

## Original Article

# Psychological burden on patients with cancer of unknown primary: from onset of symptoms to initial treatment

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## Abstract

**Objective:** Supportive care is a critical issue especially for patients with cancer of unknown primary since they often face serious situations, continuing to seek for relevant diagnosis and treatment with the primary sites unknown. However, there are only few research reports on this subject. The aim of this study was to clarify the experience on patients with cancer of unknown primary until they have their initial treatment and to obtain suggestions of supportive care for them.

**Methods:** A qualitative study using semi-structured interviews regarding the experience on patients with cancer of unknown primary was conducted.

**Results:** Data of the experience of the nine patients with cancer of unknown primary until their initial treatment were collected by semi-structured interviews. Patients' speech at interviews recorded in verbatim reports was assigned with 545 codes, 102 subcategories and 38 categories. Experience of the patients with cancer of unknown primary was categorized into five phases: Phase 1: period of making self-judgment on symptoms; Phase 2: period of suspecting serious disease, and seeking for appropriate medical treatment; Phase 3: period of searching for cause of disease while having painful symptoms and anxiety; Phase 4: period of having fear for death, frustration with unknown cause and denial of unknown state; Phase 5: period of struggling but being determined to face disease.

**Conclusions:** Experience of patients with cancer of unknown primary from onset of symptoms to their initial treatment was categorized into five phases, mainly manifesting their psychological burden. These findings will warrant for the future study of supportive care for patients with cancer of unknown primary.

**Key words:** experience, psychological burden, supportive care, cancer of unknown primary

## Introduction

Cancer of unknown primary (CUP) is an established clinical disorder, since it accounts for 3–5% of all malignant epithelial tumors (1).

Many of the patients with CUP manifest poor prognosis; the median survival time is 6–12 months (2,3). Clinical guidelines from the National Comprehensive Cancer Network (NCCN) and the National

Health Service (NHS) have been recently published (4,5), but medical staff still do not have enough knowledge and experience of this disorder (6,7).

Physicians are likely to run exhaustive and unproductive examination for diagnosis (7). Extensive examinations can provide useful results only for a minority of patients (8). The medical staff as well as patients with CUP still often feel anxious and uncertain of the diagnosis and treatment of CUP through the clinical course (6).

The period from onset of symptoms to CUP patients' visit to cancer specialists is usually long, during which patients' general condition may deteriorate (6). The fact that primary origin of cancer is unidentified is hard to accept for patients with CUP, who likely feel distressed (9,10). Several studies of patients with cancer with an identified primary lesion clarified the situation of quality of life (11,12) and the qualitative change of the patients' burden over time (13–15). However, there are only few research reports on experience of CUP (16) and the reports of active intervention to patients with CUP are only commentaries or case presentations (17–19).

Thus, under the uninvestigated situation of the experience on patients with CUP, we conducted this qualitative study to clarify their experience until they have their initial treatment and to obtain suggestions for further support.

## Methods

### Definition of terms

CUP: a disease defined as histologically proven metastatic malignant tumor whose primary site cannot be identified (4).

Experience of patients with CUP: subjective experience of patients from onset of symptoms to initial treatment.

Initial treatment: the first line treatment after the diagnosis of CUP.

### Research design

We conducted a qualitative and inductive study in a descriptive and naturalistic approach (20) using in-person interviews to extract patients' experience including thought, understanding and knowledge during the period from onset of symptoms to initial treatment for CUP. This qualitative study was performed according to reliable guidelines (21).

### Ethical procedure and participant recruitment

Institutional Review Board approval was obtained from both the University of Nagoya and the Nagoya City University before starting the study. We also obtained written consent from the participants and explained about privacy protection to them before conducting the interviews.

Patients were recruited from the Nagoya City University Hospital that functions as a core cancer treatment hospital in this region. The eligibility requirements for the participants were as follows: aged 20 or older, being informed CUP, having started his/her initial treatment, having physical pain and symptoms under control, being able to communicate and having consented to participate in this study. Patients were not selected by the theoretical sampling. Patients' recruitment ended when categories were judged to be saturated.

