

STUDY PROTOCOL

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Quality of life outcomes in terminal cancer patients attending regional cancer centers in South Korea: protocol for a prospective cohort study

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Abstract

Introduction Patients with cancer experience physical, mental, and social pain that affects themselves and their families. The increasing cancer incidence and advances in treatment have increased the number of cancer survivors in Korea, and there is an influx of patients in Seoul and other metropolitan areas, leading to shortages of continuous care and comprehensive life support facilities. Patients must travel long distances for treatment, which poses logistical and quality-of-life challenges.

Methods This prospective cohort study targets patients with incurable cancer ($n = 720$) and their families ($n = 288$) from ten regional cancer centers and two affiliated hospitals in Korea. The sub-cohorts are based on treatment refusal, spinal metastasis with symptoms, catheter-related symptoms, and skeletal-related events. Medical records and patient-reported outcomes will be collected every three months and for up to three years, with surveys for guardians conducted for one-year post-patient demise.

Discussion The dynamic nature of cancer significantly affects patients and their caregivers. It is necessary to identify the factors that affect their quality of life to integrate them into society.

Conclusion The findings of this study will inform the establishment of a regional cancer center consortium. This will address the unmet needs of local cancer patients and their families, enhance their overall quality of life, and contribute to the well-being of the local community.

Trial registration KCT0009177 (registered at <https://cris.nih.go.kr/> on 2024/02/16).

Keywords Advanced cancer, External catheter, Treatment refusal, Emergency, Terminal illness, Skeletal related events, neurological symptoms

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Background

Cancer is the most common cause of death in South Korea. The number of newly diagnosed cancer patients has been increasing, and cancer mortality has been decreasing [1]. As a result, the number of cases was predicted to reach over 2.4 million in 2021 [2]. The increasing number of cancer patients is a significant issue in the Korean National healthcare system and in society.

Advanced cancer is a devastating disease that affects the physical, psychological, social, and spiritual well-being of patients. The physical symptoms are aggravated by treatment-related toxicities [3] and patients experience a poorer quality of life than the general population [4]. This is exacerbated by their financial problems [5]. Cancer burdens patients, and increases psychological and financial stress on family members, affecting the quality of life of caregivers and burdening society.

Patients with cancer are increasingly traveling to Seoul and the metropolitan areas in South Korea for several reasons. First, medical services—including approximately 50% of the tertiary hospitals—and other infrastructure are concentrated there [6]. Patients prefer tertiary hospitals, citing reputation, medical equipment, hospital facilities, and the environment [7] as the main reasons. The number of cancer patients in the limited major hospitals in Seoul has increased over time, showing regional differences according to the distance from Seoul [8]. Second, the decentralized healthcare system, based on regional models, has essentially collapsed, overburdening the facilities in Seoul and the metropolitan areas [9]. As a result, medical service users are demanding solutions to address the healthcare disparities between the Seoul metropolitan area and regions, as well as the inequitable distribution of medical resources. A recent online survey conducted by the Hankyoreh Media Group and the Korean Cancer Patients' Rights Association (249 respondents, December 15–18, 2022) revealed that approximately 30% of patients with cancer were receiving treatment at large hospitals in Seoul and the metropolitan area rather than in their local areas [10].

Patients with cancer living in regional areas must travel long distances to visit tertiary institutions in Seoul. If they visit regional centers near their homes, these facilities do not have their medical records, which disrupts the continuity of care. During the cancer treatment journey, patients are moved to a hospital near their home that provides care for cancer when their condition deteriorates. Thus, patients receive cancer care from multiple hospitals that do not share information. This disrupts the continuity of cancer care, resulting in poor outcomes [11]. The fragility of patients, the anxiety of patients and family members, or poor socio-economic status may cause them to visit multiple hospitals [12].

Since 2003, the National Cancer Center has designated regional cancer centers to expand the public health infrastructure. The intention is for the national level to focus on comprehensive cancer treatment, research, and management, while regional cancer centers—tailored to local characteristics—should respond to the diverse cancer management needs of residents.

A thorough understanding of the healthcare utilization patterns and associated problems among advanced cancer patients, especially those in regional areas, is essential for developing national policies to address healthcare disparities and establishing a comprehensive continuum of cancer care. A decentralized healthcare system, based on regional models, is essential for developing national policies to address healthcare disparities and establish a comprehensive continuum of cancer care.

