



# Nationwide survey on family caregiver-perceived experiences of patients with cancer of unknown primary site

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## Abstract

**Purpose** Cancer of unknown primary site (CUP) is an aggressive disease with poor prognosis. As research on the experiences of CUP patients and their families is scarce, this study aimed to compare the family caregiver-perceived burden of CUP with that of common cancers (lung, colon, and stomach cancers). The association between family caregiver-perceived burden and CUP patients' quality of life (QOL) at end-of-life and family depression, respectively, was also explored.

**Methods** This was a pre-planned secondary analysis of nationwide cross-sectional survey data from the bereaved family caregivers of patients with cancer who died at 286 institutions. The major measurements were the eight-item family caregiver-perceived Burden scale (comprising specialist access, uncertainty, and prolonged diagnosis), Good Death Inventory, and Patient Health Questionnaire 9.

**Results** Of 27,591 survey responses, we analyzed 97 and 717 responses from family caregivers of patients with CUP and common cancer, respectively. The families of CUP patients scored significantly higher on all three burden subscales than those of common cancer patients (effect sizes: specialist access subscale, 0.3; uncertainty subscale, 0.66; and prolonged diagnosis subscale, 0.69; adjusted  $P < 0.01$ ). Greater family burden was significantly associated with lower patient QOL and higher family depression. Burden was significantly associated with being a spouse, second opinion consultation, and diagnosis period of  $> 1$  month.

**Conclusion** The family caregivers of CUP patients experience poor specialist access, greater uncertainty, and a prolonged diagnosis. They should be cared for from the initial stages to establish access to specialists, obtain an early diagnosis, and reduce uncertainty.

**Keywords** Unknown primary tumors · Family caregivers · Experience · Burden · Uncertainty · Early diagnosis

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## Introduction

Cancer of unknown primary site (CUP) is a clinically aggressive disease with early dissemination [1, 2], resulting in poor prognosis with a median survival time of 6 months [3]. While research on the medical aspects of CUP has been increasing [4–8], information on the experiences of CUP patients and family caregivers is scarce. To date, some qualitative studies demonstrated that CUP patients experience uncertainty and difficulty when accepting the CUP diagnosis [9, 10] and that CUP patients experience anxiety, disbelief, and frustration in addition to uncertainty from onset to initial treatment [11]. Quantitative studies are limited, and only one large quantitative study compared experiences between CUP and other cancer patients, which revealed that CUP patients were less likely to have understood the explanations of their condition [12]. Furthermore, CUP patients' family caregivers may experience considerable burden [13, 14], but very little research has focused them [10]. Empirical evidence suggests that family caregivers sometimes become more depressed than patients themselves [15] and that they face continued burden after the patient's death [16, 17]. A greater understanding of the experiences of CUP patients' family caregivers is valuable for developing an appropriate strategy to care for both CUP patients and their family caregivers.

The primary aim of this study was thus to compare the family caregiver-perceived burden of CUP patients and those with common cancers (lung, colon, and stomach cancers). The rationale for selecting patients with lung, colon, and gastric cancers as reference was that these were the most common types of cancer throughout Japan since 1975. The secondary aims were (1) to explore the association between family caregiver-perceived burden on family caregivers and the patients' quality of life (QOL) at end-of-life and depression among bereaved family caregivers, respectively, and (2) to identify factors related to family caregiver-perceived burden.

## Methods

This study was conducted as a part of the Japan Hospice and Palliative Care Evaluation (J-HOPE) with the aim to evaluate the quality of palliative care services from the perspective of bereaved family caregivers [18, 19]. This was a cross-sectional nationwide survey using anonymous, self-administered questionnaires. For the present study, data from two surveys, namely J-HOPE 2016 (conducted

May–July 2016) and J-HOPE 4 (July–September 2018) [18, 19], were combined to achieve the necessary sample size.

## Subjects

Potential subjects were bereaved family caregivers of cancer patients who had died at each participating institution between November 2013 and January 2016 (J-HOPE 2016) and between February 2016 and January 2018 (J-HOPE 4). Participating institutions were certified inpatient hospices/palliative care units (PCUs), home care services, and acute hospitals belonging to the Japan Hospice and Palliative Care Foundation. The eligibility criteria were as follows: adult bereaved family caregivers of a patient that died of cancer, the deceased patient was aged  $\geq 20$  years, and the patient was an inpatient in a PCU for  $> 3$  days. The exclusion criteria were as follows: a PCU stay  $< 3$  days, inability to identify a family caregiver, treatment-associated death or death in an intensive care unit, suffering serious psychological distress, inability to complete the self-report questionnaire because of health issues, and overall judgment of the healthcare professionals.

