Development of a complex intervention to reduce barriers in clinical trail participation and radiotherapy among Danish patients with head and neck cancer

Background

This project aims to develop a complex intervention to reduce potential barriers in clinical trial participation in order to optimize the conditions for equal use of novel and centralised radiotherapy.

Proton beam therapy (PBT) is one of more novel radiotherapy modalities introduced in Denmark within recent years. PBT is a highly specialised cancer treatment mainly available in clinical trials and in one treatment facility in Denmark.

PBT reduces the dose to normal tissue surrounding the target volume. Patients undergoing treatment for head and neck cancer may potentially benefit from PBT due to sparing of normal tissue, thus reducing acute and chronic toxicities [1]. The Danish Centre for Particle Therapy (DCPT) located at Aarhus University Hospital is a national treatment facility offering PBT to patients from all over Denmark. The Danish Head and Neck Cancer Group (DAHANCA) conduct a national randomised trial comparing PBT and conventional radiotherapy in the treatment of head and neck cancer. By accepting participation in the clinical trial, patients are informed of the randomisation procedure to receive either PBT at DCPT or conventional radiotherapy at a local hospital. The DAHANCA trial is the only access to PBT for patients with head and neck cancer.

Cancer of the head and neck is a frequent malignancy. Overall incidence rates are increasing with approximately 1200 new patients diagnosed annually in Denmark. The majority of patients with head and neck cancer are 55-65 years of age, and three times more men than women are diagnosed. The most common risk factors for head and neck cancer are HPV infection or the use of tobacco and alcohol [2].

Patients with head and neck cancer have a lower level of education as well as a lower income [3]. Socio-economic differences have an impact on the incidence and survival of head and neck cancer [4-6]. The incidence rate ratio (IRR) for laryngeal cancer is 3.2 for persons with a short education versus 1.7 for persons with a higher level of education. Furthermore, 44% of low-income patients with head and neck cancer are alive after five years compared with 65 % of patients with a high income [7].

Socioeconomically disadvantaged patients have a lower participation rate in clinical trials [6, 8], and patients with a lower level of education and income report more barriers to participate in trials [9]. Physician-related barriers for enrollment of patients in clinical trials comprise factors such as attitude, awareness of trials, extra time spent with the patients and treatment preferences [9-10]. The most common reasons for patients to decline participation include loss of control, fear of morbidity, concerns about costs, logistical barriers such as transportation and lack of personal support [9-10].

Concerning cancer treatment there is a tendency that patients with short education, low income or living alone have a higher risk of not being offered adequate treatment. This is particularly the case when there is uncertainty regarding treatment choice or in complex courses of treatment such as radiotherapy [3-4].

International cancer studies indicate that the geographical distance to a treatment facility plays an important role regarding treatment choice. The longer the distance to the treatment facility, the more patients decline the treatment [11]. Similar results were found in a Danish nationwide registry study, investigating socio-economic and structural patterns among patients referred to phase 1 cancer trials. The study found significantly decreased odds of referral for patients with long distance to the phase 1 unit, patients with a lower educational level and patients with lower income compared to patients with short distance, long education and high income [12].

When a patient is diagnosed with head and neck cancer, the national cancer pathways defines that initial treatment should begin within 14 days. In this context, the patient will be informed of the randomised clinical trial at the local hospital and decide whether or not to attend as well as accept the opportunity to receive PBT in a centralised treatment facility. In light of this complex decision-making process regarding participation in a clinical trial and thus treatment at a geographically distant clinic, it seems essential to promote and support active patient involvement in the decision-making process [13]. Patient values, experiences, and perspectives can be used at an individual and organisational level as a basis for improvement of quality of care. In addition, patient involvement is suggested to increase health care equality, as it gives voice to marginalised or vulnerable patient populations, ensuring that individual needs are expressed and met [14].

Several studies have described various interventions to support patients receiving health care services. Examples of interventions are patient navigation tools, decision aids, option grids, patient-to-patient-mentoring and patient education. In general, the results of interventions seem promising, especially among support to vulnerable patient or minority groups which seem to have significant impact on disparities leading to potential inequality in cancer health [15-17].