Method

This study aims to evaluate the quality of life of patients with advanced cancer, and their caregivers, who visit regional cancer centers throughout their disease trajectory, to contribute to this understanding. This multicenter prospective observational cohort study utilizes a comprehensive approach, consisting of two cohorts and five sub-cohorts. The aim is to explore the changes in the quality of life of patients (and caregivers) who are relatively more burdened by their disease and are likely to be socially isolated throughout the disease trajectory. Ten hospitals in a regional cancer center and two affiliated hospitals have joined the study. Through consensus, investigators have identified several clinical characteristics that are likely to impact the quality of life of patients with advanced cancer who visit regional cancer centers. These include patients who have declined active cancer treatment regardless of cancer stage (treatment refusal cohort), those with external catheters (external catheter cohort), those with primary or secondary brain tumors or neurological symptoms from spinal metastasis (neurological symptom cohort), and those with skeletal-related events (SRE) cohort (Fig. 1). SREs are defined as pathological fractures, paralysis, spinal cord compression, bone pain, or impending fractures requiring radiation therapy or surgery.

Primary aims

1. To examine changes in quality of life over the last year of life (at 3, 6, 9, and 12 months).
2. To assess depression and anxiety levels over the last year of life (at 3, 6, 9, and 12 months).
3. To evaluate pain intensity over the last year of life (at 3, 6, 9, and 12 months).