## Procedures

Questionnaires were sent by mail to identified family caregivers directly by each participating institution, and uninterested participants were asked to check the “No Participation” box and return the incomplete questionnaire. Participants were provided detailed information in the form of an enclosed letter of intent about participation being voluntary, absence of medical disadvantage due to non-participation, and assurance of complete anonymity. We asked that the respondents be family caregivers who were the main caregivers of the patient and who had the most knowledge about the treatment provided to the patient. Completed questionnaires were returned by the participants to the research secretariat, and data management at the secretariat was independent of all participating institutions. Return of a completed questionnaire was defined as consent for study participation. A reminder was sent to non-responders 1 month after the questionnaire was sent out.

## Measurements

The questionnaire for this study was developed by the authors based on a literature review [9, 10, 20, 21], a previous qualitative study using interviews with 9 CUP patients [11], and extensive discussions among the authors. Content validity was assessed and agreed upon by all authors after pilot testing, during which participants were interviewed regarding the appropriateness of the questions' wording, quantity, and sequence and possible omissions or

duplications in selected answers. Qualitative feedback was reflected in the questionnaire.

### **Burden on family caregivers associated with cancer testing and diagnosis (family caregiver-perceived burden scale: Burden)**

The Burden scale was developed to identify family caregivers' experiences with cancer testing and diagnosis. The main purpose of the scale was to help family caregivers of CUP patients understand the burden of the medical care they have experienced since the onset of the illness. Given the lack of a validated measurement tool to date, items were generated based on prior qualitative studies on CUP [9–11]. The Uncertainty Scale [20, 21] and the Decisional Conflict Scale (DCS) [22] were also referred. A total of 43 items regarding experiences from the pre-diagnosis to treatment phase were generated, among which 13 items related to tests and diagnoses that could also be shared by other cancers were extracted. The items were then carefully collapsed into eight items, eliminating duplication and complexity while not omitting elements such as uncertainty, distress, loneliness, and medical support needs. The eight items were rated on a four-point Likert scale (1: Never, 2: Rarely, 3: Sometimes, and 4: Often). Subscale scores were defined as the mean scores of the included items, and the total score was defined as the mean of the subscale scores: each was scored on a scale of 1–4, and higher scores indicated greater burden. The entire scale creation process was reviewed for content validity by seven people: three cancer nurse specialists, an oncologist, a palliative care specialist, and two psycho-oncologists.

### **Good Death Inventory**

Patients' QOL at end-of-life was assessed using the short version of the Good Death Inventory (GDI), which measures the achievement of a good death from the perspective of bereaved family caregivers in Japan. The short GDI consists of 18 representative items from each domain of the original version and its validity and reliability have been previously confirmed [23]. Responses were rated on a scale from 1 to 7, with a high total score indicating good death [23].

### **Patient Health Questionnaire 9**

Depression was assessed using Patient Health Questionnaire 9 (PHQ-9); the reliability and validity of the Japanese version have been previously confirmed [24–27]. Each of the nine items explores the extent to which a particular depressive symptom has bothered the respondent in the preceding 2 weeks. Responses are rated on a scale from 0 to 3, with total scores ranging from 0 to 27 [24, 25].

### **Participant characteristics**

The patients' age, sex, and primary cancer site from their medical records were recorded by the physician responsible for patient treatment at each of the participating institutions. We also asked bereaved family caregivers for their age, sex, relationship with the patient, and educational background as part of the questionnaire.

### **Background of the diagnosis of CUP patients**

Only the bereaved family caregivers of CUP patients were asked for details regarding patients' chief complaint at the time of the first hospital visit, length of time from the awareness of symptom to diagnosis, number of hospitals visited by patients until CUP diagnosis, type of hospital at which the patient received a confirmed CUP diagnosis, availability of a second opinion consultation, and history of any cancer other than CUP.

### **Sample size calculation**

We initially calculated a sample size of 60 cases in 2 groups based on effect size (ES) of 0.5,  $\alpha$  of 0.05, and power of 0.8. From the first survey (J-HOPE 2016), we obtained 39 responses. We added the J-HOPE 4 survey assuming that the impact of medical changes was minimal during the study period (2016–2018).

### **Statistical analyses**

For the background variables and item responses, descriptive statistics were calculated for the measured items in the CUP and common cancer groups, and between-group differences were examined using Student's *t* test and one-way analysis of variance (ANOVA) for continuous variables and chi-squared test for categorical variables. Exploratory factor analysis was performed using the maximum likelihood method. The repeated promax rotation solution was used to confirm the identity of the underlying structure of the Burden scale.

The total and subscale scores were compared using multiple regression analysis to adjust for covariates between the groups, and Cohen's *d* was used as ES.

