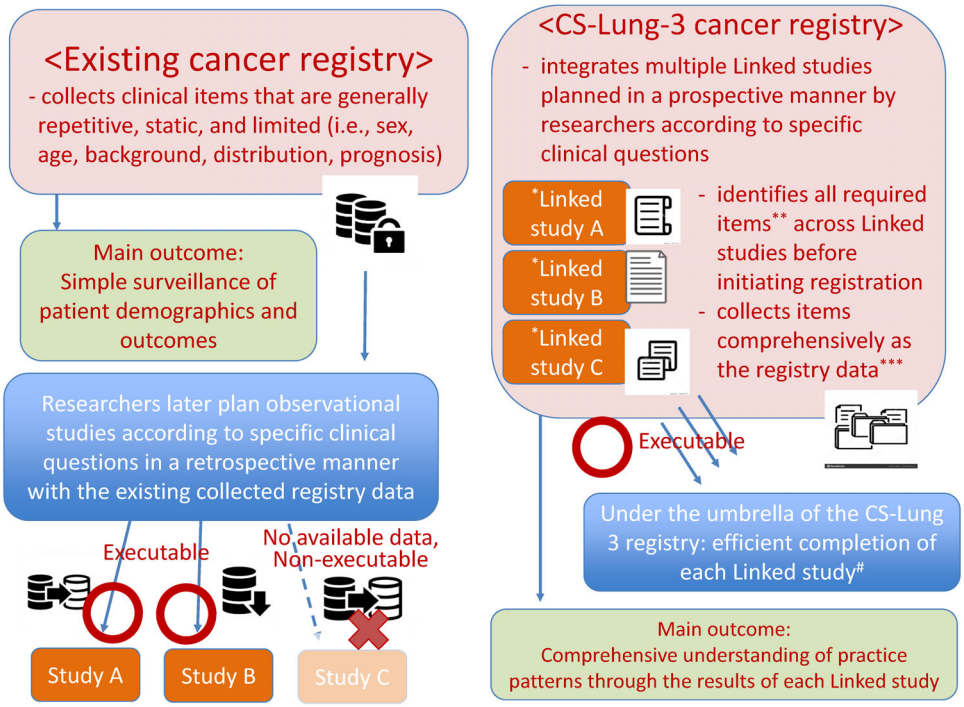

Figure 1 Conceptual diagram of CS-Lung-003. Existing cancer registries are suitable for simple surveillance of patients with cancer and are generally designed to collect relevant clinical items widely and superficially for analyses. Therefore, they are not specifically designed and constructed according to daily clinical questions raised by researchers. As a result, when planning to use these registry databases for analyses in their own studies, certain required items may be lacking for some researchers which might cause failure at the analytic stage of their study (ie, Study C). *Each linked study must fulfill all the following conditions: (i) Each are to be conducted as a prospective observational study; (ii) their common target population is to be pathologically diagnosed lung cancer patients; and (iii) their study objective is determined according to each study, with a minimum shared commonality regarding the clarification of some patterns of daily clinical practices. The latter two conditions have also been set as the eligibility criterium and the comprehensive primary endpoint of the CS-Lung-003 cancer registry study coordinating each of the linked studies, respectively. **The detected indispensable clinical items are reflected directly in the case report form of CS-Lung-003, the main cancer registry, while excluding duplicated items across the linked studies. ***Researchers are to input all these items, irrespective of their relevance to each researcher's own study. All these processes enable the registry to gather data systematically and efficiently. #At the time of analysis in each linked study, the entire registry dataset will be processed.

comprehensive primary endpoint of the CS-Lung-003 cancer registry study coordinating each of the linked studies, respectively. Notably, related studies under the umbrella of the CS-Lung-003 cancer registry are updated annually in response to the latest clinical questions that arise subsequent to the release of new evidence and guidelines; some of the linked studies will be newly created and linked to this CS-Lung-003 cancer registry and others deleted after the completion of their analysis. The ethical validity of the updated registry is to be confirmed by the institutional review board each time.