### Data collection

An interview guide was prepared based on the literature (20) upon consultation with specialist of oncology nursing. The interviews

were conducted after starting their initial treatment mainly in terms of the subjective experience of the patients with CUP from onset of symptoms to initial treatment, which included incidents that gave strong impressions, means to change knowledge about CUP and to increase the understanding, and changes in concept of values and life during this period. The first author (K.I.) carried out semi-structured, open-ended interviews according to the interview guide, and helped interviewees speak as freely as possible. The interviews were audiotaped and transcribed verbatim. The verbatim words were verified for accuracy. The interviews were conducted twice per case, with the following aims: (i) patients get the enough time to review their past experience, (ii) patients make the relationship with the interviewer to open their mind and (iii) the interviewer makes detailed interviews that reflect psychological process of experience adequately. This procedure of interview improves credibility of this study as a method of prolonged engagement. The first author confirmed whether the interpretation of verbatim data in the interview was correct in each patient on the second day of the interview.

Data on patients' background, such as age, occupation, previous illness, stage of disease, content of the informed consent, situation of medical consultation, type of examination and its result, therapeutic process and family structure, were collected from medical records (data aggregation: December 2011–October 2012).

### Data analysis

The data were coded using qualitative and inductive analysis with constant comparison technique (20). The first author coded the initial three interviews, developed definitions for each code and prepared a preliminary codebook. The second author (S.A.) reviewed the transcripts and codebook. Emerging codes and coding differences were discussed together until consensus was reached. Then they coded the remaining interviews by aggregating similar narratives and formed subcategories based on the aggregates, developing categories upon examining patients' experience of the disease (CUP) along the course of treatment process. After examining change in experience from the onset of symptoms to the initial treatment, each phase was given a name according to the main meaning of the categories constituting the phase. After interviews, the data were repeatedly checked and the mutual relation between each of the categories and phases along the time course was put into a conceptual scheme.

The first author confirmed whether the interpretation of verbatim data in the interview was correct in each patient on the second day of the interview. Additionally, we thoroughly reviewed the verbatim transcripts against the audiotaped interviews. The first author enhanced the credibility and authenticity by keeping a detailed audit trail of the coding and theoretical decisions and by reaching consensus with the second author. An experienced oncology nursing expert (S.A.) and a medical oncologist expert (H.K.) intervened in this study in all the analyses and approved the results after substantial discussion to assure the dependability and the objectivity in this qualitative study.

## Results

### Patient characteristics

Nine patients participated in this study after informed consent was obtained (Table 1). All the interviews were conducted at the Nagoya City University Hospital. The median age of the patients was 69 years (range 60–79). The median period from onset of symptoms to

**Table 1.** Patient characteristics

| Patient | Gender | Age    | Main symptoms <sup>a</sup>          | Extent of disease        | Performance status <sup>b</sup> | Initial treatment <sup>c</sup> | Duration (weeks)     |                      |                      |                      |                      |
|---------|--------|--------|-------------------------------------|--------------------------|---------------------------------|--------------------------------|----------------------|----------------------|----------------------|----------------------|----------------------|
|         |        |        |                                     |                          |                                 |                                | Phase 1 <sup>d</sup> | Phase 2 <sup>e</sup> | Phase 3 <sup>f</sup> | Phase 4 <sup>g</sup> | Phase 5 <sup>h</sup> |
|         |        | Median | 69                                  |                          |                                 |                                | 8                    | 8                    | 7                    | 1                    | 9                    |
|         |        | Range  | 60–79                               |                          |                                 |                                | 0–32                 | 0–60                 | 3–19                 | 1–11                 | 1–24                 |
| A       | Female | 79     | Right shoulder region pain          | Bone                     | 1                               | Local radiotherapy             | 8                    | 26                   | 7                    | 1                    | 2                    |
| B       | Female | 73     | Left leg swelling                   | Lymph nodes              | 2                               | Chemotherapy                   | 16                   | 12                   | 11                   | 1                    | 11                   |
| C       | Female | 65     | Back pain                           | Brain, bone              | 3                               | Local radiotherapy             | 8                    | 0                    | 9                    | 1                    | 9                    |
| D       | Male   | 63     | Dyspnea                             | Bone marrow, lymph nodes | 1                               | Chemotherapy                   | 4                    | 12                   | 4                    | 1                    | 2                    |
| E       | Male   | 62     | Left neck lymph nodes swelling      | Lymph nodes, pericardium | 1                               | Chemotherapy <sup>i</sup>      | 32                   | 6                    | 6                    | 1                    | 8                    |
| F       | Female | 73     | Right axillary lymph nodes swelling | Lymph nodes              | 3                               | Immunotherapy                  | 1                    | 1                    | 4                    | 11                   | 18                   |
| G       | Female | 60     | Fever, fatigue                      | Bone, bone marrow        | 1                               | Chemotherapy                   | 1                    | 60                   | 3                    | 1                    | 24                   |
| H       | Male   | 69     | Left neck mass, pharyngeal pain     | Lymph nodes              | 1                               | Chemotherapy                   | 12                   | 8                    | 19                   | 2                    | 1                    |
| I       | Male   | 71     | None                                | Liver                    | 0                               | Chemotherapy                   | 0                    | 0                    | 11                   | 1                    | 10                   |

