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Research article

Exploring patient-reported barriers to participating in proton therapy clinical trials

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ABSTRACT

Introduction: Clinical trials lead the progress in healthcare. To ensure reliable research conclusions, it is essential to enroll diverse patient groups. Identifying and understanding patient-reported barriers to clinical trials may help enhance recruitment among diverse patient groups.
The clinical potential of proton therapy (PT) to reduce late effects is being investigated in clinical trials worldwide. Thus, for some patients, PT is only accessible by participating in clinical trials.
Individuals with smoking-related head and neck cancer (HNC) are sometimes socioeconomically deprived, leading to barriers to trial participation. This study aims to identify barriers to their participation in a randomised controlled trial (RCT) involving PT.
Method: Interviews were conducted with 14 HNC patients declining participation in an RCT involving PT. The interviews were transcribed and systematically analysed using an inductive approach identifying categories and themes.
Results: The identified barriers to RCT-participation are: (1) existential distress, which influenced participants' mental and cognitive capacities, (2) insufficient RCT-related knowledge arising from information overload during clinical consultations, (3) the wish for safety and familiarity during the treatment trajectory, particularly for participants needing accommodation during radiotherapy, and (4) the motivation for study participation was impacted by uncertainty due to randomisation and clinical equipoise. Existential distress is identified as an overarching theme because it influences and amplifies the other three themes.
Conclusion: Existential distress is a central theme that influences and amplifies other participation barriers in PT RCTs. It affects participants' comprehension of trial information, their preference for familiar environments, and their motivation to participate in clinical trials.

Introduction

Radiotherapy is the standard treatment for Head and Neck Cancer (HNC), with significant advancements in recent decades improving patient survival rates [1–2].

Proton Therapy (PT) is expected to reduce the risk of late effects. A prior study on radiotherapy to HNC reported a 28% prevalence of grade two or higher dysphagia at six months following photon radiotherapy. With PT, the prevalence is anticipated to decrease to 16%. The prevalence of the most severe grade of xerostomia at six months with photons was 10%, which is expected to be reduced to 2% with PT [2–3].

Dysphagia and xerostomia impact patients' quality of life significantly [4]. Hence, the clinical potential of PT to reduce late effects is currently being investigated in several phase-three clinical trials worldwide [5]. Consequently, PT is primarily accessible to patients with HNC participating in such trials [6].

Compared to the general population, individuals with smoking-related HNC are characterised by having lower income and

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educational attainment, a higher likelihood of being outside the workforce, more frequently living alone, and a higher prevalence of comorbidities [7]. These factors predict reduced clinical trial participation, impacting how trials are presented and discussed with socioeconomically deprived patients [8–9]. Furthermore, some factors are associated with limited health literacy, which relates to the understanding of health-related information and the ability to communicate effectively with healthcare professionals [10]. Low health literacy has been associated with the likelihood of being invited to participate in a study [11].

Patient barriers to clinical trials encompass various factors, such as a feeling of losing control due to the randomisation process, worries about novel treatments, financial constraints, logistical challenges like transportation and the need for accommodation, insufficient personal support, as well as misconceptions or limited comprehension of the trial's purpose and the concept of clinical equipoise [8–9,12–22].

PT is typically centralised in national or regional treatment facilities, which can present a structural barrier for PT trials, given that travel and accommodation are requirements for most participants [18]. Previous studies indicate that the distance to treatment significantly influences treatment choices, with fewer patients being referred when the treatment facility is farther away [23–24].

Clinical trials form the cornerstone of progress in treatment and healthcare. Enrolling diverse patient groups that accurately mirror the target population is essential for obtaining dependable conclusions forming the basis for integrating new knowledge.

From the perspective of patients with HNC, this study aims to identify the barriers to participation in a randomised controlled trial (RCT) involving PT and gain insight into how these barriers influence participants' decisions regarding participation.

Material and method

The study is guided by interpretive description (ID) as a qualitative methodological framework. The method is an approach to understanding and exploring complex human experiences and perspectives [25–26].