A risk of inequality in the access to clinical trials and thus PBT caused by either patient and physician- related barriers or geographical distance to the treatment facility cannot be excluded, but further studies are needed to confirm this. To address this possible issue it is relevant to identify and understand the underlying determinants and how they interact and influences the shared decision-making process regarding trial participation and thus acceptance of novel and centralised cancer treatment. This will form the basis for development of a complex intervention to facilitate the shared decision-making process as well as support the patient to navigate in a complex choice in relation to cancer treatment.

Purpose

The overall purpose is to develop, pilot-test and implement a complex intervention to support patients with head and neck cancer in the decision-making process concerning clinical trial participation and thus the opportunity of referral to radiotherapy in a centralised treatment facility.

To fulfill this purpose the following aims are defined.

- To involve patients and healthcare professionals in a co-production process throughout all phases of the project
- To identify perceptions and barriers regarding trial participation among patients with head and neck cancer as well as relevant healthcare professionals
- To investigate the patient perspective on centralised cancer treatment in Denmark

Material and methods

Complex interventions are characterised by interventions including more components with mutual interplay [18]. Examples of complex interventions in the context of this project are patient decision aids or option grids, leading to a better basis for shared decision making between patients and clinicians.

Theoretical framework

The underlying theoretical framework of this project is public health, defined as:

"*The science and art of preventing disease, prolonging life and improving quality of life through organized efforts and informed choices, organizations, public and private, communities and individuals*" [19].

Determinants of behaviour in the context of decision-making regarding trial participation as well as acceptance of novel and centralised treatment will be considered through a ecological model of health behaviour [20-22]. The socio-ecological model presents five levels influencing health behaviour. The levels comprise individual or intrapersonal level, interpersonal level, organizational level, community level and a public policy level [22]. Within the frame of the socio-ecological model determinants and how they interact will be identified and interpreted. This will target the development of a complex intervention as it is essential to understand the underlying determinants of behaviour in order to identify relevant areas amenable of change.

Barriers for participation in trials and the patient perspective on centralised proton treatment – a qualitative analysis

Physician - and patient-related barriers to participation in clinical trials as well as the patient perspective regarding treatment at a national centralised treatment facility in Denmark will be

investigated. Participant observation of the dialogue between patients and physicians concerning trial participation will be carried out at the local radiotherapy clinics in Denmark [23]. The aim is to gain a deeper understanding on intrapersonal and interpersonal aspects.

Moreover, semi-structured interviews will be conducted with 10 patients who have declined participation as well as 10 clinicians, responsible of enrolling patients in clinical trials [24]. The purpose of the interviews is to let the patients and clinicians express specific needs for intervention in the decision-making process regarding participation in clinical trials and thus acceptance of centralised treatment. Interview patients will be selected purposefully to obtain variation in age, gender and place of recidence [25]. Systematic text condensation will be used to analyse data [25]. The results will show the most important themes related to barriers concerning PBT trials and the patient perspective regarding centralised treatment. The software programme Nvivo12 will support the organisation and analysis of data.

From development to implementation of a complex intervention

The complex intervention will be developed, pilot-tested, evaluated and implemented in an iterative process based on the complex interventions guidance from the Medical Research Counsil (MRC) in UK [18]. As the intervention development process is iterative the described steps will be repeated in more cycles.

Development

The complex intervention for development is supposed to be either an option grid or a patient decision aid. In both cases the tool will be aimed to support patients with head and neck cancer in the decision-making process concerning clinical trial participation and thus to receive centralised radiotherapy.

The intervention will be based on the understanding of the context and target population achieved through the socio-ecological model as well as the findings in the qualitative analysis. Prior to these activities the evidence base has been reviewed in published literature. The knowledge gained will be applied during the process of complex intervention development.