<sup>a</sup>Main symptoms at the time point of the start of initial treatment.

<sup>b</sup>Eastern Cooperative Oncology Group Performance Status at the time point of the start of initial treatment.

<sup>c</sup>The first line treatment after the diagnosis of cancer of unknown primary (CUP).

<sup>d</sup>From onset of symptoms to before visiting local physicians.

<sup>e</sup>From visiting local physicians to before visiting specialists.

<sup>f</sup>From visiting specialists to finishing detailed examinations for searching for causes.

<sup>g</sup>From being informed of CUP until the start of initial treatment.

<sup>h</sup>From the start of initial treatment to the first interview.

<sup>i</sup>Emergency pericardiocentesis was conducted for pericardiac tamponade before initial treatment (in Phase 2).

first interview and from start of initial treatment to first interview was 42 weeks (range 22–89) and 8 weeks (range 1–76), respectively. Initial treatment consisted of chemotherapy for six patients, radiation therapy for two patients and immunotherapy for one patient. Six were interviewed in initial treatment and three were in relapse phase. The background of the patients was diverse and recruitment ended after analyzing the nine patients because categories were judged to be saturated.

### Experience of patients with CUP until initial treatment

All the participants had interviews twice with some interval for this qualitative study (Table 2). The median length of the interviews was 51 minutes (range 32–72). Regarding the experience of the patients with CUP until their initial treatment, 488 codes and 99 subcategories were assigned. They were sorted into 38 categories mainly based on psychological aspects. As the patients' experience was observed to change along the clinical time course significantly, categories were developed and constructed along the time course in Fig. 1, as shown in previous reports (22,23). During this process, the categories were classified into five phases: Phase 1: period of making self-judgment on symptoms; Phase 2: period of suspecting serious disease, and seeking for appropriate medical

treatment; Phase 3: period of searching for the cause of disease while having painful symptoms and anxiety; Phase 4: period of having fear for death, frustration with unknown cause and denial of unknown state; Phase 5: period of struggling but being determined to face disease.

In Fig. 1, we arranged categories related to symptoms on the upper area and those related to medical care or disease concept on the lower area with time course, respectively. Duration of Phase 3 was long (median: 8 weeks) while various examinations were conducted to identify the primary site of cancer. Both types of categories were associated mutually in Phases 2, 3 and 5. The categories related to anxiety persisted from Phase 3 even after informed consent of their diagnosis and treatment plan in Phase 4. Phase 5 was characterized by the coexistence of burden and determination to face CUP with acceptance of their situations. The categories are depicted in outward-pointing brackets as below.

### Phase 1: Period of making self-judgment on symptoms

The period of Phase 1 corresponded to the term from onset of symptoms to before visiting local physicians. The median period of this phase was 8 weeks (range 0–32). Seven patients noticed some symptoms while the other two patients (Patients F and I) came to know about the onset from routine examination for their other chronic