Multiple regression analysis was used to explore covariate-adjusted correlations between GDI total scores (as an independent variable) and PHQ-9 (as a dependent variable) for a subset of CUP data.

Furthermore, the determinants relevant to each subscale of Burden were analyzed for a subset of CUP data. Univariate analyses were performed with chi-squared analyses, one-way ANOVA, and *t* tests, where appropriate. For multivariate analysis, multiple regression analysis was performed using items that had  $P < 0.10$  in univariate analysis.

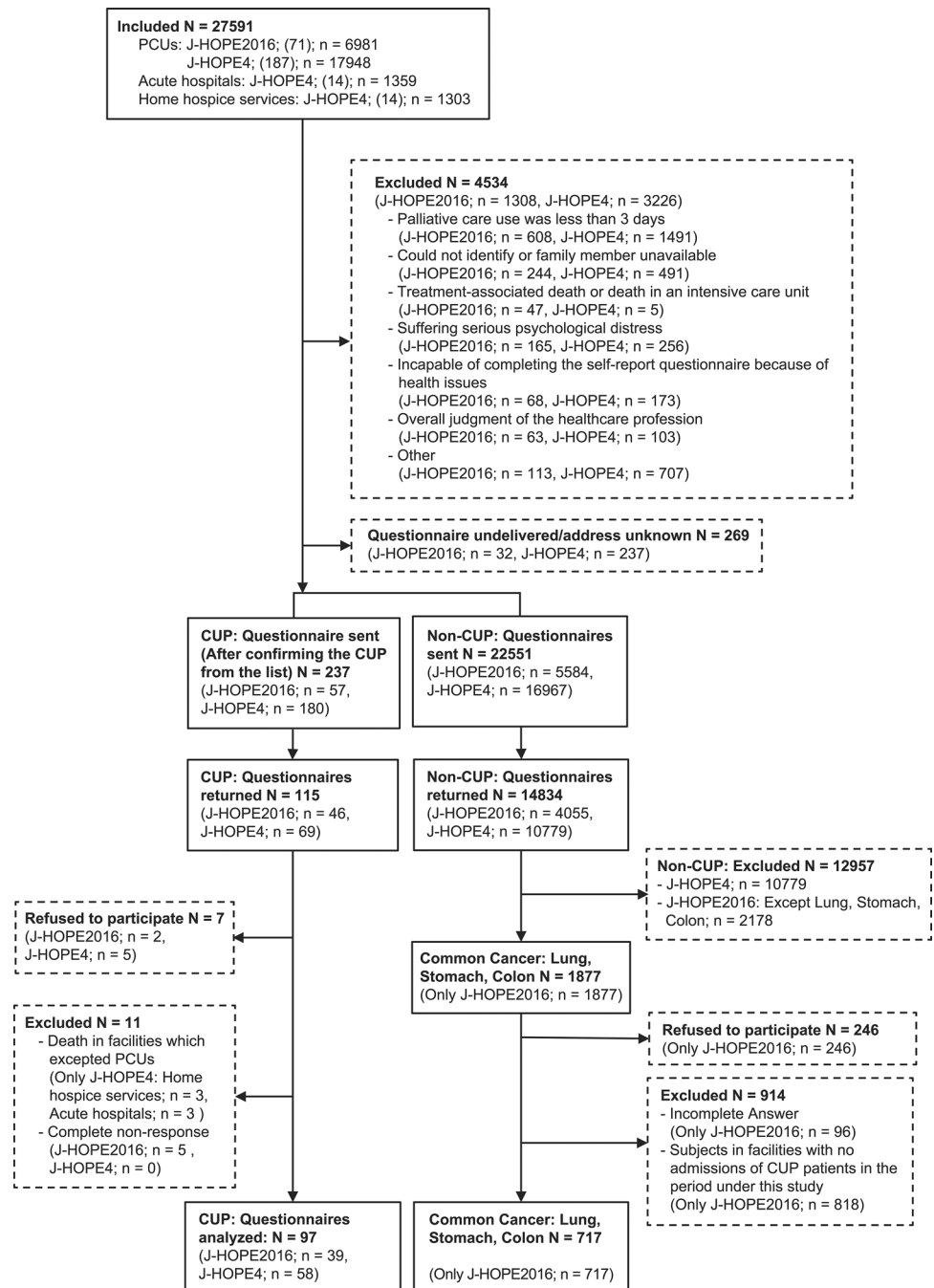
Variable selection was performed using the variable reduction method.

A  $P$  value  $< 0.05$  was considered statistically significant. All analyses were performed using SPSS version 27.0 (IBM Japan Institute, Tokyo, Japan).