The approach to intervention development will be partnership intervention development [26-27], as relevant patients and healthcare professionals from collaborating clinics in Denmark will be invited to attend a national project advisory board. The healthcare professionals attend the advisory board during all phases, but patient representatives may be replaced through the process to ensure they are able to contribute with experiences from e.g. pilot-testing. Throughout the intervention development process the advisory board are considered as co-creators on equal terms with the researchers and will be involved in identifying areas amenable of change and helping to form the content and design of the complex intervention. The method for involvement will vary between workshops and dialogue meetings with attendance of the project advisory board and members of the research team.

The intervention will be developed as a prototype for pilot testing. After pilot-testing and evaluation further development can take place prior to implementation.

Pilot-testing

The prototype will be pilot-tested in radiotherapy clinics in Denmark. The aspects that will be taken into account are patient- and clinician experiences in using the tool in the shared decision-making process. Furthermore, how the use of an option grid or patient decision aid fits into the clinical workflow

Evaluation

The national project advisory board will throughout the intervention development process be invited to dialogue meetings or workshops to evaluate on pilot-tests as well as discuss and clarify necessary changes to the tool. Further topics for evaluation is the effectiveness of the intervention and how it supports desicion-making.

The methods for evaluation in this study are qualitative, but in a later study the impact can be assessed quantitatively.

Implementation

During implementation the national advisory board are crucial. By involving their expressed needs and preferences throughout the intervention development process they are expected to support implementation of the intervention in clinical practice in a positive way. This will lead the way to successful long term implementation.

Expected results and impact

This study will demonstrate the development, pilot testing, evaluation and implementation of a complex intervention tailored to meet the patients' differentiated needs concerning support in medical decision making.

Research plan and organisation

The project is an essential part of an ongoing PhD-study at Aarhus University, Health.
The described activities will be initiated from the beginning of 2021 and and proceed until 2025.

The main supervisor, Professor Cai Grau, supervises project management and funding as well as collaboration with national and international networks.

Co- supervisor, Professor Susanne Oksbjerg Dalton, will contribute with extensive knowledge concerning health inequality as well as experience on development and testing of complex interventions.

Co- supervisor, Kenneth Jensen, MD, PhD will contribute with his extensive expertise related to patients with head and neck cancer.

Co- supervisor, Postdoc & Clinical Nurse Specialist Annesofie Lunde Jensen, will assist the supervision in qualitative and anthropological research methods; interviews and participant observations as well as guidance in qualitative data analysis and interpretation.

International co-supervisor, Professor Hilary Bekker, has accepted hosting a research stay. Moreover, she contributes with her expertise within complex intervention research methods, medical decision making and intervention design.

Other collaborating partners in this study are DAHANCA, Danish Research Center for Equality in Cancer (COMPAS), Research Centre for Patient Involvement in Central Region Denmark, radiotherapy clinics in Denmark and the Danish Centre for Particle Therapy.

Perspectives

This project addresses a very important issue in cancer care, namely how we can ensure equal access to the highly specialised and centralised treatments offered to Danish cancer patients. Such treatments are often only offered in a trial setting, so the key research question also relates to ensuring broad participation in clinical studies.

This study will contribute with new knowledge on the barriers affecting clinical trial participation and use of proton beam therapy among Danish patients with head and neck cancer. The study will also demonstrate the impact of a complex intervention and to what extend it supports patients in the decision-making process concerning trial participation and thus acceptance of treatment in a national centralised treatment facility.

The results are subsequently expected to be generalizable to similar groups of patients with cancer. This will form the basis for further development of nationwide strategies to ensure equal access to centralised cancer treatment.