**Table 2.** List of phase/category/subcategory

| Phase  | Category   | Subcategory   |
|--|--|---|
| Phase 1: period of making self-judgment on symptoms  | Uncomfortable feeling with appearing symptoms  | Feeling uncomfortable with appearing symptoms   |
|  | Response to symptoms by making self-judgment   | Coping with symptoms, using his/her past experience<br>Deciding to consult local physicians   |
| Phase 2: period of suspecting serious disease, and seeking for appropriate medical treatment         | Persistence of symptoms without knowing the cause  | His/her symptoms cannot be improved at any local physician  |
|  |  | The cause of symptoms being unidentifiable by local physicians  |
|  | Increase in physical and mental distress   | Being distressed due to strong physical symptoms  |
|  |  | Being anxious about unrelieved symptoms   |
|  |  | Feeling hurt because others do not understand about his/her symptoms  |
|  | Dissatisfaction with medical care by local physicians  | Undergoing the hardship due to extra examinations   |
|  |  | Being dissatisfied with local physicians<br>Being dissatisfied with support provided by local clinic<br>Feeling the need for self-action because unknown cause does not lead to appropriate treatment |
|  | Voluntary decision to visit another hospital   | Taking action and visiting another hospital in search of the cause of disease   |
|  | Feeling of awkwardness for changing hospitals  | Having difficulty in finding out specialists  |
|  |  | Feeling the need for courage to inform local physician of changing hospitals  |
| Shock by local physicians' explanation of suspicion of cancer  | Feeling not a little awkward for changing hospitals<br>Being shocked by local physicians' explanation of suspicion of cancer |   |
| Satisfaction with being introduced to specialists  | Being satisfied with being introduced to specialists   |   |
| Phase 3: period of searching for the cause of disease while having painful symptoms and anxiety      | Entrusting detailed examinations to specialists  | Consenting to undergoing examinations proposed by specialists while not understanding their necessity   |
|  |  | Having difficulty in contacting doctors in other consulting sections, while having detailed examinations  |
|  | Experience of much amount of examinations  | Undergoing examinations many times  |
|  |  | Having no choice but to undergo detailed examinations in order to find the cause of disease   |
|  | Unexpected pain due to detailed examinations   | Undergoing the hardship due to detailed examinations  |
|  |  | Feeling exhausted by detailed examinations  |
|  | Anxiety and expectation to the results of examinations   | Expecting favorable results of examinations   |
|  |  | Having continuous anxiety and disappointment during examinations  |
|  |  | Not expecting much about the results of examinations  |
|  | Frustration for not being treated  | Being impatient for examinations being scheduled and the results of examinations being informed   |
| Being irritated at untreated state despite undergoing many examinations                              |  |   |
| Fear and pain due to increased symptoms  | Detailed examination schedule being in progress, while his/her symptoms being not improved                                   |   |
|  | Requesting specialists to improve his/her symptoms   |   |
| Disease-related anxiety and expectation for medical care   | Feeling uncertain of his/her future due to existence of symptoms   |   |
|  | Feeling that his/her life is threatened by painful symptoms  |   |
|  | Being anxious about the possibility of cancer  |   |
|  | Trying to think about his/her disease and upcoming treatment optimistically  |   |
| Phase 4: period of having fear for death, frustration with unknown cause and denial of unknown state | Recognition of the state of disease  | Being confused by different medical systems in specialized hospitals  |
|  |  | Expecting for medical care by specialists   |
|  | Denying his/her own cancer   | Feeling a sense of security that he/she is undergoing an appropriate medical care   |
|  | Beginning to recognize the state of disease  |   |
|  | Beginning to collect the information of disease  |   |
|  | Denying the fact that he/she has cancer  |   |