This registry uses REDCap (Vanderbilt University, TN, USA) as an electronic data capture system, the operation of which is outsourced.[8] REDCap is a data collection and management system, allowing any clinicians without any IT expertise, to easily build and manage databases on the Web, and to easily and safely collect data from multiple facilities. In this study, clinical items necessary for each linked study proposed by investigators based on their clinical questions, are reflected into the REDCap EDC system. At first, under this registry, key variables (sex, birth month/year, ECOG-PS, tissue type, TNM, stage, pathological diagnosis date, last survival confirmation date and death or survival) and any truly indispensable clinical items to be collected prospectively for the analysis in each linked study are surveyed in advance and identified across all active linked studies. The detected items are displayed directly on the data entry screen of the electronic data capture system of the CS-Lung-003, the main cancer registry, while excluding duplicated items across the linked studies. Researchers are to input all these items, irrespective of their relevance to each researcher's own study. All these processes enable the registry to gather relevant data systematically and efficiently. At the time of analysis in each linked study, the entire registry dataset will be processed. Furthermore, the data entry screen in the CS-Lung-003 will be modified annually along with an update of the linked studies, always capturing all the clinical items across the active studies and excluding duplicated items to avoid excessive or insufficient data collection.

Table 1 Linked studies integrated in this registry study (excerpt)

Year	Study title	Endpoints
2017	Dissemination of short-term low-volume hydration in patients with cisplatin-based chemotherapy	Proportion of patients with the hydration method; Cr toxicity stratified by the method; other AE
	Survey on undertreated advanced lung cancer in the elderly	Proportion of those with anticancer treatment; treatment compliance; AE; survival
	Characteristics and outcome of SCLC patients without any smoking history	Proportion of non-smokers in patients with SCLC; presence of occupational risk factors; stage distribution; treatment regimen and compliance; AE; survival
	Implementation of rebiopsy for recurrent NSCLC harboring *EGFR* mutations	Rebiopsy rate at the time of failure with first- or second-generation EGFR-TKI; T790M-positive rate; frequency of osimertinib use and its efficacy; repeated rebiopsy rate in those with T790M-negative results from the first rebiopsy
	Survey on early line of treatment in ED-SCLC	Type and pattern of treatment regimens; PFS; OS; AE
	Characteristics and outcome of progressive high-grade pulmonary neuroendocrine tumor	Clinical demographics; type and pattern of treatment; ORR; PFS; OS; AE
	Survey on early line of treatment in *EGFR*-mutant; advanced NSCLC	Type and pattern of treatment regimens; PFS; OS; AE
	Effect of severity in comorbid COPD on treatment compliance	Frequency of COPD and its severity; type and pattern of treatment; treatment compliance; PFS; OS; AE
	Influence of timing of prior ICI use on EGFR-TKI-related AEs	Incidence of grade ≥3 AEs in EGFR-TKI therapy; its association with prior ICI use; efficacy of EGFR-TKI and its association with prior ICI use
	Characteristics and outcome of advanced pulmonary polymorphic cancer	Clinical demographics; type and pattern of treatment; ORR; PFS; OS
	Association of strictness in management of diabetes on outcomes in lung cancer	Type and pattern of DM treatment; time course of HbA1C and its association with frequency of acute exacerbation of DM and lung cancer survival
	Recent trend of incidence, treatment, and mortality of febrile neutropenia occurring in the treatment of advanced lung cancer	FN rate; type and pattern of its treatment; treatment outcome; association of FN event with PFS and OS
	Dissemination of early palliative care team intervention in clinical practices and its survival impact in the lung cancer treatment	Frequency of intervention by the team; association of the intervention with OS
2018	Real-world data analysis on epidemiology, treatment, and prognosis of central nerve system lesions in non-small cell lung cancer patients	Clinical characteristics; type and pattern of treatment; ORR; CNS-ORR; PFS; CNS-PFS; OS; AE
	Implementation of ramucirumab use in combination with docetaxel in clinical practices in relapsed non-small cell lung cancer	Implementation rate of ramucirumab in combination with docetaxel; reasons why not administered
	The relationship of the localization of primary lung cancer to the response and survival outcome of ICI	Association between primary tumor location and OS
	Clinical features of lung cancer complicated with polymyositis/dermatomyositis	Clinical characteristics; treatment outcome