## Results

The participating institutions were PCUs (258), home hospice services (14), and acute hospitals (14). The original dataset comprised a total of 27,591 respondents (Fig. 1). For the family caregivers of CUP patients, 237 questionnaires were sent, 115 were returned (response rate, 48.5%), and 97 were ultimately analyzed. For the family caregivers of non-CUP patients, 22,551 questionnaires were sent and 14,834 were returned (response rate, 65.8%). Among

**Fig. 1** The original dataset comprised a total of 27,591 respondents



these, 1877 responses corresponded to the family caregivers of patients with common cancers (lung, colon, and stomach). Among the 1877 responses, 246 refused to respond. Of the remaining 1631, 818 bereaved family caregivers of patients in facilities with no CUP patient admissions and 96 responses with incomplete answers were excluded. Ultimately, 717 questionnaires from bereaved family caregivers of patients with common cancers were included in the analysis.

Tables 1 and 2 show the characteristics of patients and their bereaved family caregivers. Variables that were significantly different between the groups were patient gender ( $P=0.006$ ) and the number of days elapsed since death ( $P=0.005$ ).

### Frequency distribution and factor analysis of the Burden scale

Tables 3 and 4 show the percentage of family caregivers who answered “sometimes” or “often” to each Burden item. Among the family caregivers of CUP patients, the questions that received a “sometimes” or “often” response 50% of the time or more were patient exhaustion due to a large number of evaluations (73.9%), anxiety associated with the prolonged diagnosis period (70.2%), and uncertainty about the future progression of cancer (56.3%).

Exploratory factor analysis identified three underlying structures of the Burden scale (Tables 3 and 4): (1) Factor-1: “Difficulty in accessing specialist doctors” (specialist subscale,  $\alpha=0.844$ ), comprising three items; (2) Factor-2: “Uncertainty due to lack of information about the disease” (uncertainty subscale,  $\alpha=0.821$ ), consisting three items; and (3) Factor-3: “Psychological burden associated with extensive testing and prolonged diagnosis period” (prolonged diagnosis subscale,  $\alpha=0.703$ ), consisting two items. Cronbach’s alpha across the eight items was 0.901.

### Comparison of Burden between family caregivers of CUP patients and those of common cancer patients

Table 5 shows the difference in the mean family caregiver-perceived Burden score associated with cancer testing and diagnosis between the groups, after adjusting for covariates, i.e., patient age, gender, and relationship to the patient. The scores for all three factors of burden were significantly higher for the CUP group than the common cancers group: specialist subscale (ES = 0.30, Adj  $P=0.010$ ), uncertainty subscale (ES = 0.66, Adj  $P<0.0001$ ), and prolonged diagnosis subscale (ES = 0.69, Adj  $P<0.0001$ ).

**Table 1** Characteristics of patients ( $N=814$ )

	CUP <sup>a</sup>		Common cancers <sup>b</sup>		<i>P</i> value
	<i>n</i> /mean	%/SD	<i>n</i> /mean	%/SD	
Sex					
Male	46	47.4	444	61.9	0.006 <sup>c</sup>
Female	51	52.6	273	38.1	
Age, years	76.8	12.0	75.5	11.2	0.273 <sup>d</sup>
< 65 years	16	0.2	116	16.2	0.068 <sup>e</sup>
65–75 years	21	0.2	201	28.0	
75–85 years	26	26.8	234	32.6	
≥ 85	34	35.1	166	23.2	
Primary cancer site					
Unknown	97	100.0	0	0.0	–
Lung	0	0.0	345	48.1	
Colon	0	0.0	199	27.8	
Stomach	0	0.0	173	24.1	
Chief complaint at the time of the first hospital visit					
Pain	40	23.7	–	–	
Swelling	27	16.0	–	–	
Anorexia	24	14.2	–	–	
Fatigue	24	14.2	–	–	
Dyspnea	13	7.7	–	–	
Fever	11	6.5	–	–	
Other symptoms	22	13.0	–	–	
None	8	4.7	–	–	
Length from awareness of symptom to diagnosis					
< 1 month	32	33.0	–	–	
1–3 months	35	36.1	–	–	
≥ 3 months	19	19.6	–	–	
No symptom	2	2.1	–	–	
Number of hospitals visited by patients until diagnosis					
1	15	15.5	–	–	
2–5	76	78.4	–	–	
≥ 6	2	2.1	–	–	
Hospital which received a confirmed diagnosis					
Cancer center	10	10.3	–	–	
University hospital	28	28.9	–	–	
General hospital	48	49.5	–	–	
Clinic	3	3.1	–	–	
Other hospital	3	3.1	–	–	
Second opinion consultation					
Experienced	29	29.9	–	–	
Did not experience	64	66.0	–	–	
Number of primary departments					
One	52	53.6	–	–	
Two	12	12.4	–	–	
Three	7	7.2	–	–	
Previous experience with other cancers					
Yes	19	19.6	–	–	
No	73	75.3	–	–	