Setting

Barriers to participation are explored in the context of a Danish nationwide RCT for laryngeal and pharyngeal cancer. The primary endpoints in this RCT are levels of dysphagia and xerostomia when treated with PT compared to photon radiotherapy [3].

The RCT is conducted at six Danish cancer clinics in accordance with the Declaration of Helsinki [27].

Eligible patients receive RCT-related information during clinical consultations along with accompanying materials, including a patient information leaflet and a consent form. The consultation is followed up within one or two days, either through a second consultation or via telephone. During this contact, patients obtain further details about the RCT and have the opportunity to ask questions before signing the written informed consent.

For Danish patients with HNC, the time of the recommendation of radiotherapy at a multidisciplinary team conference to treatment initiation is preferably within 11 days [28]. Radiotherapy is postponed by approximately six working days if randomised in the RCT, approved by the Danish Health Authority.

The maximum distance from anywhere in Denmark to the proton therapy facility is approximately 370 km. Patients residing beyond a 150-kilometer radius are offered lodging.

Sampling of participants

If patients declined participation in the RCT, they were eligible for inclusion as participants in the present study. Participants were approached during radiotherapy treatment at the six cancer clinics from March to December 2022. To ensure a representative sample, the recruitment was purposeful [26], focusing on gender, age, and residential location. The recruitment process was coordinated by designated clinicians at the cancer clinics in collaboration with the principal author (AWK).

Data collection continued until no new perspectives on the posed questions were obtained [26,29].

Patients who declined participation in the present study was not documented.

Ethical considerations

Before involvement in the study, participants were presented with written and verbal information about the purpose of the interview. They were also required to complete a written informed consent form,

Following an inquiry with the regional ethics committee, it was determined that this study did not require further ethical approval. The study was approved by the Danish Data Protection Agency (record no. 1–10-72–181-20) and followed the Declaration of Helsinki [27].

Data collection

Data collection was conducted from March 2022 to December 2022.

Qualitative semi-structured audio-recorded interviews were performed using an interview guide (Table 1). The interview guide searched to cover perspectives regarding participants' reactions, understanding, and views when informed of the RCT.

The interview occurred before, during, or within one week following radiotherapy. The time frame was a deliberate decision to minimise potential recall bias.

To ensure the interview questions were understandable and relevant according to the clinical context, the interview guide was pilot-tested by six pilot participants treated with radiotherapy. The pilot participants considered the interview questions appropriate after minor corrections to the wording and structure.

After obtaining consent, participants were informed that the principal author (AWK) would contact them via telephone. The first contact was made to schedule the interview, and the second contact was to conduct the interview.

Following relevant guidelines, the data were securely stored and managed. Participants were allocated anonymous identification numbers.

Data analysis

The analytic process is presented in Table 2. Transcription, coding, analysis, and interpretation were performed by AWK.

The interviews were transcribed verbatim and imported into the software program NVivo 13 [30], which was employed for systematic data organisation and analysis. Functions used in NVivo 13 included coding, case- and file classification, memos, and analytical tools like word frequencies, word clouds, and visual aids.

The analysis was conducted in four phases: 1) data transcription, with subsequent readings and note-taking to ensure immediate comprehension; 2) initial inductive text coding; 3) exploration of patterns, similarities, or interferences between codes, leading to the identification of the categories related to the study's aim; 4) interpretation of the categories resulting in the extraction of themes.

The analysis underwent continuous reflection and refinement in collaboration with a co-author (ALJ) for enhanced validity and consensus regarding the findings and conclusions. Subsequently, it was reviewed with the remaining authors, all with expertise and experience in research and radiotherapy. To harmonise the participants' statements with the interviewer's immediate understanding, seeking validation by summarising the key points was consistently employed during the

Table 1
The interview guide searched to cover perspectives regarding participants' reactions, understanding, and views when informed of the RCT.