Table 1 Continued

Year	Study title	Endpoints
	PD-L1 expression and implementation of ICI use in clinical practices in driver oncogene-positive non-small cell lung cancer	Proportions of positive PD-L1 expression level and ICI use
	Clinical influence of a palliative radiotherapy on the effect of ICI in non-small cell lung cancer	ORR; PFS; OS; AE; association of type and pattern of radiotherapy with efficacy and safety
	Implementation rate, safety and efficacy of ICI in lung cancer with interstitial pneumonia	Type and regimen of ICI treatment; ORR; acute exacerbation rate; TTF; OS; AE
2019	Implementation of ICI use and outcome in stage III NSCLC after completion of chemoradiotherapy	Proportion of ICI use in NSCLC patients after completion of chemoradiotherapy; AE; ORR; PFS; OS
	Dissemination of chemoimmunotherapy in the first-line setting in driver-negative, advanced non-small cell lung cancer	Proportion of those receiving first-line chemoimmunotherapy; AE; ORR; PFS; OS
	Recent incidence of thromboembolism, its treatment types and prognosis in advanced lung cancer patients	Incidence of comorbid thromboembolism at the initial presentation; occurrence rate of developing symptomatic/ asymptomatic thromboembolism after lung cancer diagnosis; survival stratified by the presence thromboembolism
	Occurrence of hepatitis B in HBV-careered or prior HBV-infected patients with lung cancer receiving ICI treatment	Occurrence rate of hepatitis B; other AEs; type and pattern for preventive treatment of hepatitis; ORR; PFS; OS
	Implementation of ICI use in NSCLC patients with autoimmune diseases and their treatment outcome	Proportion of those receiving ICI therapy; type and severity of autoimmune disease and its association with AE; ORR; PFS; OS

AE, adverse event; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; Cr, creatinine; DM, diabetes mellitus; ED, extensive disease; EGFR, epidermal growth factor receptor; FN, febrile neutropenia; HBV, hepatitis B virus; ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; SCLC, small cell lung cancer; TKI, tyrosine kinase inhibitor; TTF, time to treatment failure.

Approximately 2000 patients with lung cancer will be accrued in the CS-Lung-003 cancer registry, whilst the number of required cases is calculated per linked study according to its own primary endpoint. The study period has been set from March 2017 to March 2029. After the linked study has been completed, the case records for the linked study are properly discarded. The entire database will be retained for 10 years after all the proposed linked studies have been completed.

The study protocol was approved by the Okayama University Hospital Ethics Committee (approval No. 1703–055) and the institutional review boards of each participating hospital. Written informed consent was obtained from each patient prior to any registration for the study. This study is performed in accordance with the Declaration of Helsinki and the relevant Japanese regulations.

Discussion

The most remarkable feature of this CS-Lung-003 community-based registry study is that it is an umbrella-type study; it directly integrates multiple linked studies created under the umbrella of this cancer registry to solve various clinical questions regarding daily practice patterns of lung cancer treatment. Moreover, each linked study related to the main CS-Lung-003 cancer registry is designed in a prospective fashion. In most prior master protocols, the registry data, although collected prospectively, were compiled post hoc for relevant retrospective cohort studies[9]; our study structure for the prospective registry involving related prospective observational studies enables us to eliminate biases more effectively, including patient selection bias that occurs mostly in retrospective cohort studies.[10]

Another unique feature of this registry study design is the "implementation of mutative collaboration," that is, researchers will collect clinical items for their own analysis as the principal investigator in their linked study. Simultaneously, they will also act as coinvestigators for other items, whether the items are relevant to their own study or not. This structure could provide a scale of merit for each