**Table 1** (continued)

Several of the total percentage values shown above do not reach 100% due to missing data

SD standard deviation

<sup>a</sup>Cancer of unknown primary site

<sup>b</sup>The three most common cancers in Japan (lung, colon, stomach) according to cancer statistics since 1975

<sup>c</sup>Chi-squared analyses

<sup>d</sup>Student's *t* tests

<sup>e</sup>One-way ANOVA

### Association of patients' QOL at end-of-life and bereaved family caregiver's depression with Burden associated with cancer testing and diagnosis (CUP data only)

Table 6 shows the correlation of GDI or PHQ-9 score with the three factors of burden, after adjusting for patient age, gender, and relationship to the patient (only in the case of PHQ-9, the period after the patient's death was added). There was a significant association of all three factors of burden with GDI and PHQ-9. Strongly associated factors included uncertainty subscale with GDI (Std  $\beta = -0.41$ , Adj  $P < 0.0001$ ), specialist subscale with PHQ (Std  $\beta = 0.29$ , Adj  $P = 0.012$ ), and prolonged diagnosis subscale with PHQ (Std  $\beta = 0.29$ , Adj  $P = 0.011$ ).

### Factors related to family caregiver-perceived burden associated with cancer testing and diagnosis (CUP data only)

Factors associated with burden are summarized in Table 7. Multiple regression analysis identified that the independent factors for total and subscale scores for burden included relationship to the patient (spouse had higher burden), duration of diagnosis ( $\geq 1$  month was associated with a higher burden), and second opinion consultation (family caregivers who reported a second opinion consultation had a higher burden).

## Discussion

To the best of our knowledge, this is the first study comparing family caregivers' experiences between CUP and common cancer patients. Family caregiver-perceived burden associated with cancer examination and diagnosis was significantly higher in the family caregivers of CUP patients than in those of common cancer patients, and their perceived burden was significantly associated with patients' QOL at end-of-life and family depression. In addition, a diagnosis that required  $\geq 1$  month and receiving a second opinion consultation were significantly associated with burden.

**Table 2** Characteristics of bereaved family caregivers ( $N = 814$ )

	CUP <sup>a</sup>		Common cancers <sup>b</sup>		<i>P</i> value
	<i>n</i> /mean	%/SD <sup>c</sup>	<i>n</i> /mean	%/SD <sup>c</sup>	
Sex					
Male	26	26.8	217	30.3	0.732 <sup>d</sup>
Female	64	66.0	491	68.5	
Age, years	61.3	11.0	62.3	12.1	0.431 <sup>e</sup>
55 <	22	24.4	188	26.6	0.262 <sup>f</sup>
55–65 <	34	37.8	199	28.2	
65–75 <	23	25.6	198	28.0	
$\geq 75$	11	12.2	121	17.1	
Relationship with the patient					
Spouse	34	35.1	291	40.6	0.366 <sup>d</sup>
Child	39	40.2	296	41.3	
Son/daughter in law	9	9.3	40	5.6	
Parent	0	0.0	19	2.6	
Sibling	5	5.2	43		
Other	2	2.1	22	3.1	
Education					
Junior high school	3	3.1	75	10.5	0.075 <sup>d</sup>
High school	36	37.1	321	44.8	
College	21	21.6	149	20.8	
University	28	28.8	139	19.4	
Graduate university	1	1.0	6	0.8	
Other	1	1.0	6	0.8	
Religion					
Buddhism	53	54.6	428	59.7	0.397 <sup>d</sup>
Shintoism	0	0.0	13	1.8	
Christianity	2	2.1	14	2.0	
Other religion	0	0.0	11	1.5	
No religion	34	35.1	226	31.5	
Period from date of patient death to date of survey return					
Mean	318.1	133.8	278.2	130.3	0.005 <sup>c</sup>
> 6 months	8	8.2	162	22.6	0.002 <sup>f</sup>
6–12 months	63	64.9	450	62.8	
13–18 months	19	19.6	68	9.5	
19–24 months	5	5.2	26	3.6	
$\geq 25$ months	2	2.1	11	1.5	

Several of the total percentage values shown above do not reach 100% due to missing data

<sup>a</sup>Cancer of unknown primary site

<sup>b</sup>The three most common cancers in Japan (lung, colon, stomach) according to cancer statistics since 1975

<sup>c</sup>SD (standard deviation)