*Continued*

**Table 2.** Continued

| Phase   | Category  | Subcategory   |  |
|---|---|---|--|
| Phase 5: period of struggling but deciding to fight against disease                           | Determination to face his/her own cancer  | Hoping that his/her disease can be cured                              |  |
|   | Relief by being diagnosed   | Determination to face his/her own cancer                              |  |
|   | Frustration with cancer of unknown cause and denial of unknown state                  | Relief by being diagnosed   | Relief by the disease being understood by others   |
|   |   | Being frustrated with the cause of his/her cancer being unknown       | Not understanding that there is a disease entity of CUP, cancer in which primary site is unknown |
|   |   | Not accepting that the primary site of his/her cancer is unidentified | Getting nervous to others' reaction toward his/her disease                                       |
|   | Feeling that his/her disease cannot be understood by others                           | Feeling lack of others' understanding of his/her disease              |  |
|   | Realizing that his/her cancer is different from others                                | Having difficulty in explaining about his/her disease                 | Not having anyone to consult about his/her disease   |
|   |   | Fear for death  | Realizing that his/her cancer is different from others   |
|   | Phase 5: period of struggling but deciding to fight against disease                   | Anxiety and expectation regarding treatment                           | Thinking of death because he/she has cancer  |
|   |   |   | Becoming pessimistic due to cancer   |
| A thought that specialists are indispensable to him/her                                       |   | Being anxious about treatment method                                  |  |
|   |   | Thinking that he/she is undergoing the best treatment                 |  |
|   |   | Expecting the effect of treatment                                     |  |
| Determination to trust specialists for treatment  |   | Being anxious for the effect of treatment                             |  |
|   |   | Getting optimistic toward treatment, using his/her experience         |  |
|   |   | Having image of his/her life after treatment                          |  |
| Physical and mental distress deriving from cancer symptoms and/or adverse events of treatment |   | Wavering between hope and fear depending on words of specialists      |  |
|   |   | Feeling that his/her fate is left in hands of specialists             |  |
|   | Feeling that specialists are essential  |   |  |
| Fear for fatal disease  | Feeling that treatment approach is incomprehensible to amateur                        |   |  |
|   | Accepting the fact that even specialists cannot resolve the uncertainty involving CUP |   |  |
|   | Having no other choice but to entrust treatment to specialists                        |   |  |
| Dissatisfaction with the situations of having consistent unknown elements                     | Being distressed by adverse events  |   |  |
|   | Feeling like living together with anxiety due to side effects                         |   |  |
|   | Being anxious about continuous symptoms   |   |  |
| Searching for a way to go with the flow   | Being aware that he/she suffered from fatal disease                                   |   |  |
|   | Feeling that little information is available regarding his/her disease                |   |  |
|   | Having fear for appearance of new metastatic sites                                    |   |  |
| Feeling of relief from symptoms   | Feeling that little information is available regarding his/her disease                |   |  |
|   | Being dissatisfied with definition of disease, CUP, being vague                       |   |  |
|   | Feeling that the cause of disease is still unidentified                               |   |  |
| Recognition that treatment is effective   | Being still unable to convince him/herself of having CUP                              |   |  |
|   | Trying to live for today  |   |  |
|   | Having no spare to think about the future   |   |  |
| Positive feeling for treatment  | Letting things go with the flow   |   |  |
|   | Trying to find a way to deal with his/her symptoms in his/her own way                 |   |  |
|   | Learning to change viewpoint by watching other cancer patients                        |   |  |
| Thinking of his/her own way to live in the future   | Feeling relief from the symptoms by treatments  |   |  |
|   | Realizing his/her recovery in daily life  |   |  |
|   | Recognizing that treatment is effective   |   |  |
|   | Being satisfied with the treatment  |   |  |
|   | Recognizing that treatment is meaningful  |   |  |
|   | Being aware of a change in his/her state of mind                                      |   |  |

Continued

**Table 2.** Continued

| Phase | Category  | Subcategory  |
|-------|---|--|
|       |   | Thinking about his/her own way of life                                 |
|       |   | Being aware of keeping moderate distance from his/her disease          |
|       |   | Being conscious of changing mood                                       |
|       | Decrease in anxiety by nursing support                                    | Feeling relieved by advice on lifestyle in suitable timing from nurses |
|       |   | Being satisfied with mental support by nurses                          |
|       | Feeling of hurt for being unable to return to previous healthy conditions | Feeling hurt for being unable to return to previous healthy conditions |
|       | Coping with emotional ups and downs and accepting the situations          | Feeling settled down   |
|       |   | Feeling anxious intermittently   |
|       |   | Being still unable to accept his/her disease                           |
|       |   | Beginning to accept the situations                                     |

diseases. They hardly thought of malignant disease from their symptoms.

Patients had an <uncomfortable feeling with appearing symptoms>, and <responded to (the) symptoms by making self-judgment> based on their previous experience.

#### Phase 2: Period of suspecting serious disease and seeking for appropriate medical treatment

The period of Phase 2 corresponded to the term from visiting local physicians to before visiting specialists. The median period was 8 weeks (range 0–60). The process until consultation to specialist had two patterns: one was having follow-ups with local physicians for further search without knowing the causes (Patients A, B, D and G), while the other was being introduced to a specialist immediately or visiting a specialist without seeing any local physician (Patients C, E, F, H and I). This period was longer in the former cases.

In the former cases, the patients felt <persistence of symptoms without knowing the cause>, <increase in physical and mental distress> and had <dissatisfaction with medical care by local physicians>. Then, they made a <voluntary decision to visit another hospital> but had a <feeling of awkwardness for changing hospitals>. In the latter cases, the patients were <shocked by local physicians' explanation of suspicion of cancer> but were <satisfied with being introduced to specialists>.