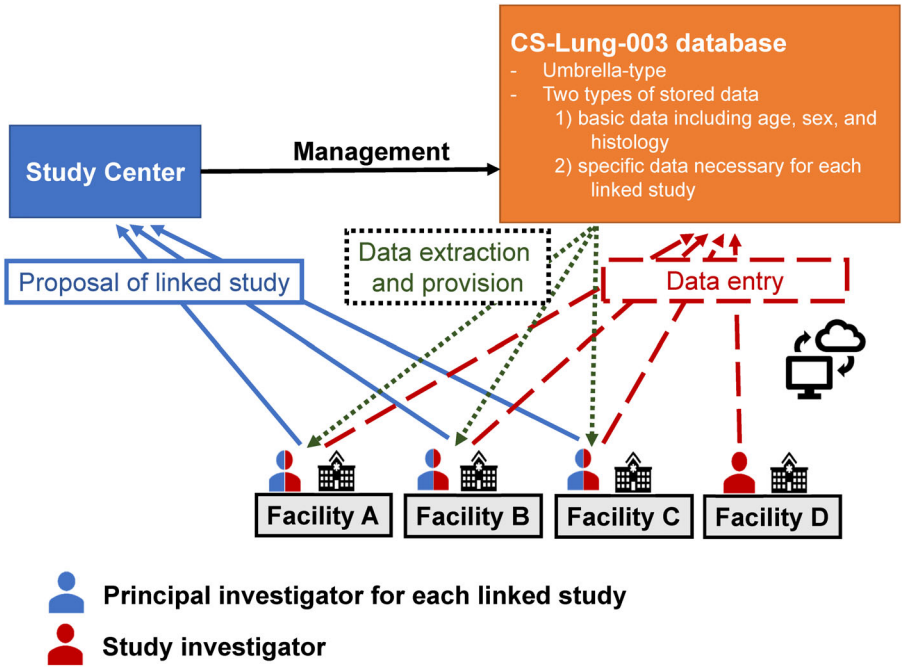

Figure 2 Structure of CS-Lung-003 registry. The principal investigators (blue persons) for the linked study propose their studies. The Study Center reflects each of them in the central umbrella-type CS-Lung-003 database. All the investigators (red persons) participating in the CS-Lung-003 registry study input any requested data. The principal investigators for their linked studies receive the prespecified data and analyze them. All patient information is anonymized and stored centrally in the secure cloud.

linked study since its targeted patients are to be recruited not by a single institute but by multiple institutes affiliated with the CS-Lung-003 cancer registry. Finally, such functional collaboration can increase the motivation for becoming involved in the registry study, leading to the potential sustainability of this registry.

The issue of gathering more or less data than required for proceeding with the planned analysis has been raised in most registry studies.[5] This is mainly because most cancer registries are intended for patient surveillance only and gather general clinical items without any prior consideration for addressing various clinical questions. Regarding our registry, to avoid excessive or insufficient data collection, we attempt to detect any indispensable items to be collected in advance across all the active linked studies involved in the CS-Lung-003 cancer registry. The prospective nature of each linked study enables this process to be guaranteed resulting in maximally efficient data collection in our registry. Thus, our registry is a breakthrough regarding solving the above-mentioned issue.

Our platform also appears to have an advantage regarding ethical issues. In the case of retrospective master protocol registry studies, the ethics of its entire framework can be confirmed by an ethical review board. However, it has been pointed out that each linked study is lacking in ethical compliance, because these studies are created after the master protocol has been launched, and, thus, are not examined by the review committee.[5] In contrast, we can ensure ethical compliance by annually submitting changes in the protocol body of the CS-Lung-003 cancer registry study that lists the latest linked studies. The limitation of this study is that we do not strictly check all pathologically diagnosed lung cancer patients have been registered, potentially affecting the results of causal relationship in each linked study.

In summary, we have successfully launched an umbrella-type lung cancer registry (CS-Lung-003) that integrates diverse prospective observational studies reflecting various daily clinical questions. Under this single registry, researchers can mutually resolve their clinical questions, collaborate on patient registration and data provision for their own study and those of other researchers. This CS-Lung-003 cancer registry has several unique features and will solve various problems with existing registry studies; it is expected to produce multiple linked studies, and provide answers to the clinical questions about lung cancer treatment raised by researchers. These outcomes may result in further comprehensive understanding and awareness of daily practices of lung cancer treatment, potentially leading to behavioral changes regarding researchers' treatment strategies.

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Disclosure

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