<sup>d</sup>Chi-squared analyses

<sup>e</sup>Student's *t* tests

<sup>f</sup>One-way ANOVA

**Table 3** Frequency distribution of burden among family caregivers of patients with CUP and common cancers

Item	CUP <sup>a</sup>				Common cancers <sup>b</sup>			
	Mean <sup>c</sup>	SD	% (n) of subjects		Mean <sup>c</sup>	SD	% (n) of subjects	
			Sometimes	Often			Sometimes	Often
Q1: I felt impatient and anxious because the patient was not quickly diagnosed	2.90	0.98	38.3 (36)	31.9 (30)	2.12	0.91	24.3 (174)	7.8 (56)
Q2: I felt that the patient was left exhausted by the large number of examinations	2.90	0.93	46.7 (43)	27.2 (26)	2.55	0.97	37.3 (265)	17.5 (124)
Q3: I thought that the doctor's recommended course of medical care might be wrong	2.08	0.88	12.9 (12)	9.7 (9)	1.95	0.85	19.4 (138)	4.8 (34)
Q4: It was hard for me to find specialists with the skills needed to treat the patient's disease	2.31	1.09	21.3 (20)	19.1 (18)	1.88	0.84	17.6 (125)	4.2 (30)
Q5: I thought that the doctor might abandon us	1.97	0.96	18.3 (17)	8.6 (8)	1.79	0.86	13.9 (99)	5.0 (36)
Q6: I thought that other people around us would not understand the unique characteristics of the patient's cancer	2.28	1.00	25.5 (24)	13.8 (13)	1.85	0.80	14.5 (102)	3.7 (26)
Q7: I experienced uncertainty due to the unpredictability of the cancer's future progression	2.62	1.02	34.0 (32)	22.3 (21)	2.16	0.91	28.2 (201)	7.6 (54)
Q8: I felt it was difficult for me to obtain information regarding the patient's disease from books, the internet, etc	2.42	1.04	24.7 (23)	19.4 (18)	1.87	0.77	14.3 (101)	3.3 (23)

SD standard deviation

<sup>a</sup>Cancer of unknown primary site

<sup>b</sup>The three most common cancers in Japan (lung, colon, stomach) according to cancer statistics since 1975

<sup>c</sup>Each item was rated on a four-point Likert scale (1: Never, 2: Rarely, 3: Sometimes, and 4: Often)

**Table 4** Factor analysis of burden among family caregivers of patients with CUP and common cancers (N=814)

Item and factor	Factor loading			
	I	II	III	<i>h</i> <sup>2</sup>
F1: Difficulty in accessing specialist doctors ( $\alpha=0.844$ )				
Q5: I thought that the doctor might abandon us	0.84	0.04	-0.07	0.67
Q4: It was hard for me to find specialists with the skills needed to treat the patient's disease	0.76	0.15	-0.05	0.71
Q3: I thought that the doctor's recommended course of medical care might be wrong	0.61	-0.13	0.35	0.62
F2: Uncertainty due to lack of information about the disease ( $\alpha=0.821$ )				
Q8: I felt it was difficult for me to obtain information regarding the patient's disease from books, the internet, etc	-0.04	0.82	-0.03	0.60
Q7: I experienced uncertainty due to the unpredictability of the cancer's future progression	0.15	0.59	0.15	0.69
Q6: I thought that other people around us would not understand the unique characteristics of the patient's cancer	0.34	0.49	-0.02	0.59
F3: Psychological burden associated with extensive testing and prolonged diagnosis period ( $\alpha=0.703$ )				
Q2: I felt that the patient was left exhausted by the large number of examinations	-0.04	-0.03	0.79	0.55
Q1: I felt impatient and anxious because the patient was not quickly diagnosed	0.03	0.29	0.52	0.60
Eigenvalue	4.767	0.766	0.643	
Factor contribution	3.921	3.779	3.264	
Cronbach's $\alpha=0.901$				

Exploratory factor analysis: a maximum likelihood method and promax rotated solution

Family caregiver-perceived burden comprises three components, namely specialist access, uncertainty, and prolonged diagnosis. All three of these subscales were significantly higher in the family caregivers of CUP patients than in those of common cancer patients. This difference may be

because CUP usually presents with atypical symptoms; thus, physicians are often unfamiliar with diagnosing CUP [6]. In particular, the uncertainty and prolonged diagnosis subscales showed significant and large differences between CUP and common cancers. These findings confirm the results

**Table 5** Comparison of burden between family caregivers of CUP patients and those of common cancer patients

	CUP <sup>a</sup>		Common cancers <sup>b</sup>		Effect size <sup>d</sup>	Adj <i>P</i> value <sup>e</sup>
	Mean <sup>c</sup>	SD	Mean <sup>c</sup>	SD		
Total score	2.42	0.77	2.01	0.66	0.60	<0.0001
F1: Specialist subscale <sup>f</sup>	2.10	0.84	1.87	0.74	0.30	0.010
F2: Uncertainty subscale <sup>g</sup>	2.43	0.89	1.96	0.70	0.66	<0.0001
F3: Prolonged diagnosis subscale <sup>h</sup>	2.90	0.85	2.34	0.82	0.69	<0.0001