#### Phase 3: Period of searching for the cause of disease while having painful symptoms and anxiety

The period of Phase 3 corresponded to the term from visiting specialists to finishing detailed examinations for searching for causes. The median period was 7 weeks (range 3–19).

After visiting specialists, patients <entrusted detailed examinations to specialists>. They had <experience of much amount of examinations> and impatiently waited for the result of each examination and for the next examination schedule. They experienced <unexpected pain due to detailed examinations> through pathological biopsies conducted to determine the diagnosis of cancer. After each examination, they had <anxiety and expectation to the results of examinations>, and some cases had <frustration for not being treated>. Particularly, one patient with serious symptoms felt <fear and pain due to increased symptoms>. Patients interpreted the meaning of their treatment in two ways: to manage the symptoms and to cure the diseases.

Patients continuously felt <disease-related anxiety and expectation for medical care> throughout this phase. The main reason for this anxiety was 'suspicion of cancer'. They expected mainly for the possibility of 'having benign disease' or 'being completely cured' and 'diagnosis and treatment by specialists and medical staff'.

#### Phase 4: Period of having fear for death, frustration with unknown cause and denial of unknown state

The period of Phase 4 corresponded to the term from being informed of CUP until the start of initial treatment. The median period was 1 week (range 1–11).

Patients put an end to the search for the causes. Being informed of the diagnosis of CUP, they finally <recognized the state of disease>. Some patients <denied his/her own cancer> and others were <determined to face his/her own cancer>. One patient felt <relieved by being diagnosed> after being informed because it took a long time for diagnosis after visiting a number of hospitals.

Then, they had <frustration with cancer of unknown cause and denial of unknown state>.

None of the patients comprehended the meaning of CUP, though all the patients understood that primary sites were not found.

Some patients had difficulty in explaining about the disease of CUP to others, and <felt that his/her disease could not be understood by others>. Unable to share the topic of their disease with another person, one patient <realized that his/her cancer was different from others>.

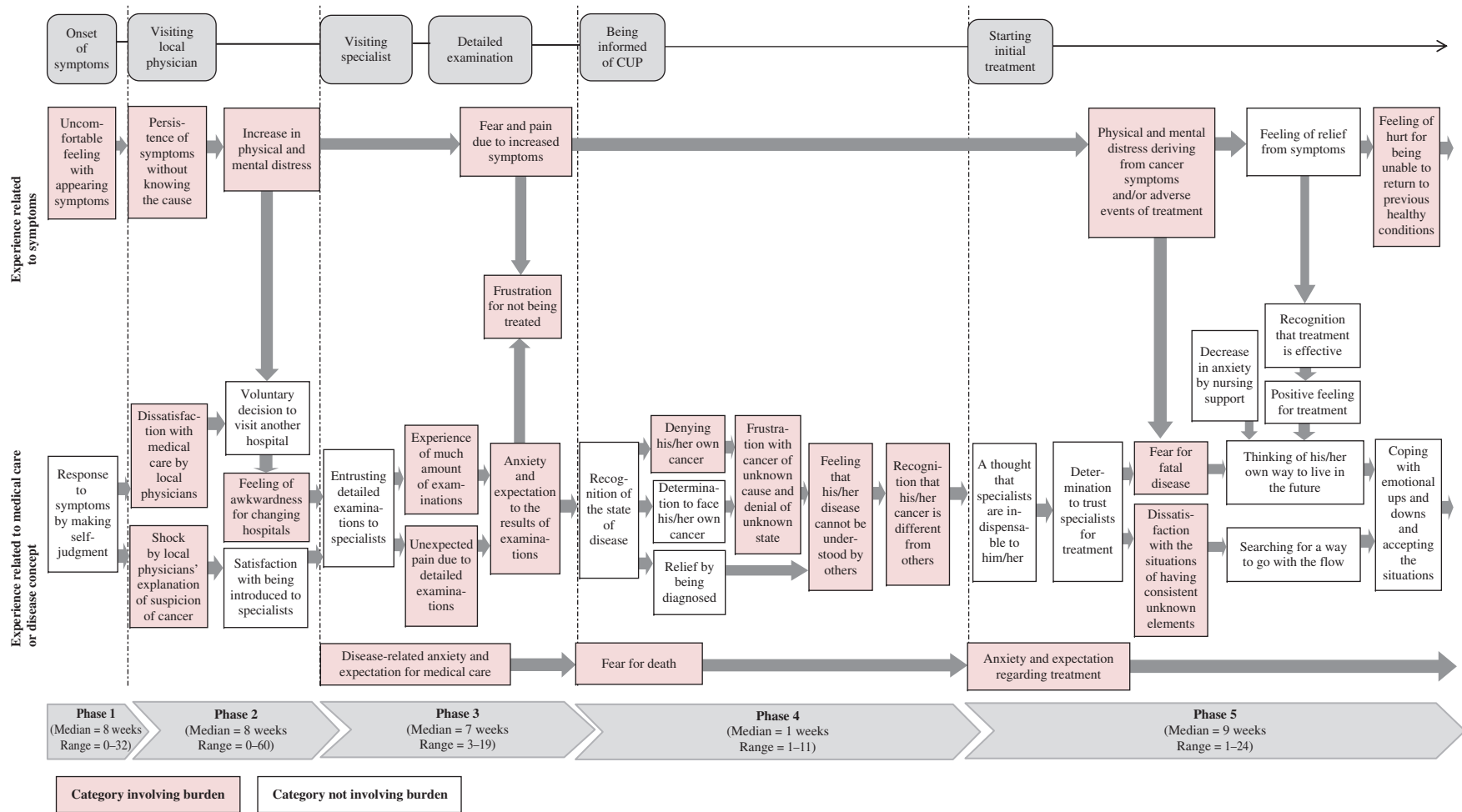
Through this phase, patients felt uncertain of future and <fear for death> because they knew cancer was a life-threatening disease.