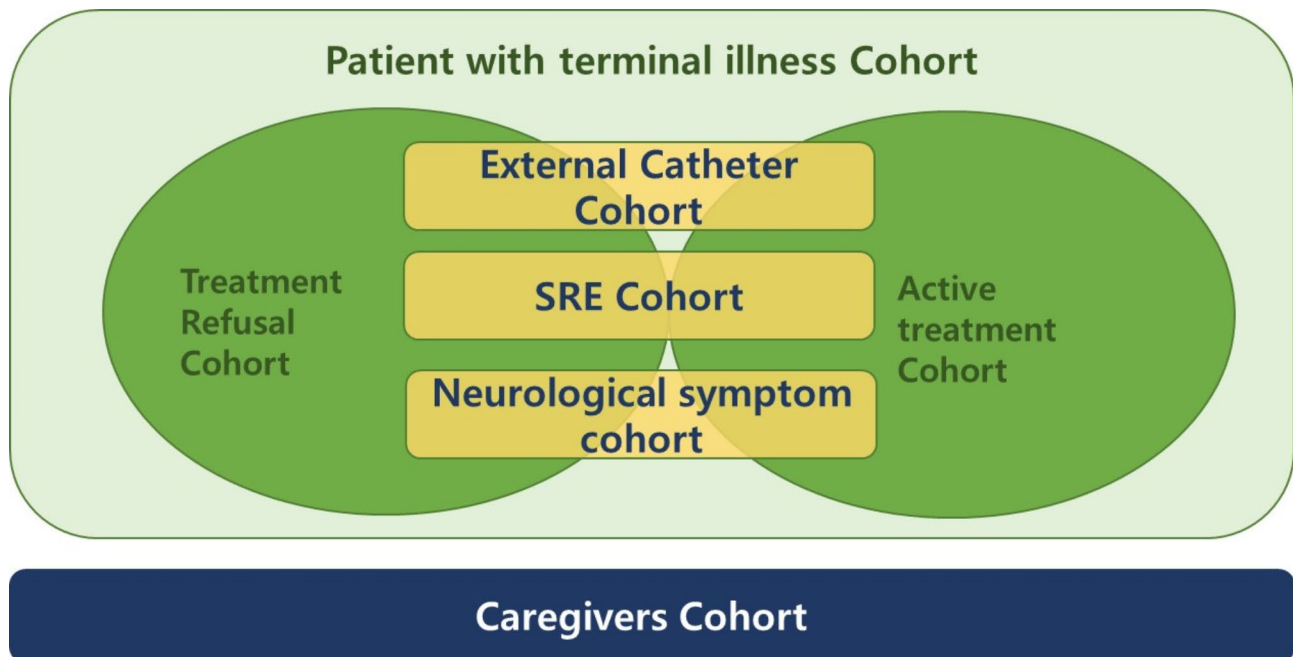


Fig. 1 Diagram of cohorts and sub-cohorts of the study

Table 1 Cohort follow-up schedule for patients

Visit	- t1	0	1M	3M	6M	9M	12M(1Y)	3M interval f/u
Patient								
Window Period			(+/-) 15days	(+/-) 30days	(+/-) 30days	(+/-) 30days	(+/-) 30days	(+/-) 30days
Registration and Informed Consent	●	●						
Screening	●	●						
Demographics		●						
Transfer Information		●						
Height/weight		●	○	●	●	●	●	●
Medical History, Comorbidities/CCIs		●	○	○	○	○	○	○
ECOG PS		●	○	●	●	●	●	●
Cancer Diagnosis		●						
Cancer Treatment Information		●	○	●	●	●	●	●
Radiation Therapy Information		●	○	●	●	●	●	●
Surgery Information		●	○	●	●	●	●	●
Emergency Department Visit Information		○	○	○	○	○	○	○
Conduit Information		○	○	○	○	○	○	○
Brain Metastases and Spinal Metastases		○	○	○	○	○	○	○
Skeletal Related Events (SRE)		○	○	○	○	○	○	○
Hospice Eligibility		○	○	○	○	○	○	○
Creating an End-of-life Care Plan		○	○	○	○	○	○	○
Patient (PROM)								
HADS	●	●	○	●	●	●	●	●
NRS 2002	●	●	○	●	●	●	●	●
ESAS	●	●	○	●	●	●	●	●
EQ-5D-5 L	●	●	○	●	●	●	●	●
K-MBI*	○	○	○	○	○	○	○	○
MDAS**	○	○	○	○	○	○	○	○
K-MMSE-2**	○	○	○	○	○	○	○	○

* SRE, brain metastasis and spinal metastasis cohorts only. ** Brain tumor patients only. ○ Additional data collected only if variable. ● When applicable

Secondary aims

1. Survival time, quality of life, and complications following external catheter insertion procedures.
2. Survival time, quality of life, and related factors in patients who did not receive active treatment.
3. Quality of life in patients with spinal metastases, brain metastases, and neurological symptoms.
4. Quality of life in patients with skeletal-related events (SREs).
5. Transfer status, treatment modalities, and outcomes of patients transferred from other hospitals.
6. Hospice utilization rate, hospice death, and length of stay.
7. Emergency department and intensive care unit utilization at 1, 3, 6, 9, and 12 months before death.
8. Hospitalization rate, reasons for hospitalization, and deaths at 1, 3, 6, 9, and 12 months before death.
9. Types, completion rates, and decision makers of end-of-life care-related documents for terminal patients.
10. Confirmation of active cancer treatment within 1, 3, and 6 months before death 1-month mortality rate of cancer patients using the emergency department.
11. Quality of life and bereavement of caregivers due to caregiving burden.

Inclusion criteria

Common criteria for patients

Common criteria include patients who are aged 19 or older and who have cancer (solid or hematologic) for which a cure is not expected at the time of enrollment.

For the treatment refusal cohort, enrollment is possible regardless of stage.

Written informed consent was obtained from all the patients.

Criteria for patient sub-cohorts

- ① Treatment refusal cohort: Cancer patients who have refused anticancer, surgical, or radiation therapy for treatment purposes, regardless of stage.
- ② External catheter cohort: Cancer patients who have external catheters or who have been transferred with external catheters (urinary catheters and vascular catheters are excluded).
- ③ Neurological symptom cohort: Patients with primary or secondary brain metastasis or spinal metastasis with neurological symptoms.
- ④ SRE cohort: patients with SREs (SREs are defined as pathological fractures, paralysis, spinal cord compression, pain, or impending fractures requiring radiation therapy or surgery).

Patients who meet the criteria for two or more cohorts can be enrolled multiple times.

Criteria for caregivers

Inclusion criteria include caregivers of enrolled patients, who are aged 19 or older, and who accompany the patient to medical appointments, primarily provide care, or are actively involved in the patient's treatment decisions.

Exclusion criteria

Patients whose cancer has not been histologically confirmed are excluded from the study.

Sample size calculation

The total sample size of this study is 720 patients from ten hospitals. This number is based on the testing of the primary outcome, which is the degree of change in the continuously measured Numerical Rating Scale (NRS) scores for one year. The sample size is determined using a longitudinal (repeated measures) cluster prospective cohort study design.