Trajectory	Open-ended questions	Probing questions
Diagnosis Before the first consultation	Please tell me about the consultation with the doctor when you were first informed of the head and neck cancer diagnosis.	• What were you told during the consultation? • What happened during the consultation? • What did it mean to you to be diagnosed with cancer?
Diagnosis After the first consultation	Do you remember your thoughts after the consultation?	• Describe your emotions after the consultation.
Treatment Information	Please tell me about the following consultation where you discussed treatment options with the doctor.	• What were you told about your treatment options?
Radiotherapy Decision	Please describe your thoughts and considerations regarding conventional radiotherapy and proton therapy.	• What were your thoughts on conventional radiotherapy? • What were your thoughts concerning the possibility of proton therapy?
Clinical trial Decision	Please describe your thoughts and considerations regarding undergoing radiotherapy as part of a clinical trial.	• What were you told about the clinical trial with proton therapy? • What did you think of the clinical trial with proton therapy?
Decision-making Perspectives and barriers	Please describe the decision-making process regarding radiotherapy.	• What was most important to you in the decision? • What do you think prevented you from participating in the clinical trial with proton therapy? • What would have been necessary for you to want to participate in the clinical trial - was there anything that could have helped you? • Who engaged in the decision-making process regarding participation in the clinical trial?
After decision-making Decisional regret	What are your thoughts on the decision regarding non-participation in the clinical trial with proton therapy?	• Do you think differently about your decision now compared to what you felt in the days following the decision?

interviews.

Results

Fourteen participants, including six females, were interviewed: two before radiotherapy, seven during the treatment trajectory, and five after. Ages ranged from 53 to 75 years. Further participant characteristics are presented in Table 3.

The interviews lasted from 15 to 30 min.

In the initial analysis, 29 codes were extracted from the transcripts. Subsequently, an analysis of interactions across these codes identified 12 categories, describing participants' barriers to participating in the RCT. These categories were interpreted based on the authors' reflections. Following this analysis, four themes emerged, clarifying how the identified barriers influenced participants' decisions regarding participation in the RCT.

The themes are presented in the following sections.

Existential distress

Participants described their experiences of receiving a cancer diagnosis with a range of emotions, including shock, fear, uncertainty, and confusion. Many had witnessed the loss of family members or friends to cancer, which had a notable impact on their perceptions of the disease.

"it was indeed a big shock, that's all I can say." (id6)

On the contrary, participants indicated a theoretical understanding of the high likelihood of survival due to the curative intended treatment. Nevertheless, the word "cancer" evoked a fear of mortality, leading to emotional distress.

"you hope to overcome the cancer, and my primary focus is on surviving." (id11)

Participants experienced the pre-treatment period as stressful due to uncertainties regarding treatment effects and concerns about how disease and late effects might burden their physical and mental well-being.

"the physician who informed me of radiotherapy made it clear to me that the treatment would be a tough game." (id12)

Cancer and the prospect of extensive treatment evoked a profound fear, leading to existential distress as participants considered the possibilities of life and death. Existential distress became a barrier to the RCT as it seemed to influence participants' mental and cognitive capacities.

Table 2
Analytic steps illustrating how codes, categories, and themes were extracted from the data material.

Codes	Categories	Themes
Fear and anxiety Shock when diagnosed Perceptions of cancer Hope and Faith	Emotions when diagnosed with cancer	Existential distress
Confusion Pre-treatment period	Pre-treatment stressors	
Clinical information Trial-related information Clinical consultations	Comprehensive clinical and trial-related information	Insufficient knowledge
Photon radiotherapy Proton radiotherapy	Perspectives on radiotherapy modalities	
Importance of the family Friends and colleges	Supportive relations	The safe and familiar
Home Relation to local hospital	Known surroundings and maintenance of daily life	
Pets Job Fragile family member	Responsibilities	
Accommodation Transportation	Inconvenience	
Treatment burdens Disease burdens	Demand for self-management skills	
Thoughts on participation Pros and cons (RCT)	Altruism versus egoism	Uncertainty and lack of motivation
Treatment effect Side effects Experimental treatment	Clinical equipoise	
Randomisation procedure Later treatment start	Uncertainty	

Insufficient knowledge

The RCT-related information and communication process occurred towards the end of the clinical consultation following the delivery of an

Table 3
Participant characteristics include sex, age, proximity to the proton treatment facility, occupational status, cohabitation status, and the time of the interview.