References

1. Kim, J.K., et al., Proton Therapy for Head and Neck Cancer. Curr Treat Options Oncol, 2018. 19(6): p. 28.
2. Danish Cancer Society; https://www.cancer.dk/hoved-halskraeft-halscancer/
3. Boing, A.F. and J.L. Antunes, [Socioeconomic conditions and head and neck cancer: a systematic literature review]. Cien Saude Colet, 2011. 16(2): p. 615-22.
4. Olsen, M.H., et al., Socioeconomic position and stage at diagnosis of head and neck cancer - a nationwide study from DAHANCA. Acta Oncol, 2015. 54(5): p. 759-66.
5. Dalton, S.O., et al., Socioeconomic inequality in cancer survival - changes over time. A population-based study, Denmark, 1987-2013. Acta Oncol, 2019. 58(5): p. 737-744.
6. Kjaer, T.K., et al., Influence of social factors on patient-reported late symptoms: Report from a controlled trial among long-term head and neck cancer survivors in Denmark. Head Neck, 2016. 38 Suppl 1: p. E1713-21.
7. Society, D.C., Hvidbog, Social ulighed i kræft i Danmark. 2019.
8. Kjaer, T., et al., Do we reach the patients with the most problems? Baseline data from the WebCan study among survivors of head-and-neck cancer, Denmark. J Cancer Surviv, 2016. 10(2): p.251-60.
9. Manne, S., et al., Attitudinal barriers to participation in oncology clinical trials: factor analysis and correlates of barriers. Eur J Cancer Care (Engl), 2015. 24(1): p. 28-38.
10. Unger, J.M., et al., Systematic Review and Meta-Analysis of the Magnitude of Structural, Clinical, and Physician and Patient Barriers to Cancer Clinical Trial Participation. J Natl Cancer Inst, 2019. 111(3): p. 245-255.
11. Acharya, S., et al., Distance to Radiation Facility and Treatment Choice in Early-Stage Breast Cancer. Int J Radiat Oncol Biol Phys, 2016. 94(4): p. 691-9.
12. Gad, K.T., et al., Socioeconomic Differences in Referral to Phase I Cancer Clinical Trials: A Danish Matched Cancer Case-Control Study. J Clin Oncol, 2019. 37(13): p. 1111-1119.
13. Born, K.B., et al., Engaging patients and the public in Choosing Wisely. BMJ Qual Saf, 2017. 26(8): p. 687-691.
14. de Haes, H., Dilemmas in patient centeredness and shared decision making: a case for vulnerability. Patient Educ Couns, 2006. 62(3): p. 291-8.
15. Enard, K.R., et al., Are cancer-related decision aids appropriate for socially disadvantaged patients? A systematic review of US randomized controlled trials. BMC Med Inform Decis Mak, 2016. 16: p. 64.
16. Stacey, D., et al., Decision aids for people facing health treatment or screening decisions. Cochrane Database Syst Rev, 2017. 4: p. Cd001431.
17. Durand, M.A., et al., Do interventions designed to support shared decision-making reduce health inequalities? A systematic review and meta-analysis. PLoS One, 2014. 9(4): p. e94670.
18. Craig P., Dieppe P., Macintyre S. et al. (2013) Developing and evaluating complex interventions: new guidance [Homepage of Medical Research Council], [Online]. Available: http://www.mrc.ac.uk/documents/pdf/complex-interventions-guidance/ [12/11, 2017].
19. Winslow, C.E., THE UNTILLED FIELDS OF PUBLIC HEALTH. Science, 1920. 51(1306): p.

23-33.
20. Glanz, K., et. al., Health behaviour and health education: Theory, research and practice, 4th ed. – PsycNET. (Book) 2008.
21. Bronfenbrenner, U., The Ecology of Human Development. 1979.
22. McLeroy, K.R., et al., An ecological perspective on health promotion programs. Health Educ Q, 1988. 15(4): p. 351-77
23. Feltarbeid i egen kultur. 2014.
24. Kirsti, M., Kvalitative Forskningsmetoder for Medisin og Helsefag. Vol. 4. Utgave. 2017:Universitetsforlaget.
25. Malterud, K., Systematic text condensation: a strategy for qualitative analysis. Scand J Public Health, 2012. 40(8): p. 795-805.
26. O'Cathain, A., Croot, L., Sworn, K. et al. Taxonomy of approaches to developing interventions to improve health: a systematic methods overview. Pilot Feasibility Stud 5, 41 (2019). https://doi.org/10.1186/s40814-019-0425-6v
27. O'Cathain A, Croot L, Duncan E, et al, Guidance on how to develop complex interventions to improve health and healthcare, BMJ Open 2019;9:e029954. doi: 10.1136/bmjopen-2019-029954