To calculate the required number of patients for one hospital, the change in the NRS score is assumed to be 5.5-point based on a previous study that measured a change from 6.5 to 1.0 in NRS scores among palliative care patients [13]. The minimal clinically important difference (MCID)—the smallest change in the clinical outcome that a patient would consider meaningful—is assumed to be 4.0, based on consensus among the participating researchers. The agreement at each measurement point at which the NRS is scheduled to be measured four times is assumed to be 0.6. The Type I error (α), Type II error (β), and dropout rate are set at 0.05, 0.20, and 10%, respectively. When we apply the equation (Supplementary 1) to the longitudinal cluster prospective cohort study [14], the number is 24 patients. Since this study involves ten hospitals over one year, the total sample size of patients is 240 (or 720 over three years).

However, because the number of patients available for treatment at each participating hospital varies, weights are applied to the required number of patients at each hospital based on the number of patients treated over the previous three years. The weights are listed in Supplementary 2.

Statistical analysis

The mean ($\pm$ SD) is presented for continuous variables when the data meets the assumptions of normal distribution and homoscedasticity. To check these assumptions, the Shapiro-Wilk test is used for normality, and Levene's test is used for homoscedasticity. If either assumption is violated, the median (interquartile range) is presented instead. Categorical variables are presented as frequencies and percentages ($N\%$).

The baseline characteristics of the enrolled patients, including age, sex, cancer type, stage, ECOG performance status, Charlson Comorbidity index, treatments,

hospital information, and outcomes (e.g., EQ-5D-5 L, the Hospital Anxiety and Depression Scale (HADS), Edmonton symptoms assessment scale (ESAS [15]) score, Krea-Modified Barthel Index (K-MBI [16]), and Korean version of Memorial Delirium Assessment Scale (K-MDAS [17])), Korean-Mental State Examination2 (K-MMSE [18]) are presented. Outcomes are measured at three-month intervals. These are described and plotted. Generalized estimating equation (GEE) analysis is performed to assess the changes in these outcomes over time.

The characteristics of patients with and without catheter therapy are compared using standardized differences, with values greater than 0.2 indicating meaningful differences. The difference in 1-year mortality between the two groups is evaluated using survival analysis. Subsequently, multivariate Cox proportional regression analysis is used to calculate the hazard ratio (HR) for the catheter insertion group after adjusting for significant patient characteristics. These analyses are conducted to compare patients with and without brain metastases, those transferred from other hospitals, those receiving systemic chemotherapy, and those visiting the emergency room.

The Cochran Q test is conducted to assess changes in hospice utilization, emergency room visits, intensive care unit admissions, hospitalization rates, and reasons for hospitalization at one, three, six, nine, and twelve months before death. All statistical analyses are performed using the R 4.3.2 (Vienna, Austria).

Recruitment and data collection

This study protocol and study-related documents, including an informed consent form, an electronic case recording form, and questionnaires, have been approved by each participating hospital. This study was registered at [https://cris.nih.go.kr\(KCT0009177\)](https://cris.nih.go.kr(KCT0009177)) on February 16, 2024. Patients and their caregivers who meet the inclusion and exclusion criteria will be enrolled in the study for three years.

Baseline clinical characteristics, comorbidities, cancer diagnosis, cancer treatment, socioeconomic status, and healthcare system utilization data of patients will be collected at the time of registration. The caregivers' demographic data, relationships with patients, jobs, and religion will be collected at the time of registration.

Clinical information and patient-reported outcomes (PROMs) will be collected every three months until death or the end of the study. The caregiver will respond to the PROMs every three months after the patient dies for one year. The allowable window period for a 3-month visit is one month. Anti-cancer treatments, medical utilities (Intensive care unit care, emergency room visit, hospitalization, or hospice care), ECOG performance status, co-morbidities, laboratory work (CBC, chemistry), and writing advance directives will be collected for each visit. The patients and caregivers will be asked to complete a quality-of-life questionnaire at each visit. These include: the HADS, Nutritional Risk Screening 2002, ESAS, and EQ-5D-5 L. The caregivers will complete the HADS and the Korean version of the Caregiver Quality of Life Index-cancer [19] at each visit. After the patient's death, the caregivers' questionnaires will include the Good Death Inventory [20].

The patients with neurological symptoms and SRE cohorts will have an additional one-month follow-up with a 15-day window. The K-MBI, K-MDAS, and Korean-Mental State Examination2 will be applied for those cohorts.

A schedule for collecting information and implementing PROMs are provided (Tabel 1 and Table 2).

This study is part of the KOREAN CANCER SURVIVOR HEALTHCARE R&D PROJECT (KOCAS) and will be conducted using the data collection e-CRF and an electronic survey system in the cloud system provided by KOCAS. The data will be anonymized and made publicly available in the system after the completion of the study.