ID	Sex	Age (years)	Distance to PT (km)	Occupational status	Cohabitation status	Time of interview
1	Male	75	307	Retired	Married	Before treatment
2	Female	72	115	Retired	Married	During treatment
3	Male	56	35	Working	Married	During treatment
4	Male	65	345	Retired	Single	After treatment
5	Male	56	280	Working	Married	After treatment
6	Male	66	300	Retired	Married	During treatment
7	Male	68	185	Retired	Married	During treatment
8	Female	61	308	Working	Married	During treatment
9	Male	66	301	Retired	Single	After treatment
10	Male	63	150	Retired	Single	During treatment
11	Female	53	300	Working	Married	During treatment
12	Female	67	146	Retired	Single	Before treatment
13	Female	71	147	Retired	Married	After Treatment
14	Female	70	300	Retired	Single	After treatment

extensive diagnosis and standard treatment information. Consequently, participants reported challenges in processing the additional RCT-related information.

"the amount of information is overwhelming, making it challenging to keep up and recall half of what is being said. "(id10)

The combination of information overload and the timing of RCT-related communication challenged the participants in comprehending and recalling the information presented during and after the consultation.

"the information went over my head as my mind was occupied with other thoughts. Where exactly were my thoughts? Well, they were swirling around in my mind ". (id9)

Information overload seemed to influence participants' understanding of information related to the RCT, creating a barrier that resulted in insufficient knowledge about the RCT, thereby impeding participants' ability to make informed decisions regarding their participation.

The safe and familiar

Participants found the possibility of accommodation during proton therapy challenging due to concerns about being away from home.

My greatest source of strength lies in my home. Regardless of the circumstances, my family always cares for me and keeps my spirit high ". (id5)

Being separated from home, family, and friends during cancer treatment appeared to cause a fear of isolation and loneliness. Furthermore, a sense of uncertainty in handling the challenges related to the disease and the treatment alone was reported. Some participants relied on the support and care provided by their families and friends. In contrast, others mentioned difficulties in leaving home due to responsibilities related to family members, pets, or employment.

Participants longed for normality during treatment and believed that maintaining their daily routines would be more manageable if they could stay at home during the treatment. Additionally, the convenience of receiving radiotherapy at the local hospital was a prominent factor.

"The most important aspect for me was the necessity to be present at the hospital every day, and from my home, it only takes me 5–10 minutes to get to the hospital". (id1)

This finding held particular importance for participants residing near the local hospital.

The desire for safety and familiarity during treatment represents a notable barrier to participation in the RCT, particularly for those participants residing far from the proton facility.

Uncertainty and lack of motivation

Participants described a general motivation to participate in RCTs to support research and future patients. However, in the context of PT, they perceived that the stakes were too high. Despite the altruistic motivation to participate in the RCT, personal interests ultimately drove the decision.

"Due to the lack of proven benefits of proton therapy, I questioned its advantages? Additionally, being separated from my family and dealing with cancer only added to my concerns ". (id8).

Emotional considerations were prioritised over rational attitudes in the decision-making process regarding participation. Participants appeared to make decisions based on emotions and intuition rather than objective reflections.

Participants considered the RCT's primary endpoints related to side effects uncertain due to the concept of clinical equipoise. Furthermore, they expressed greater interest in their survival, particularly considering that side effects were challenging to anticipate before the treatment. Consequently, the primary endpoints related to side effects may serve as a barrier to participation.

Participants experienced the randomisation process to a lottery.

"the element of chance, particularly the drawing of lots, contributed to my feeling of uncertainty"? (id2)

The concept of randomisation increased uncertainty and entailed a feeling of loss of control, which affected the motivation for participation. Finally, participants described cancer as a ticking clock and preferred treatment as soon as possible.