*SD* standard deviation

<sup>a</sup>Cancer of unknown primary site

<sup>b</sup>The three most common cancers in Japan (lung, colon, stomach) according to cancer statistics since 1975

<sup>c</sup>Each item was rated on a four-point Likert scale (1: Never, 2: Rarely, 3: Sometimes, and 4: Often)

<sup>d</sup>Effect size: Cohen's *d*

<sup>e</sup>Adjusted *P* value for characteristics (patient: age, sex; bereaved family members: relationships), a multiple regression analysis

<sup>f</sup>F1: Difficulty in accessing specialist doctors

<sup>g</sup>F2: Uncertainty due to lack of information about the disease

<sup>h</sup>F3: Psychological burden associated with extensive testing and prolonged diagnosis period

**Table 6** Association of patients' QOL at end-of-life and bereaved family caregivers' depression with burden associated with cancer testing and diagnosis (CUP data only)

	GDI		PHQ-9	
	Total score		Total score	
	Std $\beta$	Adj <i>P</i> value <sup>a</sup>	Std $\beta$	Adj <i>P</i> value <sup>b</sup>
Total score	-0.37	0.001	0.32	0.005
F1: Specialist subscale <sup>c</sup>	-0.30	0.006	0.29	0.012
F2: Uncertainty subscale <sup>d</sup>	-0.41	<0.0001	0.25	0.026
F3: Prolonged diagnosis subscale <sup>e</sup>	-0.23	0.047	0.29	0.011

*GDI* Good Death Inventory, *PHQ-9* Patient Health Questionnaire-9

<sup>a</sup>Adjusted *P* value for characteristics (patient: age, sex; bereaved family members: relationships), a multiple regression analysis

<sup>b</sup>Adjusted *P* value for characteristics (patient: age, sex; bereaved family members: relationships, five groups after patient's death [one group every 6 months]), a multiple regression analysis

<sup>c</sup>F1: Difficulty in accessing specialist doctors

<sup>d</sup>F2: Uncertainty due to lack of information about the disease

<sup>e</sup>F3: Psychological burden associated with extensive testing and prolonged diagnosis period

of previous qualitative studies [9–11]. Uncertainty is the highest and most distressing during the waiting period for a diagnosis, and prolonged uncertainty [20], which subjects assess as dangerous, leads to substantial emotional exhaustion [20, 28]. The burden associated with CUP patients and family caregivers is characterized by the experience of serious and prolonged uncertainty, such as not being able to find a primary site and being forced to undergo multiple repeated tests, and the difficulty in obtaining disease information, which differs considerably from common cancers. Nevertheless, credible authority, social support, and/or education can be used as resources to manage uncertainty [20]. Apart from improving the CUP healthcare system, such as establishing access to specialists and creating mechanisms for early diagnosis, a comprehensive strategy is required that

includes care to reduce the uncertainties among patients and their family caregivers from an early stage.

Another important finding is that a higher Burden score was significantly correlated with lower patient QOL at end-of-life (GDI) and higher depression among bereaved family caregivers. CUP patients are often symptomatic before the definitive diagnosis [29], are typically diagnosed during an unplanned hospital admission, and have very poor survival [30]. Owing to these characteristics, the family caregiver-perceived burden during the diagnostic process affects not only the CUP patients at the end-of-life but also their bereaved family caregivers. Establishing a comprehensive care strategy for CUP patients and their family caregivers may improve patients' QOL at end-of-life and post-bereavement depression.



**Table 7** Factors related to family caregiver-perceived burden associated with cancer testing and diagnosis (CUP data only)