#### Phase 5: Period of struggling but being determined to face disease

The period of Phase 5 corresponded to the term from the start of initial treatment to the first interview. The median period was 9 weeks (range 1–24).

Since the start of their initial treatment, all the patients had <anxiety and expectation regarding treatment>. They were disappointed at no option for surgical operation and worried about side effects of chemotherapy. They had <a thought that specialists were (the more) indispensable to him/her> because the disease was unknown. They made a <determination to trust specialists for treatment>.

<Physical and mental distress deriving from cancer symptoms and/or adverse events of treatment> increased in the course of time.



**Figure 1.** Phases and categories in the experience of patients with cancer of unknown primary (CUP)—from onset of symptoms to initial treatment. Phase 1: period of making self-judgment on symptoms; Phase 2: period of suspecting serious disease, and seeking for appropriate medical treatment; Phase 3: period of searching for the cause of disease while having painful symptoms and anxiety; Phase 4: period of having fear for death, frustration with unknown cause and denial of unknown state; Phase 5: period of struggling but being determined to face disease. The description in each square is a category.

They strongly felt <fear for fatal disease> and <dissatisfaction with the situations of having consistent unknown elements> and started <searching for a way to go with the flow>.

Some patients with very few side effects had <feeling of relief from symptoms>. Patients were relieved by specialists' explanation of <recognition that treatment was effective> or by <positive feelings for treatment>. They <thought of his/her own way to live in the future>, which lead to changing their states of mind and reconsidering how to live. <Decrease in anxiety by nursing support> facilitated these acts and maintained their thought to fight against diseases.

Because patients still had some symptoms even after starting the treatment, they had <feeling of hurt for being unable to return to previous healthy conditions>. As time passed, they settled down and started <coping with emotional ups and downs and accepting the situations> despite mental conflict with their disease.

## Discussion

### A viewpoint of the process of the experience of patients with CUP until initial treatment

This study categorized 'Experience of patients with CUP until their initial treatment' into five phases, which described the state of psychological burden on the patients with CUP. The main psychological characteristics of these phases are as follows: uncomfortable feeling on the symptoms in Phase 1; dissatisfaction with medical care in Phase 2; various types of pain and increased anxiety during detailed examinations under undetermined diagnosis in Phase 3; fear for death, frustration and denial with cancer of unknown cause in Phase 4 and persistent fear and anxiety with acceptance of their own disease in Phase 5.