Considering the significance of time, I didn't want to wait another week for treatment". (id3)

In summary, the study endpoints, the randomisation process, and the delayed treatment initiation caused by activities associated with the RCT generated uncertainty and impacted participants' motivation to participate.

Discussion

This study explored patients' perceptions of barriers to participating in an RCT within PT. The identified barriers included: existential distress related to cancer mortality and pre-treatment stressors; limited knowledge about the RCT; a desire for familiarity during treatment; and uncertainties and motivational factors concerning the RCT design and the concept of clinical equipoise.

Existential distress is a term employed to encompass a wide range of psychological disturbances that arise in uncertainty regarding the meaning and value of life [31]. Prior studies describe existential distress as a fear of death and the consequences of cancer treatment, which can

lead to loneliness, grief, regret, loss of autonomy, and a fear of missed life [32]. This aligns with the findings in the present study, where existential distress appears to stem from reflections on life and death and stressors in the pre-treatment period.

Prior research has described the informed consent process in clinical trials as complicated. This complexity arises from the dual challenge of providing detailed information and determining the most appropriate timing for trial-related communication [33]. The extensive amount of information can potentially result in information overload, which may hinder the comprehensive understanding of health-related information [34]. Previous studies have indicated that individuals with insufficient trial-related knowledge are significantly less likely to volunteer for participation [12,35]. Additionally, individuals with limited health literacy are at a higher risk of not being invited to participate in trials [10–11]. The current study illustrates that information overload impacts participants' capacity to comprehend trial-related information, influencing their understanding of the RCT and, consequently, their ability to make an informed decision about participation.

International cancer studies indicate that the distance to a treatment facility is essential in treatment decision-making. The longer the distance to the treatment center, the more decline the treatment [36–38]. In the context of the host RCT in this study, distance to PT appears to create a barrier to participation, as indicated by two perspectives: firstly, participants preferred the convenience of staying near the local cancer clinic, and secondly, they expressed concerns about isolation, loneliness and the added self-management demands that arise from the necessity for being accommodated without any significant others during PT.

The literature indicates that individuals rejecting trial participation often struggle to balance potential drawbacks and benefits [39]. This is consistent with the findings of this study, where participants described challenges in reconciling rational attitudes with personal needs or preferences. The selection of relevant trial endpoints, from a patient perspective, and the randomisation process have been recognised as common barriers to participation in RCTs [40]. This aligns with the present study's findings, where the selection of endpoints related to late effects and the uncertainties stemming from the randomisation procedure emerged as barriers to participation. However, it is crucial to continue conducting RCTs to collect level-A evidence for novel therapies [41].

Existential distress is found to impact and amplify the other three themes: "Insufficient Knowledge," "The Safe and Familiar," and "Uncertainty and Lack of Motivation." (Fig 1).

Existential distress can affect participants' cognitive capacities and focus. When individuals are preoccupied with the fear of death or the overarching existential questions associated with their diagnosis, it becomes challenging for them to engage with and comprehend complex RCT-related information, contributing to the theme of "insufficient knowledge.".

The desire for safety, familiarity, and support from family and friends during treatment is intensified by existential distress. Patients may seek comfort and support in their familiar environments, preferring to stay at home, which further underscores the importance of the "safe and familiar" theme.

Existential distress can increase uncertainty and generate a sense of loss of control. The profound fear of mortality may lead to an urgency for immediate treatment as patients deal with the significance of time, thereby impacting their motivation to participate in the RCT. Additionally, the emotional considerations of existential distress can outweigh rational attitudes, influencing participants' motivation and decision-making process regarding participation.