	Total score		F1: Specialist subscale <sup>a</sup>		F2: Uncertainty subscale <sup>b</sup>		F3: Prolonged diagnosis subscale <sup>c</sup>	
	Std $\beta$	<i>P</i> value	Std $\beta$	<i>P</i> value	Std $\beta$	<i>P</i> value	Std $\beta$	<i>P</i> value
Family caregivers								
Relationship with the patient			–	–				
Others	Ref		–	–	Ref		Ref	
Spouse	0.28	0.009	–	–	0.24	0.025	0.28	0.009
Family caregivers' religion								
No	–	–	–	–	–	–	Ref	
Yes	–	–	–	–	–	–	0.26	0.017
Patients								
Age, years			–	–				
< 65	–0.05	0.669	–	–	0.06	0.629	–0.08	0.479
65–75 years	–0.02	0.890	–	–	–0.10	0.433	0.10	0.430
75–85 years	0.07	0.533	–	–	0.15	0.167	0.22	0.046
≥ 85	Ref				Ref		Ref	
Length from symptom onset to diagnosis								
< 1 month	Ref		Ref		Ref		Ref	
1–3 months	0.25	0.039	–0.03	0.792	0.24	0.045	0.32	0.008
≥ 3 months	0.35	0.004	0.14	0.217	0.35	0.004	0.23	0.047
Number of hospitals visited by patients until diagnosis								
1	Ref		Ref		Ref		–	–
2 or higher	0.03	0.823	0.25	0.024	0.04	0.755	–	–
Hospital that received a confirmed diagnosis								
Specialty hospital of cancer	0.11	0.298	0.20	0.065	–	–	0.10	0.374
Other	Ref		Ref		–	–	Ref	
Second opinion consultation								
Non-experienced	Ref		Ref		Ref		Ref	
Experienced	0.26	0.014	0.15	0.172	0.21	0.046	0.21	0.050
Chief complaint at the time of the first hospital visit								
Fatigue			–	–			–	–
No	Ref		–	–	Ref		–	–
Yes	0.15	0.153	–	–	0.14	0.195	–	–
Other symptom								
No	–	–	–	–	–	–	Ref	
Yes	–	–	–	–	–	–	–0.18	0.098
<i>R</i> <sup>2</sup>	0.275		0.093		0.201		0.329	
Adj <i>R</i> <sup>2</sup>	0.221		0.070		0.157		0.257	

A multiple regression analysis

<sup>a</sup>F1: Difficulty in accessing specialist doctors

<sup>b</sup>F2: Uncertainty due to lack of information about the disease

<sup>c</sup>F3: Psychological burden associated with extensive testing and prolonged diagnosis period

A notable result of our analysis is the identification of a reasonable diagnosis period from the perspective of a healthcare recipient as being “within 1 month”; this is in agreement with the guidelines [31] for the appropriate diagnosis of CUP, which is typically associated with a prolonged diagnostic period [32–34]. Clarifying specific periods in

diagnosing CUP may be helpful for clinicians during the initial diagnostic phase.

Of note, the difference in the specialist subscale was relatively lower than that in the other two subscales. This may be due to the presence of a national health insurance system covered by the government that is available to the

Japanese population [35]. In the Japanese healthcare system, all patients can freely choose medical institutions and receive medical treatment anytime within the upper limits of expenses (~ 1000 USD per month); therefore, it is rare for anyone to have no access to healthcare at all [35, 36]. Additionally, most Japanese, particularly the elderly, prefer the traditional culture of “leave it to the doctor” [37]. Although there are indications of inequalities in access to services in CUP [32–34], it is possible that this cultural background in Japan is reflected in our results.

## Strengths and limitations

This study has multiple strengths, including the use of a nationwide sample, use of common cancer patients as a reference group to make comparisons, and use of validated measures of good death (GDI). However, this study also has several limitations. First, the response rate was moderate (48.5%) and we could not compare the backgrounds between responding and non-responding family caregivers; thus, there may be some selection bias. Second, although the responses of the 97 bereaved family caregivers of CUP patients were from nationwide surveys, they are not fully representative because the patients were mainly recruited from a convenient sample of specialized palliative care services. Third, recall bias may have occurred owing to retrospective assessment by bereaved family caregivers. Fourth, although the outcome measures had good psychometric properties, including factor validity and internal consistency, reliability and validity were not formally tested.

## Conclusions

Family caregiver-perceived burden associated with cancer testing and diagnosis was higher among the family caregivers of CUP patients than those with common cancers, and the higher burden was correlated with lower patient QOL at end-of-life and higher depression among bereaved family caregivers. Burden comprised three factors: specialist access, uncertainty, and prolonged diagnosis; it was significantly associated with the relationship to the patient (spouse), prolonged diagnosis (> 1 month), and second opinion consultation. CUP patients and their family caregivers should be cared for from the initial stages to establish access to specialists, obtain an early diagnosis, and reduce uncertainty.

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**Data availability** The data supporting the study results are available from the corresponding author upon reasonable request.

## Declarations

**Ethics approval** This study was conducted with the approval of the ethics committee of Tohoku University School of Medicine (No: 2016–1-015, 2017–2-236–1), Nagoya University School of Medicine (No: 17–167), and the ethics committees of all participating institutions. All study procedures were conducted according to the principles of World Medical Association Declaration of Helsinki.

**Consent to participate** Informed consent was obtained from all family members included in the study.

**Consent for publication** Informed consent was obtained from all family members for the possible publication of the results.

**Competing interests** The authors declare no competing interests.

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