'Experience of patients with CUP' in this study manifested some similar aspects to 'the illness course experienced by the patients with hematopoietic malignancy and hematopoietic stem cell transplantation' (23). They identified seven phases of the mental/emotional processes of the patients and integrated these phases from the illness onset up to the post-transplantation. The resemblance with our study lays in the phases where the patients had strong psychological burden persisting from the stage of diagnosis to the stage of initial treatment. The main and common burden between these studies was anxiety and fear. However, the period from the first visit to local physicians to being informed of diagnosis (Phase 2 to Phase 3) was longer in our patients with CUP. Especially, in our CUP cases, anxiety persisted with loneliness even after diagnosis, which was thought to derive from 'uncertainty' and 'orphan disease' characterizing CUP (24,25).

### 'Anxieties' in patients with CUP with 'uncertainty' and coping

Since Phase 3, anxiety persisted in the patients. The main source of anxiety was awareness to disease and death at first, and changed to treatment-related matters including elements of uncertainty. These anxieties seemed to be concerned with and get serious by the state of uncertainty, which was described as a comprehensive theme in the experience of CUP in Boyland's pilot study (16).

Regarding uncertainty in chronic disease including cancer, Mishel reported 'Uncertainty in illness', which explained that uncertainty is a cognitive state created when a person cannot adequately structure or categorize an event because of lack of sufficient cue (26). According to this report, in illness experience, uncertainty has four

forms: (i) ambiguity concerning the state of illness, (ii) complexity regarding treatment and system of care, (iii) lack of information about the diagnosis and seriousness of the illness and (iv) unpredictability of the course of the disease and prognosis (26). The experience of patients with CUP in this study involved all these forms: (i) ambiguity from the disease state of unknown origin, (ii) complexity regarding system of care through detailed examinations to find out primary site of cancer, (iii) lack of information about rare and unsolved cancer CUP and (iv) unpredictability of the clinically refractory course of CUP. Thus, we recognized that uncertainty was the most characteristic in the early experience of time course of CUP.

Mishel also described that 'uncertainty may be a condition under which a person can make a transition during illness from one perspective of life toward a new, higher order, a more complex orientation toward life' (27). In addition, Boss advocated that incomplete or uncertain loss can be interpreted as 'ambiguous loss', and 'ambiguity can make people less dependent on stability and feel more comfortable with spontaneity and change' (28). In Phase 5, the patients with CUP tended to restrain their thoughts and hopes for the future because of experience of uncertainty such as <fear for fatal disease> and <dissatisfaction with the situations of having consistent unknown elements>. However, they still expected the possibility of the identification of the origin of their cancer in the future. With treatment and assistance by healthcare workers, they <thought of his/her own way to live in the future> and <searched for a way to go with the flow>, <coping with emotional ups and downs and accepting the situations>. These show that patients with CUP spontaneously try to accept their 'uncertainty' as a part of reality to change for a new view of life (26) and to keep hope alive during treatment, which suggested the importance of medical support for promoting the patients' positive attitude.

### 'Loneliness' in patients with CUP and the relationship with medical staffs

The patients with CUP had another characteristic experience, loneliness. In Phase 4, these patients had a <feeling that his/her disease could not be understood by others> and <recognition that his/her cancer was different from others>, feeling bewildered by the unfamiliar disease and hard to obtain the information of CUP, which was thought to have brought loneliness to the patients with CUP. In such terms, CUP is called an 'orphan' disease (23).

In Phase 5, while the doctor-patient relationship was very close and the patients had <a thought that specialists were indispensable to him/her>, the patients had the tendency to repress their own emotions more because they wanted to keep good relationship with the specialists. The patients thought that the specialists were the only ones to understand their CUP. Therefore, the patients with CUP sometimes felt tensions for the relationship (data not shown). Supportive and nursing care needs to be provided beyond the otherwise disadvantageous situation of patients with CUP from outpatient visit period to in-hospital period in order to reduce psychological burden from loneliness by 'orphan' state (24).

### Limitations of this study

In this study, we clarified that the patients with CUP persistently had psychological burden of anxiety, loneliness and fear in the phases of the process of 'Experience of patients with CUP until initial treatment' (Fig. 1). Yet, on this study, the following matters need to be elucidated in further studies: the degree of psychological burden in



each phase, the critical categories that require the more active health-care intervention and the concrete proposal for supportive care.

Moreover, the results of this study need to be interpreted with caution, given the patients relatively stable in psychological and physical conditions were recruited in this study, and the study was carried out at a single institution which functions as one of the core cancer treatment hospitals. The possibility of response bias cannot be removed in these respects.

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## Conflict of interest statement

None declared.

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