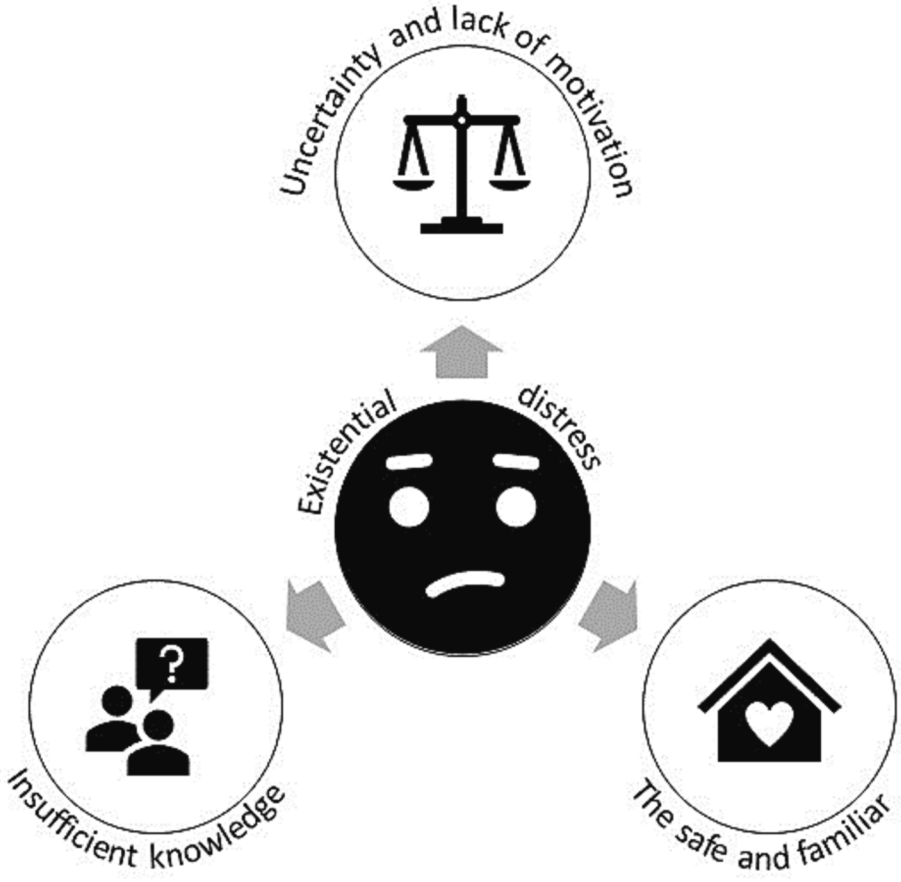

Fig. 1. Existential distress impacts and amplifies the other three themes: "Insufficient Knowledge," "The Safe and Familiar," and "Uncertainty and Lack of Motivation.".

A limitation of the study may be that the interviews, for logistical reasons, are performed on the telephone. This choice was considered when developing and evaluating the interview guide, which comprised well-worded questions in an easily understood everyday language. Furthermore, the interviewer was precise in speaking slowly and clearly and asked for elaboration from the participants if something needed to be clarified [42]. The interviewer described the participants as verbally informative and did not find the absence of body language essential to support the validity of the study findings.

Even though this study focused on barriers to a Danish RCT within PT, from the perspective of HNC patients, the findings may potentially be transferable to other patient groups, RCTs, and centralised treatment settings.

The clinical implications of the study involve the ability to identify and understand patient-reported barriers to clinical trials. This understanding is valuable in developing targeted interventions to enhance the recruitment process for clinical trial participation among diverse patient groups.

Conclusion

The motivation for participation in an RCT in the context of PT indicates that existential distress is an overarching theme that influences and amplifies the other three themes: Insufficient Knowledge; The Safe and Familiar; and Uncertainty and Lack of Motivation.

The emotional aspects of confronting a cancer diagnosis and the fear of mortality considerably impact how patients engage with clinical trial information, their preference for familiar environments, and their motivation to participate in trials.

Ethics approval

Following an inquiry to the regional ethics committee, it was determined that this study did not require ethical approval.

The study was approved by the Danish Data Protection Agency (record no. 1-10-72-181-20) and followed the Declaration of Helsinki consent to participate.

Participants signed informed consent before participation.

Availability of data and materials

The data from the current study are available from the corresponding author upon reasonable request.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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