Table 2 Cohort follow-up schedule for caregivers

Visit	- t1	0	1 M	3 M	6 M	9 M	12 M(1Y)	3 M interval f/u until death	Dead/3 M interval f/u for 1Y**
Parent									
Registration	●								
Screening	●								
Informed Consent	●								
Demographics	●								
Age/Gender	●								
Patient Relationships	●								
Religion/Occupation	●								
Protector (PROM)									
HADS	●	◐	●	●	●	●	●	●	●
CQOLC-K	●	◐	●	●	●	●	●	●	●
GDI									●

* For caregivers of patients in the brain metastasis and spinal metastasis cohorts only. **Follow-up surveys conducted every 3 months for 1 year after patient's death.
◐ When applicable

Ethical statement

The current study will comply with ethical standards presented in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The study protocol was approved by the institutional review boards at Kangwon National University Hospital (KNUH 2023-10-003), Gyeongsang National University Hospital (GNUH 2023-07-012), Gachon University Gil Medical Center (GBIRB2023-277), Pusan National University Hospital (2307-008-129), Chungnam National University Sejong Hospital (CNUSH 2023-05-010), Ajou University Hospital (AJOURB-OB-2023-330), Ulsan University Hospital (UUH2023-06-022), Jeonbuk National University Hospital (CUH IRB 2023-11-026), Jeju National University Hospital (JEJUNUH 2023-08-006), Gyeongsang National University Changwon Hospital (GNUCH 2024-05-018), Chungbuk National University Hospital (CBNUH 2023-06-029), Chungnam National University Hospital (CNUH 2023-09-023) and registered with cris.nih.go.kr (KCT0009177); research nurses and investigators will screen and explain the aim and procedure of the study to the participants (patients with cancer and their caregivers) and will obtain the informed consent.

Discussion

This study aims to describe the quality of life and medical conditions of patients with advanced cancer who visit regional cancer centers, and their caregivers, throughout their disease trajectory.

The structure of the Korean healthcare system means that patients with terminal cancer who visit community cancer centers are likely to be economically and socially disadvantaged. This study aims to inform policies designed to improve the quality of life of patients with cancer who remain in the community during their treatment.

The formation of the sub-cohorts is based on the researchers' clinical experiences in treating socially and medically vulnerable patients at a regional cancer center. Patients who choose not to undergo treatment, despite the availability of standard treatments for each stage of the disease, may be economically, socially, or emotionally disadvantaged. Further, they may be unable to overcome denial—a stage of the disease. These populations may be relatively underserved as most studies and practices focus on patients undergoing active treatment. Identifying the clinical course and sociopsychological issues experienced by these patients will help to inform cancer policy in South Korea.

Cancer patients with neurological symptoms due to brain or spinal lesions and the SRE sub-cohort, are more likely than other patients to be localized because of physical barriers to and distance from healthcare resources. It is important to identify their unmet needs because they

are more likely than groups with fewer impairments in physical mobility to experience emotional challenges in addition to their physical limitations. Moreover, their caregivers may be more likely than other caregivers to experience burnout because of the significant burden that they carry. This study can help to establish data on the need for social support for these patients which can inform community policies.

Patients with cancer who have multiple inserted catheters and are exposed outside the body due to blockages or fluid retention may be at a higher risk of infection or complications from the catheter itself than other patients. By identifying the unique symptoms and challenges that these patients experience, it may be possible to organize support for them.

This study is expected to provide a basis for establishing appropriate support systems for vulnerable patients with cancer by identifying the quality of life and unmet needs of patients with late-stage cancer at community cancer centers.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12885-024-13341-z>.

Supplementary Material 1

Author contributions

JH Kwon is a principal investigator who conceptualized, developed, and drafted the "Quality of Life Outcomes in Terminal Cancer Patients Attending Regional Cancer Centers in South Korea" protocol and the study. JH Kang, J-S Huh, SJ Koh, K-H Lim, B Choi, Y J Choi, E-K Song, HW Lee, Y-S Kim, S-I Go, HJ Yun, SJ Sym, H Ryu, M-W Lee contributed to the concept, study design, and draft of the protocol and guided participant recruitment in a regional cancer centers and affiliated hospitals in Korea. RB Kim collaborated in developing strategies for the statistical data analysis. All authors have approved the submitted version of this manuscript and have agreed to be personally accountable for the integrity of this work.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Competing interests

The authors declare no competing interests.

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